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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF DISORDERS RELATED TO FRATAXIN DEFICIENCY

(57) Abstract: The disclosure relates to compositions and methods for, *inter alia*, altering, *e.g.*, enhancing, the level of frataxin protein via delivery using an adeno-associated viral (AAV) capsid variant. The compositions and methods of the present disclosure are useful, *inter alia*, in the treatment of subjects who have, have been diagnosed with, or suspected of having a disorder associated with frataxin (FXN) deficiency, e.g., Friedreich's Ataxia.

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF DISORDERS RELATED TO FRATAXIN DEFICIENCY

RELATED APPLICATIONS

[01] This application claims the benefit of and priority to US Provisional Application Serial No. 63/463,840, filed May 3, 2023, and US Provisional Application Serial No. 63/593,795 filed October 27, 2023, the contents of each of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[02] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file, entitled 14640_0082-00304_SL.xml, was created on March 20, 2024, and is 5,513,009 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD

[03] Described herein are compositions and methods relating to adeno-associated virus (AAV) viral particles for the delivery of polynucleotides, e.g., polynucleotides encoding a frataxin (FXN) protein for use in the treatment of Friedreich's Ataxia (FA). In some embodiments, compositions described herein may be used to treat a subject in need thereof, such as a human subject diagnosed with FA, or as a research tool in the study of diseases or conditions in cells or animal models of FA.

BACKGROUND

[04] Friedreich's Ataxia (FA) is an autosomal recessive inherited disease that causes progressive damage to the nervous system. See Parkinson et al., Journal of Neurochemistry, 2013, 126 (Suppl. 1), 103-117, the contents of which are herein incorporated by reference in their entirety. FA typically results from the degeneration of nervous tissue in the spinal cord due to reduced expression of the mitochondrial protein frataxin (FXN) in sensory neurons that direct muscle movement of the arms and legs. See Koeppen, Arnulf; J Neurol Sci., 2011, April 15; 303(1-2): 1–12. Onset usually occurs at puberty or by age 25. See Campuzano, et al., Science, 271.5254 (Mar 8, 1996): 1423. Initial symptoms of FA include poor coordination such as gait disturbance, poor balance, leg weakness, decreased walking, impaired coordination, dysarthria, nystagmus, impaired sensation, kyphoscoliosis, and foot deformities. See Parkinson et al., Journal of Neurochemistry, 2013, 126 (Suppl. 1), 103-117. FA is also associated with scoliosis, heart disease, and diabetes. The disease generally progresses until a wheelchair is required for mobility. Incidence of FA among Caucasian populations is between about 1 in 20,000 and about 1 in 50,000, with a deduced carrier frequency of about 1 in 120 in European populations. See Nageshwaran and Festenstein, Frontiers in Neurology, Vol. 6, Art. 262 (2015); Campuzano, et al., Science, 271.5254 (Mar 8, 1996): 1423, the contents of each of which are herein

incorporated by reference in their entirety. The expansion of an intronic GAA triplet repeat in the FXN gene is the genetic cause of reduced expression of FXN resulting in FA. See Parkinson et al., Journal of Neurochemistry, 2013, 126 (Suppl. 1), 103-117. Over time, the deficiency causes the aforementioned symptoms, as well as frequent fatigue due to effects on cellular metabolism. Currently, omaveloxolone (Skyclarys®) is the only FDA approved treatment for FA. Omaveloxolone is a semisynthetic oleanane triterpenoid that activates Nrf2, a master transcription factor that regulates genes with antioxidative, anti-inflammatory, and mitochondrial bioenergetic properties. See Reisman et al. (2019) Drug Des Devel Ther. 13:1259-1270. While gene therapy constructs for delivering a frataxin protein have been described in the arm, there remains a need to develop improved constructs for better targeting of the appropriate tissues in the body.

[05] Adeno-associated viruses (AAVs) have emerged as a widely studied and utilized viral particles for delivery of therapeutically effective polypeptides to mammalian cells. See, e.g., Tratschin et al., Mol. Cell Biol., 5(11):3251-3260 (1985) and Grimm et al., Hum. Gene Ther., 10(15):2445-2450 (1999). As such, this modality is well suited to exploitation toward treatment of FA and the delivery of FXN and FXN related proteins and peptides.

[06] Prior attempts at providing AAV capsids with improved properties, e.g., improved tropism suitable for delivery to the brain or CNS, have met with limited success. As such, there remains a need for effective methods of treatment using AAV capsid variants that are capable of delivering a payload of interest, e.g., human FXN, to a target cell or tissue, e.g., a CNS cell or tissue.

SUMMARY

[07] The present disclosure addresses these challenges by providing AAV-based compositions and methods for treating Friedreich's Ataxia (FA) in subjects. Disclosed herein are compositions and methods directed to AAV-based gene delivery of FXN (e.g., human FXN) to ameliorate loss-of-function and to improve FXN expression (e.g., in the brain, e.g., in neurons). The compositions and methods are useful to slow, halt, or reverse symptoms of FA.

[08] In some embodiments, the present disclosure provides an AAV particle comprising a nucleotide sequence encoding a FXN protein (e.g., a human FXN protein) and an AAV capsid. In some embodiments, the present disclosure provides an AAV particle comprising a viral genome encoding a FXN protein (e.g., a human FXN protein) and an AAV capsid variant. In some embodiments, the viral genome comprises a truncated CBA promoter operably linked to the FXN-encoding sequence, and the AAV capsid variant is an AAV9 capsid variant.

[09] In some embodiments, the AAV capsid variant is an AAV9 capsid variant comprising a peptide insert in the loop IV region. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPH in loop IV. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPH in loop IV wherein the amino acid sequence (SPH) is present immediately subsequent to position 455 as numbered according to SEQ ID NO: 138.

[010] In some embodiments, the present disclosure provides an adeno-associated virus (AAV) particle comprising: a) an AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3], wherein: (i) optionally [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G; (ii) [N2] comprises the amino acid sequence of SPH; and (iii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid; and b) a viral genome comprising a frataxin (FXN)-encoding sequence. In some embodiments, the amino acid sequence [N1]-[N2]-[N3] is in hypervariable loop IV of the AAV capsid variant. In some embodiments, the AAV capsid variant is an AAV9 capsid variant. In some embodiments, [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G. In some embodiments, [N2]-[N3] comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941).

[011] In some embodiments, the present disclosure provides an AAV particle comprising a viral genome comprising a frataxin (FXN)-encoding sequence and an AAV9 capsid variant comprising the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is in hypervariable loop IV of the AAV9 capsid variant. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 4 or SEQ ID NO: 36.

[012] In some embodiments, the AAV9 capsid variant comprises one, two, or all of: an N at an amino acid position corresponding to position 452, an E at an amino acid position corresponding to position 451, and/or a V at an amino acid position corresponding to position 453 of SEQ ID NO: 4. In some embodiments, the AAV9 capsid variant comprises the amino acid sequence of KTENVSGSPHSKAQNQQT (SEQ ID NO: 3272).

[013] In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 90% identity to SEQ ID NO: 4; (ii) a VP2 protein comprising an amino acid sequence having at least 90% identity to positions 138-742 of SEQ ID NO: 4; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 4. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 4; (ii) a VP2 protein comprising an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 4; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 4. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 99% identity to SEQ ID NO: 4; (ii) a VP2 protein comprising an amino acid sequence having at least 99% identity to positions 138-742 of SEQ ID NO: 4; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 4. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4; (ii) a VP2 protein

comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4; and/or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

[014] In some embodiments, the AAV9 capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 4; (ii) an E at an amino acid position corresponding to position 451 and a V at an amino acid position corresponding to position 453 of SEQ ID NO: 4; and (iii) no other modifications relative to wild type AAV9.

[015] In some embodiments, the AAV9 capsid variant comprises one, two, or all of: an E at an amino acid position corresponding to position 451, an R at an amino acid position corresponding to position 452, and/or a V at an amino acid position corresponding to position 453 of SEQ ID NO: 36. In some embodiments, the AAV9 capsid variant comprises the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589).

[016] In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 90% identity to SEQ ID NO: 36; (ii) a VP2 protein comprising an amino acid sequence having at least 90% identity to positions 138-742 SEQ ID NO: 36; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 36. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 36; (ii) a VP2 protein comprising an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 36; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 36. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising an amino acid sequence having at least 99% identity to SEQ ID NO: 36; (ii) a VP2 protein comprising an amino acid sequence having at least 99% identity to positions 138-742 of SEQ ID NO: 36; and/or (iii) a VP3 protein comprising an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 36. In some embodiments, the AAV9 capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 36; and/or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

[017] In some embodiments, the AAV9 capsid variant comprises: (i) the amino acid sequence SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 36; (ii) an E at an amino acid position corresponding to position 451, an R at an amino acid position corresponding to position 452, and a V at an amino acid position corresponding to position 453 of SEQ ID NO: 36; and (iii) no other modifications relative to wild type AAV9.

[018] In some embodiments, [N1]-[N2]-[N3] is present immediately subsequent to a position corresponding to the amino acid position 452 of SEQ ID NO: 982; wherein the AAV capsid variant comprises an amino acid sequence at least 90% identical, e.g., at least 91%, at least 92%, at least 93%,

at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical, to the amino acid sequence of SEQ ID NO: 982, e.g., to positions 203-742 of SEQ ID NO: 982. In some embodiments, [N1] comprises GHD. In some embodiments, [N1] comprises the amino acid G at a position corresponding to position 453, the amino acid H at position 454, and the amino acid D at position 455 of SEQ ID NO: 138 or SEQ ID NO: 982. In some embodiments, [N3] comprises KSG.

[019] In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to SEQ ID NO: 982; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 138-742 SEQ ID NO: 982; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 982. In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to SEQ ID NO: 982; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 982; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 982. In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to SEQ ID NO: 982; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to positions 138-742 SEQ ID NO: 982; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 982. In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982.

[020] In some embodiments, the FXN protein encoded by the FXN-encoding sequence is not a cynomolgus FXN protein. In some embodiments, FXN-encoding sequence encodes a human FXN protein.

[021] In some embodiments, the FXN-encoding sequence comprises SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824. In some embodiments, the FXN-encoding sequence comprises SEQ ID NO: 1824.

[022] In some embodiments, the viral genome further comprises a promoter operably linked to the FXN-encoding sequence. In some embodiments, the promoter comprises a human elongation factor

1α-subunit (EF1α) promoter, a cytomegalovirus (CMV) immediate-early enhancer and/or promoter, a chicken β-actin (CBA) promoter, a CAG promoter, a β glucuronidase (GUSB) promoter, a ubiquitin C (UBC) promoter, a neuron-specific enolase (NSE) promoter, a platelet-derived growth factor (PDGF) promoter, a platelet-derived growth factor B-chain (PDGF-β) promoter, a intercellular adhesion molecule 2 (ICAM-2) promoter, a synapsin (Syn) promoter, a methyl-CpG binding protein 2 (MeCP2) promoter, a Ca2+/calmodulin-dependent protein kinase II (CaMKII) promoter, a metabotropic glutamate receptor 2 (mGluR2) promoter, a neurofilament light chain (NFL) or neurofilament heavy chain (NFH) promoter, a β-globin minigene nβ2 promoter, a preproenkephalin (PPE) promoter, a enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) promoter, a glial fibrillary acidic protein (GFAP) promoter, a myelin basic protein (MBP) promoter, a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512), or a functional fragment or truncation of any of the foregoing.

[023] In some embodiments, the promoter is a CMV promoter or CBA promoter, or a functional fragment or truncation thereof. In some embodiments, the promoter is a truncated CBA promoter. In some embodiments, the truncated CBA promoter is 50-400 nucleotides in length, e.g., 100-332 nucleotides in length. In some embodiments, the promoter comprises or consists of the nucleotide sequence of any one of SEQ ID NOs: 1738, 1740, and 1742 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to any one of SEQ ID NOs: 1738, 1740, and 1742. In some embodiments, the promoter is a truncated CMV promoter. In some embodiments the truncated CMV promoter is 109 nucleotides in length. In some embodiments, the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1750 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1750.

[024] In some embodiments, the viral genome further comprises a miRNA (miR) binding site that modulates expression of the encoded FXN protein in a cell or tissue of the liver. In some embodiments, the viral genome comprises 3 copies of the miR binding site. In some embodiments, the 3 copies of the miR binding site are identical. In some embodiments, the 3 copies of the miR binding site are continuous. In some embodiments, the miR binding site is a miR122 binding site.

[025] In some embodiments, the miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1827 or a sequence having one, two, three, or at most four substitutions relative to SEQ ID NO: 1827; or the 3 copies of continuous miR122 binding sites (miR122 binding site series) comprises the nucleotide sequence of SEQ ID NO: 1826 or a sequence having one, two, three, four, five, six, seven, eight, nine, or at most ten substitutions relative to SEQ ID NO: 1826.

[026] In some embodiments, the viral genome further comprises at least one inverted terminal repeat (ITR) region. In some embodiments, the at least one ITR region comprises an AAV2 ITR. In some embodiments, the viral genome comprises a 5' ITR region and a 3' ITR region. In some embodiments, the 5' ITR region and the 3' ITR region is each an AAV2 ITR.

[027] In some embodiments, the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or the 3' ITR region comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[028] In some embodiments, the viral genome further comprises an intron/exon region comprising an intron region and/or an exon region, wherein the intron/exon region comprises: an immediate-early 1 (ie1) intron region and/or a human beta-globin (hBglobin) intron region; and/or an ie1 exon region and/or an hBglobin exon region.

[029] In some embodiments, the intron region comprises: an ie1 intron 1 comprising of the nucleotide sequence of SEQ ID NO: 1819 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or a hBglobin intron 2 comprising the nucleotide sequence of SEQ ID NO: 1820 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[030] In some embodiments, the exon region comprises: an ie1 exon region comprising the nucleotide sequence of SEQ ID NO: 1817 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or an hBglobin exon region comprising the nucleotide sequence of SEQ ID NO: 1821 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[031] In some embodiments, the viral genome further comprises a polyadenylation (polyA) region. In some embodiments, the polyA region comprises a human growth hormone (hGH) polyA region. In some embodiments, the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[032] In some embodiments, the viral genome comprises: (i) a 5' inverted terminal repeat (ITR) region; (ii) a promoter; (iii) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at

least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824; and (iv) a 3' ITR region.

[033] In some embodiments, the viral genome comprises:(i) a 5' ITR region; (ii) a promoter; (iii) an intron and/or exon region; (iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824; (v) at least one miR122 binding site; and (vi) a 3' ITR region.

[034] In some embodiments, the viral genome comprises: (i) a 5' ITR region; (ii) a promoter; (iii) an intron and/or exon region; (iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824; (v) at least one miR122 binding site; (vi) a polyadenylation (polyA) region; and (vii) a 3' ITR region.

[035] In some embodiments, the viral genome comprises: (i) a 5' ITR region; (ii) a promoter; (iii) an intron and/or exon region; (iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824; (v) at least one miR122 binding site; (vi) a polyA region; (vii) a filler sequence; and (viii) a 3' ITR region.

[036] In some embodiments, the (i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1742 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (vi)

the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[037] In some embodiments, the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1841 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

[038] In some embodiments, (i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1750 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[039] In some embodiments, the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1840 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

[040] In some embodiments, (i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1738 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[041] In some embodiments, the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1838 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

[042] In some embodiments, (i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1740 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[043] In some embodiments, the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1839 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

[044] In some embodiments, the viral genome comprises: (a) the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1797; (b) the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1801; (c) the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1808; or (d) the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1809.

[045] In some embodiments, the present disclosure provides an adeno-associated virus (AAV) particle comprising a viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 and an AAV capsid variant comprising: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4; and/or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

[046] In some embodiments, the present disclosure provides an adeno-associated virus (AAV) particle comprising a viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 and an AAV capsid variant comprising: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO:

36; and/or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

[047] In some embodiments, the viral genome is single-stranded.

[048] In some embodiments, the present disclosure provides a cell comprising the AAV particle described herein. In some embodiments, the cell is a mammalian cell (e.g., an HEK293 cell), an insect cell (e.g., an Sf9 cell), or a bacterial cell.

[049] In some embodiments, the present disclosure provides a method of making an AAV particle described herein, wherein the method comprises: (i) providing a cell comprising the viral genome comprising a frataxin (FXN)-encoding sequence and a nucleic acid encoding the AAV capsid variant; and (ii) incubating the cell under conditions suitable to encapsulate the viral genome in the AAV capsid variant; thereby making the AAV particle.

[050] In some embodiments, the viral genome of the AAV particle comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and the AAV capsid variant of the AAV particle comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 4; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 4; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 4. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 4, the amino acid sequence of positions 138-742 of SEQ ID NO: 4, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

[051] In some embodiments, the viral genome of the AAV particle comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and the AAV capsid variant of the AAV particle comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 36; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at

least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 36; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 36. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 36, the amino acid sequence of positions 138-742 of SEQ ID NO: 36, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

[052] In some embodiments, the viral genome of the AAV particle comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and the AAV capsid variant of the AAV particle comprises: (i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 982; (ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 982; or (iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 982. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982, the amino acid sequence of positions 138-742 of SEQ ID NO: 982, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 982.

[053] In some embodiments, the method of making an AAV particle further comprises, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the cell. In some embodiments, the cell comprises a second nucleic acid molecule encoding the AAV capsid variant. In some embodiments, the method of making an AAV particle further comprises, prior to step (i), introducing the second nucleic acid molecule into the cell. In some embodiments, the cell comprises a mammalian cell (e.g., an HEK293 cell), an insect cell (e.g., an Sf9 cell), or a bacterial cell.

[054] In some embodiments, the present disclosure provides a pharmaceutical composition comprising an AAV particle described herein and a pharmaceutically acceptable excipient.

[055] In some embodiments, the present disclosure provides a method of delivering a frataxin (FXN) protein to a subject, comprising administering to the subject an effective amount of a pharmaceutical composition or AAV particle described herein, thereby delivering the FXN protein. In some embodiments, the subject has, has been diagnosed with having, or is at risk of having a disorder

associated with FXN deficiency. In some embodiments, the disorder associated with FXN deficiency is Friedreich's Ataxia (FA).

[056] In some embodiments, the present disclosure provides a method of treating a disorder associated with frataxin (FXN) deficiency in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition or AAV particle described herein, thereby treating the disorder. In some embodiments, the subject has, has been diagnosed with having, or is at risk of having a disorder associated with FXN deficiency. In some embodiments, the disorder is Friedreich's Ataxia (FA). In some embodiments, the administration results in an increase in the subject's FXN protein level as compared to baseline. In some embodiments, the treatment results in amelioration of at least one symptom of Friedreich's Ataxia (FA). In some embodiments, the at least one symptom of FA comprises impaired sensory functions, impaired motor function (e.g., ataxia and/or involuntary movements), fatigue, chronic pain, seizures, impaired speech, sleep disturbances, metabolic disorders (e.g., diabetes), and/or increased spasticity. In some embodiments, the treatment stabilizes, slows the progression of, or improves the subject's FA as determined by the modified Friedreich Ataxia Rating Scale (mFARS), the Scale for the Assessment and Rating of Ataxia (SARA), and/or the International Cooperative Ataxia Rating Scale (ICARS). In some embodiments, the treatment slows the subject's progression of FA as measured by mFARS, SARA, and/or ICARS relative to an individual with the disorder associated with FXN deficiency who has not been administered the pharmaceutical composition or the AAV particle.

[057] In some embodiments, the subject is a human.

[058] In some embodiments, the AAV particle or the pharmaceutical composition is delivered to a cell or tissue of the CNS, optionally wherein the AAV particle or the pharmaceutical composition is delivered via intravenous administration.

[059] In some embodiments, the method of delivering or treating further comprises evaluating, e.g., measuring, the level of FXN expression, e.g., FXN gene, FXN mRNA, and/or FXN protein expression, in the subject, e.g., in a cell, tissue, or fluid, of the subject. In some embodiments, the level of FXN protein expression is measured by an enzyme-linked immunosorbent assay (ELISA), a Western blot, an immunohistochemistry assay, or a frataxin biofluid assay. In some embodiments, the cell or tissue is a cell or tissue of the central nervous system (CNS). In some embodiments, the cell or tissue is a peripheral cell or tissue.

[060] In some embodiments, the administration results in an increase in: (i) the level of FXN protein or FXN gene expression in a cell, tissue, (e.g., a cell or tissue of the CNS, e.g., the cortex, striatum, thalamus, cerebellum, and/or brainstem), and/or fluid (e.g., CSF and/or serum), of the subject; and/or (ii) the level of viral genomes (VG) per cell in a CNS tissue (e.g., the cortex, striatum, thalamus, cerebellum, brainstem, and/or spinal cord) of the subject, optionally wherein the VG level is increased by greater than 50 VGs per cell, as compared to a peripheral tissue.

[061] In some embodiments, the method described herein further comprises administering to the subject at least one additional therapeutic agent and/or therapy. In some embodiments, the at least one additional therapeutic agent and/or therapy comprises an agent and/or therapy for treating the disorder associated with FXN deficiency (e.g., Friedreich's Ataxia). In some embodiments, the at least one additional therapeutic agent and/or therapy comprises omaveloxolone or idebenone.

[062] In some embodiments, the method of delivering or treating further comprises administering an immunosuppressant to the subject. In some embodiments, the immunosuppressant comprises a corticosteroid (e.g., prednisone, prednisolone, methylprednisolone, and/or dexamethasone), rapamycin, mycophenolate mofetil, tacrolimus, rituximab, and/or eculizumab hydroxychloroquine.

[063] In some embodiments, the present disclosure provides a pharmaceutical composition or AAV particle described herein for use in a method of treating a disorder described herein.

[064] In some embodiments, the present disclosure provides a pharmaceutical composition or AAV particle described herein for use in the treatment of a disorder associated with FXN deficiency in a subject. In some embodiments, the disorder is Friedreich's Ataxia. In some embodiments, the subject has, has been diagnosed with having, or is at risk of having Friedreich's Ataxia.

[065] In some embodiments, the present disclosure provides a use of an effective amount of a pharmaceutical composition or AAV particle described herein in the manufacture of a medicament for the treatment of a disorder associated with FXN deficiency in a subject. In some embodiments, the disorder is Friedreich's Ataxia. In some embodiments, the subject has, has been diagnosed with having, or is at risk of having Friedreich's Ataxia.

Enumerated Embodiments

1. An adeno-associated virus (AAV) particle comprising an AAV capsid variant (e.g., an AAV9 capsid variant) and a viral genome and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises an amino acid sequence having the following formula: [N1]-[N2]-[N3], wherein:

(i) optionally [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G;

(ii) [N2] comprises the amino acid sequence of SPH; and

(iii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R.

2. The AAV particle of embodiment 1, wherein X4, X5, or both of [N3] is a K.

3. The AAV particle of embodiment 1 or 2, wherein X4, X5, or X6 of [N3] is an R.

4. The AAV particle of any one of embodiments 1-3, wherein:

(a) X4 of [N3] is: K, S, A, V, T, G, F, W, V, N, or R;

(b) X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R; and/or

(c) X6 of [N3] is: G, A, R, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

5. The AAV particle of any one of embodiments 1-4, wherein [N3] comprises SK, KA, KS, AR, RM, VK, AS, SR, VK, KR, KK, KN, VR, RS, RK, KT, TS, KF, FG, KI, IG, KL, LG, TT, TY, KY, YG, KD, KP, TR, RG, VR, GA, SL, SS, FL, WK, SA, RA, LR, KW, RR, GK, TK, NK, AK, KV, KG, KH, KM, TG, SE, SV, SW, SN, HG, SQ, LW, MG, MA, or SG.

6. The AAV particle of any one of embodiments 1-5, wherein [N3] is or comprises SKA, KSG, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLG, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG, KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG.

7. The AAV particle of any one of embodiments 1-6, wherein [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), SPHAR (SEQ ID NO: 4705), SPHVK (SEQ ID NO: 4706), SPHAS (SEQ ID NO: 4707), SPHKK (SEQ ID NO: 4708), SPHVR (SEQ ID NO: 4709), SPHRK (SEQ ID NO: 4710), SPHKT (SEQ ID NO: 4711), SPHKF (SEQ ID NO: 4712), SPHKI (SEQ ID NO: 4713), SPHKL (SEQ ID NO: 4714), SPHKY (SEQ ID NO: 4715), SPHTR (SEQ ID NO: 4716), SPHKR (SEQ ID NO: 4717), SPHGA (SEQ ID NO: 4718), SPHSR (SEQ ID NO: 4719), SPHSL (SEQ ID NO: 4720), SPHSS (SEQ ID NO: 4721), SPHFL (SEQ ID NO: 4722), SPHWK (SEQ ID NO: 4723), SPHGK (SEQ ID NO: 4724), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), SPHAK (SEQ ID NO: 4727), SPHKH (SEQ ID NO: 4728), SPHKM (SEQ ID NO: 4729), or SPHRS (SEQ ID NO: 4730).

8. The AAV particle of any one of embodiments 1-7, wherein [N2]-[N3] is or comprises:

(i) SPHSKA (SEQ ID NO: 941), SPHKSG (SEQ ID NO: 946), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLG (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHSKD (SEQ ID NO: 967), SPHSKP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID NO: 973), SPHKRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKSA (SEQ ID NO: 977), SPHKSR (SEQ ID NO: 951), SPHSKL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHSKR (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSSR (SEQ ID

NO: 970), SPHFLR (SEQ ID NO: 979), SPHSKW (SEQ ID NO: 953), SPHSKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVRR (SEQ ID NO: 980), SPHSKT (SEQ ID NO: 4731), SPHSKG (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHSKN (SEQ ID NO: 4735), SPHAKA (SEQ ID NO: 4736), SPHSKV (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKSL (SEQ ID NO: 4740), SPHKSE (SEQ ID NO: 4741), SPHKSV (SEQ ID NO: 4742), SPHKSW (SEQ ID NO: 4743), SPHKSN (SEQ ID NO: 4744), SPHKHG (SEQ ID NO: 4745), SPHKSQ (SEQ ID NO: 4746), SPHKSK (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPHKMG (SEQ ID NO: 4750), SPHKMA (SEQ ID NO: 4751), or SPHRSG (SEQ ID NO: 976);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

9. The AAV particle of any one of embodiments 1-8, wherein the AAV capsid variant comprises an amino acid other than G at position 453 (e.g., V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C), an amino acid other than S at position 454 (e.g., V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q), and/or an amino acid other than G at position 455 (e.g., C, L, D, E, Y, H, V, A, N, P, or S), numbered according to any one of SEQ ID NOs: 36-59, 138, 981, 982.

10. The AAV particle of any one of embodiments 1-8, wherein the AAV capsid variant comprises the amino acid G at position 453, the amino acid S at position 454, and the amino acid G at position 455, numbered according to SEQ ID NO: 138 or 981.

11. The AAV particle of any one of embodiments 1-9, wherein the AAV capsid variant comprises the amino acid G at position 453, the amino acid H at position 454, and the amino acid D at position 455, numbered according to SEQ ID NO: 138 or 982.

12. The AAV particle of any one of embodiments 1-11, wherein [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G.

13. The AAV particle of any one of embodiments 1-12, wherein:

(a) X1 of [N1] is: G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C;

(b) X2 of [N1] is: S, V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q; and/or

(c) X3 of [N1] is: G, C, L, D, E, Y, H, V, A, N, P, or S;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

14. The AAV particle of any one of embodiments 1-13, wherein [N1] comprises GS, SG, GH, HD, GQ, QD, VS, CS, GR, RG, QS, SH, MS, RN, TS, IS, GP, ES, SS, GN, AS, NS, LS, GG, KS, GT, PS, RS, GI, WS, DS, ID, GL, DA, DG, ME, EN, KN, KE, AI, NG, PG, TG, SV, IG, LG, AG, EG, SA, YD, HE, HG, RD, ND, PD, MG, QV, DD, HN, HP, GY, GM, GD, or HS.

15. The AAV particle of any one of embodiments 1-14, wherein [N1] is or comprises GSG, GHD, GQD, VSG, CSG, GRG, CSH, GQS, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GQV, GHN, GHP, or GHS.

16. The AAV particle of any one of embodiments 1-15, wherein [N1]-[N2] comprises:

(i) SGSPH (SEQ ID NO: 4752), HDSPH (SEQ ID NO: 4703), QDSPH (SEQ ID NO: 4753), RGSPH (SEQ ID NO: 4754), SHSPH (SEQ ID NO: 4755), QSSPH (SEQ ID NO: 4756), DDSPH (SEQ ID NO: 4757), HESPH (SEQ ID NO: 4758), NYSPH (SEQ ID NO: 4759), VGSPH (SEQ ID NO: 4760), SCSPH (SEQ ID NO: 4761), LLSPH (SEQ ID NO: 4762), NGSPH (SEQ ID NO: 4763), PGSPH (SEQ ID NO: 4764), GGSPH (SEQ ID NO: 4765), TGSPH (SEQ ID NO: 4766), SVSPH (SEQ ID NO: 4767), IGSPH (SEQ ID NO: 4768), DGSPH (SEQ ID NO: 4769), LGSPH (SEQ ID NO: 4770), AGSPH (SEQ ID NO: 4771), EGSPH (SEQ ID NO: 4772), SASPH (SEQ ID NO: 4773), YDSPH (SEQ ID NO: 4774), HGSPH (SEQ ID NO: 4775), RDSPH (SEQ ID NO: 4776), NDSPH (SEQ ID NO: 4777), PDSPH (SEQ ID NO: 4778), MGSPH (SEQ ID NO: 4779), QVSPH (SEQ ID NO: 4780), HNSPH (SEQ ID NO: 4781), HPSPH (SEQ ID NO: 4782), or HSSPH (SEQ ID NO: 4783);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

17. The AAV particle of any one of embodiments 1-16, wherein [N1]-[N2] is or comprises:

(i) GSGSPH (SEQ ID NO: 4695), GHDSPH (SEQ ID NO: 4784), GQDSPH (SEQ ID NO: 4785), VSGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791),

GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

18. The AAV particle of any one of embodiments 1-17, wherein [N1]-[N2]-[N3] comprises:

(i) SGSPHSK (SEQ ID NO: 4839), HDSPHKS (SEQ ID NO: 4840), SGSPHAR (SEQ ID NO: 4841), SGSPHVK (SEQ ID NO: 4842), QDSPHKS (SEQ ID NO: 4843), SGSPHKK (SEQ ID NO: 4844), SGSPHVR (SEQ ID NO: 4845), SGSPHAS (SEQ ID NO: 4846), SGSPHRK (SEQ ID NO: 4847), SGSPHKT (SEQ ID NO: 4848), SHSPHKS (SEQ ID NO: 4849), QSSPHRS (SEQ ID NO: 4850), RGSPHAS (SEQ ID NO: 4851), RGSPHSK (SEQ ID NO: 4852), SGSPHKF (SEQ ID NO: 4853), SGSPHKI (SEQ ID NO: 4854), SGSPHKL (SEQ ID NO: 4855), SGSPHKY (SEQ ID NO: 4856), SGSPHTR (SEQ ID NO: 4857), SHSPHKR (SEQ ID NO: 4858), SGSPHGA (SEQ ID NO: 4859), HDSPHKR (SEQ ID NO: 4860), DDSPHKS (SEQ ID NO: 4861), HESPHKS (SEQ ID NO: 4862), NYSPHKI (SEQ ID NO: 4863), SGSPHSR (SEQ ID NO: 4864), SGSPHSL (SEQ ID NO: 4865), SGSPHSS (SEQ ID NO: 4866), VGSPHSK (SEQ ID NO: 4867), SCSPHRK (SEQ ID NO: 4868), SGSPHFL (SEQ ID NO: 4869), LLSPHWK (SEQ ID NO: 4870), NGSPHSK (SEQ ID NO: 4871), PGSPHSK (SEQ ID NO: 4872), GGSPHSK (SEQ ID NO: 4873), TGSPHSK (SEQ ID NO: 4874), SVSPHGK (SEQ ID NO: 4875), SGSPHTK (SEQ ID NO: 4876), IGSPHSK (SEQ ID

NO: 4877), DGSPHSK (SEQ ID NO: 4878), SGSPHNK (SEQ ID NO: 4879), LGSPHSK (SEQ ID NO: 4880), AGSPHSK (SEQ ID NO: 4881), EGSPHSK (SEQ ID NO: 4882), SASPHSK (SEQ ID NO: 4883), SGSPHAK (SEQ ID NO: 4884), HDSPHKI (SEQ ID NO: 4885), YDSPHKS (SEQ ID NO: 4886), HDSPHKT (SEQ ID NO: 4887), RGSPHKR (SEQ ID NO: 4888), HGSPHSK (SEQ ID NO: 4889), RDSPHKS (SEQ ID NO: 4890), NDSPHKS (SEQ ID NO: 4891), QDSPHKI (SEQ ID NO: 4892), PDSPHKI (SEQ ID NO: 4893), PDSPHKS (SEQ ID NO: 4894), MGSPHSK (SEQ ID NO: 4895), HDSPHKH (SEQ ID NO: 4896), QVSPHKS (SEQ ID NO: 4897), HNSPHKS (SEQ ID NO: 4898), NGSPHKR (SEQ ID NO: 4899), HDSPHKY (SEQ ID NO: 4900), NDSPHKI (SEQ ID NO: 4901), HDSPHKL (SEQ ID NO: 4902), HPSPHWK (SEQ ID NO: 4903), HDSPHKM (SEQ ID NO: 4904), or HSSPHRS (SEQ ID NO: 4905);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, or 6 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

19. The AAV particle of any one of embodiments 1-18, wherein [N1]-[N2]-[N3] is or comprises:

(i) GSGSPHSKA (SEQ ID NO: 4697), GHDSPHKSG (SEQ ID NO: 4698), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHSKA (SEQ ID NO: 4913), CSGSPHSKA (SEQ ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKSG (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHSKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKLG (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID NO: 4927), GSGSPHSKD (SEQ ID NO: 4928), GSGSPHSKP (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKSG (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGAR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKSG (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHSKL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSKR (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHSKA (SEQ ID NO: 4949), GSCSPHRKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSKW (SEQ ID NO: 4952), GSGSPHSKS (SEQ ID NO: 4953), GLLSPHWKA (SEQ

ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSKV (SEQ ID NO: 4956), MSGSPHSKA (SEQ ID NO: 4957), RNGSPHSKA (SEQ ID NO: 4958), TSGSPHSKA (SEQ ID NO: 4959), ISGSPHSKA (SEQ ID NO: 4960), GPGSPHSKA (SEQ ID NO: 4961), GSGSPHSKT (SEQ ID NO: 4962), ESGSPHSKA (SEQ ID NO: 4963), SSGSPHSKA (SEQ ID NO: 4964), GNGSPHSKA (SEQ ID NO: 4965), ASGSPHSKA (SEQ ID NO: 4966), NSGSPHSKA (SEQ ID NO: 4967), LSGSPHSKA (SEQ ID NO: 4968), GGGSPHSKA (SEQ ID NO: 4969), KSGSPHSKA (SEQ ID NO: 4970), GGGSPHSKS (SEQ ID NO: 4971), GSGSPHSKG (SEQ ID NO: 4972), HSGSPHSKA (SEQ ID NO: 4973), GTGSPHSKA (SEQ ID NO: 4974), PSGSPHSKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHSKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHSKA (SEQ ID NO: 4979), WSGSPHSKA (SEQ ID NO: 4980), DSGSPHSKA (SEQ ID NO: 4981), IDGSPHSKA (SEQ ID NO: 4982), GSGSPHNKA (SEQ ID NO: 4983), GLGSPHSKS (SEQ ID NO: 4984), DAGSPHSKA (SEQ ID NO: 4985), DGGSPHSKA (SEQ ID NO: 4986), MEGSPHSKA (SEQ ID NO: 4987), ENGSPHSKA (SEQ ID NO: 4988), GSASPHSKA (SEQ ID NO: 4989), GNGSPHSKS (SEQ ID NO: 4990), KNGSPHSKA (SEQ ID NO: 4991), KEGSPHSKA (SEQ ID NO: 4992), AIGSPHSKA (SEQ ID NO: 4993), GSGSPHSKN (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHSKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHSKA (SEQ ID NO: 4913), GRDSPHKSG (SEQ ID NO: 5004), GNDSPHKSV (SEQ ID NO: 5005), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), GHDSPHKSN (SEQ ID NO: 5011), GMGSPHSKT (SEQ ID NO: 5012), GHDSPHKHG (SEQ ID NO: 5013), GQVSPHKSG (SEQ ID NO: 5014), GDDSPHKSV (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), GNGSPHKRG (SEQ ID NO: 5017), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSQ (SEQ ID NO: 5019), GNDSPHKIG (SEQ ID NO: 5020), GHDSPHKSK (SEQ ID NO: 5021), GHDSPHKLW (SEQ ID NO: 5022), GHPSPHWKG (SEQ ID NO: 5023), GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GHSSPHRSG (SEQ ID NO: 5026);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

20. The AAV particle of any one of embodiments 1-19, wherein [N3] comprises SK, KA, KS, or SG.

21. The AAV particle of any one of embodiments 1-20, wherein [N3] is or comprises SKA, KSG, or KYG.

22. The AAV particle of any one of embodiments 1-21, wherein [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), or SPHKY (SEQ ID NO: 4715).

23. The AAV particle of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHSKA (SEQ ID NO: 941).

24. The AAV particle of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHKSG (SEQ ID NO: 946).

25. The AAV particle of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHKYG (SEQ ID NO: 966).

26. The AAV particle of any one of embodiments 1-25, wherein [N1] comprises GS, SG, GH, or HD.

27. The AAV particle of any one of embodiments 1-26, wherein [N1] is or comprises GSG.

28. The AAV particle of any one of embodiments 1-26, wherein [N1] is or comprises GHD.

29. The AAV particle of any one of embodiments 1-23 or 26-27, wherein [N1]-[N2]-[N3] comprises SGSPHSK (SEQ ID NO: 4839).

30. The AAV particle of any one of embodiments 1-22, 24, 26, or 28, wherein [N1]-[N2]-[N3] comprises HDSPHKS (SEQ ID NO: 4840).

31. The AAV particle of any one of embodiments 1-22 or 25-27, wherein [N1]-[N2]-[N3] comprises SGSPHKYG (SEQ ID NO: 5027).

32. The AAV particle of any one of embodiments 1-8, 10, 12-23, 26-27, or 29, wherein [N1]-[N2]-[N3] is or comprises GSGSPHSKA (SEQ ID NO: 4697).

33. The AAV particle of any one of embodiments 1-9, 11-22, 24, 26, 28, or 30, wherein [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

34. The AAV particle of any one of embodiments 1-8, 10, 12-22, 25-27, or 31, wherein [N1]-[N2]-[N3] is or comprises GSGSPHKYG (SEQ ID NO: 4927).

35. The AAV particle of any one of embodiments 1-34, wherein [N1]-[N2]-[N3] replaces positions 453-455, numbered according to SEQ ID NO: 138.

36. The AAV particle of any one of embodiments 1-35, wherein the AAV capsid variant comprises an amino acid other than Q at position 456 (e.g., W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F), an amino acid other than N at position 457 (e.g., Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L), an amino acid other than Q at position 458 (e.g., G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y), and/or an amino acid other than Q at position 459 (e.g., H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V), as numbered according to SEQ ID NO: 138.

37. The AAV particle of any one of embodiments 1-36, wherein the AAV capsid variant comprises an amino acid other than Q at position 462 (e.g., W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F), an amino acid other than N at position 463 (e.g., Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L), an amino acid other than Q at position 464 (e.g., G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y), and/or an amino acid other than Q at position 465 (e.g., H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V), as numbered according to SEQ ID NO: 981, 982, 36, 37, 39, 40, 42-46, 48, 49, 50, 52, 53, 56, or 57.

38. The AAV particle of any one of embodiments 1-37, wherein the AAV capsid variant comprises:

(a) the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, and/or the amino acid Q at position 459, numbered according to SEQ ID NO: 138; or

(b) the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, and/or the amino acid Q at position 465, numbered according to SEQ ID NO: 981, 982, 36, 37, 39, 40, 42-46, 48, 49, 50, 52, 53, 56, or 57.

39. The AAV particle of any one of embodiments 1-38, wherein the AAV capsid variant further comprises [N4], wherein [N4] comprises X7 X8 X9 X10, and wherein:

(a) X7 is: Q, W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F;

(b) X8 is: N, Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L;

(c) X9 is: Q, G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y; and

(d) X10 is: Q, H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

40. The AAV particle of embodiment 39, wherein:

(a) X7 of [N4] is Q or R;

(b) X8 of [N4] is N or R;

(c) X9 of [N4] is Q or R; and

(d) X10 of [N4] is Q, L, or R.

41. The AAV particle of embodiment 39 or 40, wherein [N4] is or comprises:

(i) QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO: 5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ (SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100), QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAQQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ

ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO: 5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGHH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168), HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191), QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVP (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

42. The AAV particle of any one of embodiments 39-41, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 1800-2241;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

43. The AAV particle of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHSKAQNQQ (SEQ ID NO: 6415).

44. The AAV particle of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQ (SEQ ID NO: 1800).

45. The AAV particle of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKYGQNQQT (SEQ ID NO: 910).

46. The AAV particle of any one of embodiments 1-45, wherein the AAV capsid variant comprises an amino acid other than T at position 450 (e.g., S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G), an amino acid other than I at position 451 (e.g., M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L), and/or an amino acid other than N at position 452 (e.g., M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S), as numbered according to any one of SEQ ID NOs: 36-59, 138, 981, or 982.

47. The AAV particle of any one of embodiments 1-46, wherein the AAV capsid variant comprises the amino acid T at position 450, the amino acid I at position 451, and/or the amino acid N at position 452, as numbered according to any one of SEQ ID NOs: 138, 981, or 982.

48. The AAV particle of any one of embodiments 1-47, wherein the AAV capsid variant further comprises [N0], wherein [N0] comprises X_A X_B and X_C, and wherein:

(a) X_A is: T, S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G;

(b) X_B is: I, M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L; and

(c) X_C is: N, M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S; and

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

49. The AAV particle of embodiment 48, wherein [N0] is or comprises TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW, ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEI, LEY, ADW, IEI, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI. VEY, IIN, TSN, IEV, MEM, AEV, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ. HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ. TEI, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN. TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA, NNL, or any dipeptide thereof.

50. The AAV particle of embodiment 48 or 49, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 2242-2886;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

51. The AAV particle of any one of embodiments 48-50, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHSKAQNQQ (SEQ ID NO: 2242).

52. The AAV particle of any one of embodiments 48-50, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGHDSPHKSGQNQQ (SEQ ID NO: 2243).

53. The AAV particle of any one of embodiments 48-52, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHKYGQNQQT (SEQ ID NO: 5246).

54. The AAV particle of any one of embodiments 1-53, wherein [N1]-[N2]-[N3] is present in loop IV.

55. The AAV particle of any one of embodiments 48-54, wherein [N0] and [N4] are present in loop IV.

56. The AAV particle of any one of embodiments 48-55, wherein [N0] is present immediately subsequent to position 449, numbered according to SEQ ID NO: 138.

57. The AAV particle of any one of embodiments 48-56, wherein [N0] is present immediately subsequent to position 449, numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

58. The AAV particle of any one of embodiments 48-57, wherein [N0] replaces positions 450, 451, and 452 (e.g., T450, I451, and N452), numbered according to SEQ ID NO: 138.

59. The AAV particle of any one of embodiments 48-58, wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

60. The AAV particle of any one of embodiments 48-59, wherein [N0] corresponds to positions 450-452 of any one of SEQ ID NOs: 36-59, 138, 981 or 982.

61. The AAV particle of any one of embodiments 48-60, wherein [N0] is present immediately subsequent to position 449 and wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), numbered according to SEQ ID NO: 138.

62. The AAV particle of any one of embodiments 48-61, wherein [N0] is present immediately subsequent to position 449 and wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

63. The AAV particle of any one of embodiments 1-62, wherein [N1] is present immediately subsequent to position 452, numbered according to the amino acid sequence of SEQ ID NO: 138.

64. The AAV particle of any one of embodiments 1-63, wherein [N1] is present immediately subsequent to position 452, numbered according to SEQ ID NO: 981 or 982.

65. The AAV particle of any one of embodiments 1-61, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 138.

66. The AAV particle of any one of embodiments 1-64, wherein [N1] replaces positions 453 (e.g., G453), numbered according to SEQ ID NO: 138.

67. The AAV particle of any one of embodiments 1-65, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 981.

68. The AAV particle of any one of embodiments 1-65 or 67, wherein [N1] replaces positions 453-455, numbered according to SEQ ID NO: 982.

69. The AAV particle of any one of embodiments 1-65, 67, or 68, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 138.

70. The AAV particle of any one of embodiments 1-64 or 66, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453 (e.g., G453), numbered according to SEQ ID NO: 138.

71. The AAV particle of any one of embodiments 1-64, 66 or 70, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453-455, numbered according to SEQ ID NO: 4, 36, 981, or 982.

72. The AAV particle of any one of embodiments 1-71, wherein [N1] corresponds to positions 453-455, numbered according to any one of SEQ ID NOs: 4, 36-59, 981, or 982.

73. The AAV particle of any one of embodiments 1-72, wherein the AAV capsid variant comprises an amino acid other than S at position 454 and/or an amino acid other than G at position 455, numbered according to SEQ ID NO: 138, 981, or 982.

74. The AAV particle of any one of embodiments 1-73, wherein the AAV capsid variant comprises the amino acid H at position 454 and the amino acid D at position 455, numbered according to SEQ ID NO: 138 or 982.

75. The AAV particle of any one of embodiments 1-74, wherein the AAV capsid variant comprises a substitution at position 454 (e.g., S454H) and/or a substitution at position 455 (e.g., G455D), numbered according to SEQ ID NO: 138.

76. The AAV particle of any one of embodiments 1-75, wherein the AAV capsid variant comprises the amino acid H at position 454 and the amino acid D at position 455, and further comprises the amino acid sequence SPHSKA (SEQ ID NO: 941) immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

77. The AAV particle of any one of embodiments 1-76, wherein the AAV capsid variant comprises the amino acid H at position 454 and the amino acid D at position 455, numbered according to SEQ ID NO: 982.

78. The AAV particle of any one of embodiments 1-77, wherein the AAV capsid variant comprises the amino acid H at position 454 and the amino acid D at position 455, and further comprises the amino acid sequence SPHSKA (SEQ ID NO: 941) immediately subsequent to position 455, numbered according to SEQ ID NO: 982.

79. The AAV particle of any one of embodiments 1-72, wherein the AAV capsid variant comprises the amino acid S at position 454 and the amino acid G at position 455, numbered according to SEQ ID NO: 138.

80. The AAV particle of any one of embodiments 1-72 or 79, wherein the AAV capsid variant comprises the amino acid S at position 454 and the amino acid G at position 455, and further comprises the amino acid sequence SPHSKA (SEQ ID NO: 941) immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

81. The AAV particle of any one of embodiments 1-72, 79, or 80, wherein the AAV capsid variant comprises the amino acid S at position 454 and the amino acid G at position 455, numbered according to SEQ ID NO: 981.

82. The AAV particle of any one of embodiments 1-72 or 79-81, wherein the AAV capsid variant comprises the amino acid S at position 454 and the amino acid G at position 455, and further comprises the amino acid sequence SPHSKA (SEQ ID NO: 941) immediately subsequent to position 455, numbered according to SEQ ID NO: 981.

83. The AAV particle of any one of embodiments 1-82, wherein [N2] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

84. The AAV particle of any one of embodiments 1-83, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, H458) of SEQ ID NO: 981 or 982.

85. The AAV particle of any one of embodiments 1-83, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, H458) of any one of SEQ ID NOs: 4 or 36-59.

86. The AAV particle of any one of embodiments 1-85, wherein [N2]-[N3] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

87. The AAV particle of any one of embodiments 1-86, wherein [N2] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 4, 36, 981, or 982.

88. The AAV particle of any one of embodiments 1-87, wherein [N2]-[N3] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 4, 36, 981, or 982.

89. The AAV particle of any one of embodiments 1-88, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

90. The AAV particle of any one of embodiments 1-88, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

91. The AAV particle of any one of embodiments 1-90, wherein [N2] is present immediately subsequent to [N1].

92. The AAV particle of any one of embodiments 1-64, 66, 70, or 71, wherein [N3] is present immediately subsequent to [N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

93. The AAV particle of any one of embodiments 1-1-64, 66, 70, 71, or 92, wherein [N3] is present immediately subsequent to [N1]-[N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

94. The AAV particle of any one of embodiments 39-93, wherein [N4] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

95. The AAV particle of any one of embodiments 39-94, wherein [N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

96. The AAV particle of any one of embodiments 39-95, wherein [N4] corresponds to positions 462-465 (e.g., Q462, N463, Q464, Q465) of SEQ ID NO: 4, 36, 981, or 982.

97. The AAV particle of any one of embodiments 39-96, wherein [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

98. The AAV particle of any one of embodiments 39-97, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

99. The AAV particle of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 (e.g., S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

100. The AAV particle of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 (e.g., S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

101. The AAV particle of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 of any one of SEQ ID NOs: 4 or 36-59.

102. The AAV particle of any one of embodiments 39-101, wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

103. The AAV particle of any one of embodiments 39-102, wherein [N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 452, and wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

104. The AAV particle of any one of embodiments 39-99, 102, or 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

105. The AAV particle of any one of embodiments 39-98, 100, 102, or 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

106. The AAV particle of any one of embodiments 39-98, 102, or 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 of any one of SEQ ID NOs: 4 or 36-59.

107. The AAV particle of any one of embodiments 1-99 or 102-104, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

108. The AAV particle of any one of embodiments 1-98, 100, 102, 103, or 105, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

109. The AAV particle of any one of embodiments 39-98, 102, 103, or 106, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 of any one of SEQ ID NOs: 36-59.

110. The AAV particle of any one of embodiments 48-109, wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

111. The AAV particle of any one of embodiments 48-110, wherein [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 449, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

112. The AAV particle of any one of embodiments 48-99, 102-104, or 106, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 (e.g., T450, I451, N452, G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

113. The AAV particle of any one of embodiments 48-98, 100, 102, 103, 105, or 108, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 (e.g., T450, I451, N452, G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

114. The AAV particle of any one of embodiments 48-98, 102, 103, 106, or 109, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 of any one of SEQ ID NOs: 36-59.

115. The AAV particle of any one of embodiments 39-114, wherein [N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), numbered according to SEQ ID NO: 4, 36, 981, or 982.

116. The AAV particle of any one of embodiments 39-115, wherein [N2]-[N3]-[N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), numbered according to SEQ ID NO: 4, 36, 981, or 982.

117. The AAV particle of any one of embodiments 39-116, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), numbered according to SEQ ID NO: 4, 36, 981, or 982.

118. The AAV particle of any one of embodiments 1-117, wherein [N3] is present immediately subsequent to [N2].

119. The AAV particle of any one of embodiments 1-118, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N2]-[N3].

120. The AAV particle of any one of embodiments 1-119, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3].

121. The AAV particle of any one of embodiments 48-120, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3].

122. The AAV particle of any one of embodiments 39-121, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4].

123. The AAV particle of any one of embodiments 48-122, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

124. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid other T at position 460 (e.g., N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S), numbered according to SEQ ID NO: 138.

125. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises the amino acid N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S at position 460, numbered according to SEQ ID NO: 138.

126. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid other T at position 466 (e.g., N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S), numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

127. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises the amino acid N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S at position 466, numbered according to any one of SEQ ID NOs: 36-59, 981 or 982.

128. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid other K at position 449 (e.g., an E, an N, or a T), numbered according to any one of SEQ ID NOs: 36-59, 138, 981, or 982.

129. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises the amino E, N, or T at position 449, numbered according to any one of SEQ ID NOs: 36-59, 138, 981 or 982.

130. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises [A][B] (SEQ ID NO: 4694), wherein:

(i) [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695); and

(ii) [B] comprises X1 X2 X3 X4 X5 X6 X7, wherein:

(a) X1 is: S, C, F, or V;

(b) X2 is: K, L, R, I, E, Y, V, or S;

(c) X3 is: A, R, L, G, I, Y, S, F, or W;

(d) X4 is: W, Q, R, G, L, V, S, or F;

(e) X5 is: N, Y, R, C, K, or L;

(f) X6 is: Q, G, K, R, T, L, or Y; and

(g) X7 is: Q, L, R, or V;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(g).

131. The AAV particle of embodiment 130, wherein

(a) X1 is S;

(b) X2 is K or L;

(c) X3 is: A, R, or L;

(d) X4 is: Q or R;

(e) X5 is: N or R;

(f) X6 is: Q or R; and

(g) X7 is: Q, L, or R.

132. The AAV particle of embodiment 130 or 131, wherein [B] comprises:

(i) SLLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259), CLAQNQQ (SEQ ID NO: 5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRL (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, or 6 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

133. The AAV particle of any one of embodiments 130-132, wherein [A][B] comprises:

(i) GSGSPHSLLWNQQ (SEQ ID NO: 5285), GSGSPHSKAQYYV (SEQ ID NO: 2060), GSGSPHSKLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNQQ (SEQ ID NO: 5286), GSGSPHSKAGCGQ (SEQ ID NO: 2062), GSGSPHSRAQNQQ (SEQ ID NO: 2063), GSGSPHSKRLRQQ (SEQ ID NO: 2064), GSGSPHSLRRNQQ (SEQ ID NO: 2065), GSGSPHSRGRNQQ (SEQ ID NO: 2066), GSGSPHSEIVNQQ (SEQ ID NO: 5287), GSGSPHSSRRNQQ (SEQ ID NO: 2067), GSGSPHCLLQNQQ (SEQ ID NO: 5288), GSGSPHSKAFRLQ (SEQ ID NO: 2068), GSGSPHCLAQNQQ (SEQ ID NO: 5289), GSGSPHFLRQNQQ (SEQ ID NO: 2070), GSGSPHSLRFNQQ (SEQ ID NO: 2071), GSGSPHSYLRNQQ (SEQ ID NO: 5290), GSGSPHCSLQNQQ (SEQ ID NO: 5291), GSGSPHVLWQNQQ (SEQ ID NO: 5292), GSGSPHSKWLLQQ (SEQ ID NO: 2072), GSGSPHSLWSNQQ (SEQ ID NO: 5293), GSGSPHSKRRLQQ (SEQ ID NO: 2073), GSGSPHSVYLNQQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHSKAQRKL (SEQ ID NO: 2074), GSGSPHSKALRRQ (SEQ ID NO: 2075), GSGSPHSKAQRLR (SEQ ID NO: 2076), GSGSPHSKAQNQQ (SEQ ID NO: 6415), GSGSPHSKAQRRL (SEQ ID NO: 2077), GSGSPHSKARRQQ (SEQ ID NO: 2078), GSGSPHSKARRLQ (SEQ ID NO: 2079), GSGSPHSKSRRQQ (SEQ ID NO: 2080),

GSGSPHSKARLRQ (SEQ ID NO: 2082), GSGSPHSKASKRQ (SEQ ID NO: 2083), GSGSPHVRRQNQQ (SEQ ID NO: 2084), GSGSPHSKAQLYR (SEQ ID NO: 2085), GSGSPHSLFRNQQ (SEQ ID NO: 5296), GSGSPHSKAQLTV (SEQ ID NO: 2086);.

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i)

134. The AAV particle of any one of embodiments 130-133, wherein the AAV capsid variant further comprises one, two, or all of an amino acid other than T at position 450 (e.g., S, Y, or G), an amino acid other than I at position 451 (e.g., M or L), and/or an amino acid other than N at position 452 (e.g., S), numbered according to SEQ ID NO: 138.

135. The AAV particle of any one of embodiments 130-134, wherein the AAV capsid variant further comprises an S at position 450 and an M at position 451, numbered according to SEQ ID NO: 138.

136. The AAV particle of any one of embodiments 130-134, wherein the AAV capsid variant further comprises a Y at position 450, an L at position 451, and an S at position 452, numbered according to SEQ ID NO: 138.

137. The AAV particle of any one of embodiments 130-134, wherein the AAV capsid variant further comprises a G at position 450, an L at position 451, and an S at position 452, numbered according to SEQ ID NO: 138.

138. The AAV particle of any one of embodiments 130-137, wherein [A][B] is present in loop IV.

139. The AAV particle of any one of embodiments 130-138, wherein [A] is present immediately subsequent to position 452, numbered according to SEQ ID NO: 138.

140. The AAV particle of any one of embodiments 130-139, wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), numberedd according to SEQ ID NO: 138.

141. The AAV particle of any one of embodiments 130-140, wherein [A] is present immediately subsequent to position 452, and wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), numbered according to SEQ ID NO: 138.

142. The AAV particle of any one of embodiments 130-141, wherein [B] is present immediately subsequent to [A].

143. The AAV particle of any one of embodiments 130-142, wherein [B] replaces positions 456-459 (e.g., Q456, N457, Q458, Q459), numbered according to SEQ ID NO: 138.

144. The AAV particle of any one of embodiments 130-143, wherein [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), numbered according to SEQ ID NO: 138.

145. The AAV particle of any one of embodiments 130-144, wherein [A][B] is present immediately subsequent to position 452, and wherein [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), numbered according to SEQ ID NO: 138.

146. The AAV particle of any one of embodiments 130-145, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [A][B].

147. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises [A][B] (SEQ ID NO: 4699), wherein:

(i) [A] comprises X1 X2 X3 X4 X5 X6, wherein

(a) X1 is T, M, A, C, I, R, L, D, F, V, Q, N, or H;

(b) X2 is I, P, E, N, D, S, A, T, M, or Q;

(c) X3 is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L;

(d) X4 is G, D, R, or E;

(e) X5 is H, Q, N, or D;

(f) X6 is D or R;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(f); and

(ii) [B] comprises SPHKSG (SEQ ID NO: 946).

148. The AAV particle of embodiment 147, wherein

(a) X1 is: T, M, A, or I;

(b) X2 is: E, I or D;

(c) X3 is: N, Q, Y, I, M, or V;

(d) X4 is G;

(e) X5 is H; and

(f) X6 is D.

149. The AAV particle of embodiment 147 or 148, wherein [A] comprises:

(i) TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGHD (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGHD (SEQ ID NO: 5306), ADYGHD (SEQ ID NO: 5307), IETGHD (SEQ ID NO: 5308), MEWGHD (SEQ ID NO: 5309), CEYGHD (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGHD (SEQ ID NO: 5312), LEYGHD (SEQ ID NO: 5313), ADWGHD (SEQ ID NO: 5314), IEIGHD (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGHD (SEQ ID NO: 5317), FEQGHD (SEQ ID NO: 5318), MEFGHD (SEQ ID NO: 5319), CDQGHD (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGHD (SEQ ID NO: 5323), AEIGHD (SEQ ID NO: 5324), VEYGHD (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGHD (SEQ ID NO: 5327), MEMGHD (SEQ ID NO: 5328), AEVGHD (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGHD (SEQ ID NO: 5331), AEQGHD (SEQ ID NO: 5332), LEWGHD (SEQ ID NO: 5333), MELGHD (SEQ ID NO: 5334), METGHD (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGHD (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGHD (SEQ ID NO: 5340), CEIGHD (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGHD (SEQ ID NO: 5344), ADQGHD (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347), IEMGHD (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGHD (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGHD (SEQ ID NO: 5352), IEGGHD (SEQ ID NO: 5353)

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

150. The AAV particle of any one of embodiments 147-149, wherein [A][B] comprises:

(i) TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370),

ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS (SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390), MELGHDSPHKS (SEQ ID NO: 5391), METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411)

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

151. The AAV particle of any one of embodiments 147-150, wherein the AAV capsid variant further comprises one, two, three, four, or all of an amino acid other than Q at position 456 (e.g., R or L), N at position 457 (e.g., H, K, or R), Q at position 458 (e.g., R or T), Q at position 459 (H), and/or T at position 460 (N or S), numbered according to SEQ ID NO: 138.

152. The AAV particle of any one of embodiments 147-151, wherein the AAV capsid variant further comprises an R at position 456, numbered according to SEQ ID NO: 138.

153. The AAV particle of any one of embodiments 147-151, wherein the AAV capsid variant further comprises an L at position 456, numbered according to SEQ ID NO: 138.

154. The AAV particle of any one of embodiments 147-153, wherein the AAV capsid variant further comprises an H at position 457 and an R at position 458, numbered according to SEQ ID NO: 138.

155. The AAV particle of any one of embodiments 147-153, wherein the AAV capsid variant further comprises a K at position 457 and an N at position 460, numbered according to SEQ ID NO: 138.

156. The AAV particle of any one of embodiments 147-153, wherein the AAV capsid variant further comprises a T at position 458, an H at position 459, and an S at position 460, numbered according to SEQ ID NO: 138.

157. The AAV particle of any one of embodiments 147-151, wherein the AAV capsid variant further comprises an R at position 456, an R at position 457, and an R at position 458, numbered according to SEQ ID NO: 138.

158. The AAV particle of any one of embodiments 147-157, wherein [A][B] is present in loop IV.

159. The AAV particle of any one of embodiments 147-158, wherein [A] is present immediately subsequent to position 449, numbered according to SEQ ID NO: 138.

160. The AAV particle of any one of embodiments 147-159, wherein [A] replaces positions 450-453 (e.g., T450, I451, N452, G453), numbered according to SEQ ID NO: 138.

161. The AAV particle of any one of embodiments 147-160, wherein [A] is present immediately subsequent to position 449, and wherein [A] replaces positions 450-453 (e.g., T450, I451, N452, G453), numbered according to SEQ ID NO: 138.

162. The AAV particle of any one of embodiments 147-161, wherein [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

163. The AAV particle of any one of embodiments 147-162, wherein [A][B] is present immediately subsequent to position 449, and wherein [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

164. The AAV particle of any one of embodiments 147-163, wherein [B] is present immediately subsequent [A], and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

165. The AAV particle of any one of embodiments 147-164, wherein [B] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 4, 36, 981, or 982.

166. The AAV particle of any one of embodiments 147-165, wherein [B] is present immediately subsequent to [A].

167. The AAV particle of any one of embodiments 147-166, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [A][B].

168. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6407), wherein:

(i) [N1] comprises X1, X2, and X3, wherein X2 is S and X3 is G;

(ii) [N2] comprises the amino acid sequence SPH; and

(iii) [N3] comprises X4, X5, and X6, wherein X5 is K.

169. The AAV particle of embodiment 168, wherein:

(i) X4 of [N3] is S, T, N, or A; and

(ii) X5 of [N3] is A, V, T, S, G, R, L, or N;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i) or (ii).

170. The AAV particle of embodiment 168 or 169, wherein X4 is S and/or X5 is A.

171. The AAV particle of any one of embodiments 168-170, wherein [N3] comprises SK, TK, NK, AK, KA, KV, KT, KS, KG, KR, KL, or KN.

172. The AAV particle of any one of embodiments 168-171, wherein [N3] is or comprises SKA, SKV, SKT, SKS, SKG, SKR, TKA, NKA, SKL, SKN, or AKA.

173. The AAV particle of any one of embodiments 168-172, wherein [N3] is or comprises SKA.

174. The AAV particle of any one of embodiments 168-173, wherein [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), or SPHAK (SEQ ID NO: 4727).

175. The AAV particle of any one of embodiments 168-174, wherein [N2]-[N3] is or comprises:

(i) SPHSKA (SEQ ID NO: 941), SPHSKV (SEQ ID NO: 4737), SPHSKT (SEQ ID NO: 4731), SPHSKS (SEQ ID NO: 962), SPHSKG (SEQ ID NO: 4732), SPHSKR (SEQ ID NO: 978), SPHTKA (SEQ ID NO: 4739), SPHNKA (SEQ ID NO: 4734), SPHSKL (SEQ ID NO: 960), SPHSKN (SEQ ID NO: 4735), or SPHAKA (SEQ ID NO: 4736);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2. 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

176. The AAV particle of any one of embodiments 168-175, wherein [N2]-[N3] is or comprises SPHSKA (SEQ ID NO: 941).

177. The AAV particle of any one of embodiments 168-176, wherein the AAV capsid variant comprises an amino acid other than G at position 453 (e.g., M, T, I, E, S, A, N, V, L, K, H, P, R, W, or D), numbered according to SEQ ID NO: 138 or 981.

178. The AAV particle of any one of embodiments 168-177, wherein the AAV capsid variant comprises the amino acid G at position 453, numbered according to SEQ ID NO: 138 or 981.

179. The AAV particle of any one of embodiments 168-178, wherein X1 of [N1] is G, M, T, I, E, S, A, N, V, L, K, H, P, R, W, or D; optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids.

180. The AAV particle of any one of embodiments 168-179, wherein [N1] comprises SG, GS, MS, TS, IS, ES, SS, AS, NS, VS, LS, KS, HS, PS, RS, WS, or DS.

181. The AAV particle of any one of embodiments 168-180, wherein [N1] is or comprises: GSG, MSG, TSG, ISG, ESG, SSG, ASG, NSG, VSG, LSG, KSG, HSG, PSG, RSG, WSG, or DSG.

182. The AAV particle of any one of embodiments 168-181, wherein [N1] is or comprises GSG.

183. The AAV particle of any one of embodiments 168-182, wherein [N1]-[N2] comprises SGSPH (SEQ ID NO: 4752).

184. The AAV particle of any one of embodiments 168-183, wherein [N1]-[N2] is or comprises:

(i) GSGSPH (SEQ ID NO: 4695), MSGSPH (SEQ ID NO: 4798), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), VSGSPH (SEQ ID NO: 4786), LSGSPH (SEQ ID NO: 4808), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), PSGSPH (SEQ ID NO: 4813), RSGSPH (SEQ ID NO: 4815), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

185. The AAV particle of any one of embodiments 168-184, wherein [N1]-[N2]-[N3] is or comprises:

(i) GSGSPHSKA (SEQ ID NO: 4697), GSGSPHSKV (SEQ ID NO: 4956), MSGSPHSKA (SEQ ID NO: 4957), TSGSPHSKA (SEQ ID NO: 4959), ISGSPHSKA (SEQ ID NO: 4960), GSGSPHSKT (SEQ ID NO: 4962), ESGSPHSKA (SEQ ID NO: 4963), SSGSPHSKA (SEQ ID NO: 4964), GSGSPHSKS (SEQ ID NO: 4953), ASGSPHSKA (SEQ ID NO: 4966), NSGSPHSKA (SEQ ID NO: 4967), VSGSPHSKA (SEQ ID NO: 4913), LSGSPHSKA (SEQ ID NO: 4968), KSGSPHSKA (SEQ ID NO: 4970), GSGSPHSKG (SEQ ID NO: 4972), GSGSPHSKR (SEQ ID NO: 4945), HSGSPHSKA (SEQ ID NO: 4973), PSGSPHSKA (SEQ ID NO: 4975), RSGSPHSKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), WSGSPHSKA (SEQ ID NO: 4980), DSGSPHSKA (SEQ ID NO: 4981), GSGSPHNKA (SEQ ID NO: 4983), GSGSPHSKL (SEQ ID NO: 4943), GSGSPHSKN (SEQ ID NO: 4994), or GSGSPHAKA (SEQ ID NO: 4995);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, or 9 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

186. The AAV particle of any one of embodiments 168-185, wherein [N1]-[N2]-[N3] is or comprises GSGSPHSKA (SEQ ID NO: 4697).

187. The AAV capsid variant of any one of embodiments 168-186, which comprises an amino acid other than Q at position 456 (e.g., R, P, H, L, K, I, G, S, M, or E), an amino acid other than N at position 457 (e.g., D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M), an amino acid other than Q at

position 458 (e.g., R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, or D), an amino acid other than Q at position 459 (e.g., H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G), and/or an amino acid other than T at position 460 (e.g., I, N, S, H, R, L, D, Y, A, or Q), numbered according to SEQ ID NO: 138.

188. The AAV particle of any one of embodiments 168-187, wherein the AAV capsid variant comprises an amino acid other than Q at position 462 (e.g., R, P, H, L, K, I, G, S, M, or E), an amino acid other than N at position 463 (e.g., D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M), an amino acid other than Q at position 464 (e.g., R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, or D), an amino acid other than Q at position 465 (e.g., H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G), and/or an amino acid other than T at position 466 (e.g., I, N, S, H, R, L, D, Y, A, or Q), numbered according to SEQ ID NO: 981.

189. The AAV particle of any one of embodiments 168-188, wherein the AAV capsid variant comprises the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, the amino acid Q at position 459, and/or the amino acid T at position 460, numbered according to SEQ ID NO: 138.

190. The AAV particle of any one of embodiments 168-189, wherein the AAV capsid variant comprises the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, the amino acid Q at position 465, and/or the amino acid T at position 466, numbered according to SEQ ID NO: 981.

191. The AAV particle of any one of embodiments 168-190, wherein the AAV capsid variant further comprises [N4] wherein [N4] comprises X7, X8, X9, X10, and X11, wherein:

(a) X7 is Q, R, P, H, L, K, I, G, S, M, or E;

(b) X8 is N, D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M;

(c) X9 is Q, R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, D;

(d) X10 is Q, H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G; and

(e) X11 is T, I, N, S, H, R, L, D, Y, A, Q;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

192. The AAV particle of embodiment 191, wherein [N4] is or comprises:

(i) QNQQT (SEQ ID NO: 5412), QNRHT (SEQ ID NO: 5413), RDQQT (SEQ ID NO: 5414), PNLQT (SEQ ID NO: 5415), HVRQT (SEQ ID NO: 5416), PNQHT (SEQ ID NO: 5417), QSQQT (SEQ ID NO: 5418), QNQQI (SEQ ID NO: 5419), QPAKT (SEQ ID NO: 5420), QTQQN (SEQ ID NO: 5421), QNLAT (SEQ ID NO: 5422), QNQLT (SEQ ID NO: 5423), QGQQT (SEQ ID

NO: 5424), LNRQS (SEQ ID NO: 5425), HNQQT (SEQ ID NO: 5426), QNPPT (SEQ ID NO: 5427), QNLQT (SEQ ID NO: 5428), QYQQT (SEQ ID NO: 5429), QDQET (SEQ ID NO: 5430), QNHQT (SEQ ID NO: 5431), QDQQT (SEQ ID NO: 5432), HWQQT (SEQ ID NO: 5433), PNQQT (SEQ ID NO: 5434), QNQLI (SEQ ID NO: 5435), PEQQT (SEQ ID NO: 5436), QRTMT (SEQ ID NO: 5437), QNQQH (SEQ ID NO: 5438), LHQHT (SEQ ID NO: 5439), QHRIT (SEQ ID NO: 5440), QYIHT (SEQ ID NO: 5441), QKFET (SEQ ID NO: 5442), QFPST (SEQ ID NO: 5443), HNQQR (SEQ ID NO: 5444), QAIKT (SEQ ID NO: 5445), QNRQT (SEQ ID NO: 5446), QYQHT (SEQ ID NO: 5447), QNPQS (SEQ ID NO: 5448), QHQLT (SEQ ID NO: 5449), QSPPT (SEQ ID NO: 5450), QAKLT (SEQ ID NO: 5451), KSQQT (SEQ ID NO: 5452), QDRPT (SEQ ID NO: 5453), QSQQL (SEQ ID NO: 5454), QAFHT (SEQ ID NO: 5455), QKQQD (SEQ ID NO: 5456), QNAQT (SEQ ID NO: 5457), HNQLT (SEQ ID NO: 5458), QNQQY (SEQ ID NO: 5459), QKLNT (SEQ ID NO: 5460), QNVQT (SEQ ID NO: 5461), QAQQT (SEQ ID NO: 5462), QNLQA (SEQ ID NO: 5463), QTPPT (SEQ ID NO: 5464), QYQHA (SEQ ID NO: 5465), QGQQA (SEQ ID NO: 5466), QPPAT (SEQ ID NO: 5467), QERPT (SEQ ID NO: 5468), QDLQT (SEQ ID NO: 5469), QAMHT (SEQ ID NO: 5470), LNQQT (SEQ ID NO: 5471), QHPST (SEQ ID NO: 5472), PGLQT (SEQ ID NO: 5473), QGIRT (SEQ ID NO: 5474), QAPAT (SEQ ID NO: 5475), QSQQI (SEQ ID NO: 5476), QIPPT (SEQ ID NO: 5477), QTQLT (SEQ ID NO: 5478), QAPST (SEQ ID NO: 5479), QNTYA (SEQ ID NO: 5480), QNQHI (SEQ ID NO: 5481), QNHLT (SEQ ID NO: 5482), QIGMT (SEQ ID NO: 5483), LNKQT (SEQ ID NO: 5484), QLQQT (SEQ ID NO: 5485), QRMST (SEQ ID NO: 5486), QGILT (SEQ ID NO: 5487), QDRQT (SEQ ID NO: 5488), RDWQT (SEQ ID NO: 5489), QNTHD (SEQ ID NO: 5490), PNLQI (SEQ ID NO: 5491), QERST (SEQ ID NO: 5492), QNYQT (SEQ ID NO: 5493), QRTCT (SEQ ID NO: 5494), QIGHT (SEQ ID NO: 5495), QGAIT (SEQ ID NO: 5496), QVPPT (SEQ ID NO: 5497), QVQQI (SEQ ID NO: 5498), LMRQT (SEQ ID NO: 5499), QYSVT (SEQ ID NO: 5500), QAITT (SEQ ID NO: 5501), QKTLT (SEQ ID NO: 5502), QNQWT (SEQ ID NO: 5503), QLHHT (SEQ ID NO: 5504), QNIII (SEQ ID NO: 5505), QGHHT (SEQ ID NO: 5506), QSKVT (SEQ ID NO: 5507), QLPST (SEQ ID NO: 5508), IGKQT (SEQ ID NO: 5509), QAIHT (SEQ ID NO: 5510), QHGLT (SEQ ID NO: 5511), QFMCT (SEQ ID NO: 5512), QHLQT (SEQ ID NO: 5513), QNHQN (SEQ ID NO: 5514), QPART (SEQ ID NO: 5515), QSLQT (SEQ ID NO: 5516), QSQLT (SEQ ID NO: 5517), QDRQS (SEQ ID NO: 5518), QMPST (SEQ ID NO: 5519), QGSLT (SEQ ID NO: 5520), QVPAT (SEQ ID NO: 5521), QDKQT (SEQ ID NO: 5522), HYQQT (SEQ ID NO: 5523), QVPST (SEQ ID NO: 5524), RGEQT (SEQ ID NO: 5525), PGQQT (SEQ ID NO: 5526), QSLQI (SEQ ID NO: 5527), LEQQT (SEQ ID NO: 5528), QNQST (SEQ ID NO: 5529), QKVIT (SEQ ID NO: 5530), QNNDQ (SEQ ID NO: 5531), QSVHT (SEQ ID NO: 5532), QPLGT (SEQ ID NO: 5533), HNQET (SEQ ID NO: 5534), QNLQI (SEQ ID NO: 5535), QIQQT (SEQ ID NO: 5536), QVRNT (SEQ ID NO: 5537), PSNQT (SEQ ID NO: 5538), QVGHT (SEQ ID NO: 5539), QRDIT (SEQ ID NO: 5540), QMPNT (SEQ ID NO: 5541), RGLQT (SEQ ID NO: 5542), QKQQT (SEQ ID NO: 5543), PSLQT (SEQ ID NO: 5544), QRDQT (SEQ ID NO: 5545), QAKGT

(SEQ ID NO: 5546), QSAHT (SEQ ID NO: 5547), QSTMT (SEQ ID NO: 5548), QREMT (SEQ ID NO: 5549), QYRAT (SEQ ID NO: 5550), QWQQT (SEQ ID NO: 5551), QRMNT (SEQ ID NO: 5552), GDSQT (SEQ ID NO: 5553), QKIST (SEQ ID NO: 5554), PSMQT (SEQ ID NO: 5555), SPRQT (SEQ ID NO: 5556), MEQQT (SEQ ID NO: 5557), QYQNT (SEQ ID NO: 5558), QHQQT (SEQ ID NO: 5559), INQQT (SEQ ID NO: 5560), PNQQH (SEQ ID NO: 5561), ENRQT (SEQ ID NO: 5562), QTQQA (SEQ ID NO: 5563), or QNQAT (SEQ ID NO: 5564);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

193. The AAV particle of embodiment 191 or 192, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 200 or 2887-3076;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

194. The AAV particle of any one of embodiments 191-193, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHSKAQNQQT (SEQ ID NO: 200).

195. The AAV particle of any one of embodiments 191-193, wherein [N1]-[N2]-[N3]-[N4] is or comprises VSGSPHSKAQNQQT (SEQ ID NO: 903).

196. The AAV particle of any one of embodiments 168-195, wherein the AAV capsid variant comprises an amino acid other than K at position 449 (e.g., T, E, or N), T at position 450 (e.g., S, E, A, N, V, Q, or G), an amino acid other than I at position 451 (e.g., F, E, V, L, D, S, C, T, A, N, H, R, G, or W), and/or an amino acid other than N at position 452 (e.g., I, P, K, R, H, S, M, Q, D, T, L, A, Y, V, F, E, W, or G), numbered according to SEQ ID NO: 138 or 981.

197. The AAV particle of any one of embodiments 168-196, wherein the AAV capsid variant comprises the amino acid K at position 449, the amino acid T at position 450, the amino acid I at

position 451, and/or the amino acid N at position 452, numbered according to SEQ ID NO: 138 or 981.

198. The AAV particle of any one of embodiments 168-197, wherein the AAV capsid variant further comprises [N0], wherein [N0] comprises X_A, X_B, X_C, and X_D, wherein:

(a) X_A is K, T, E, or N;

(b) X_B is T, S, E, A, N, V, Q, or G;

(c) X_C is I, F, E, V, L, D, S, C, T, A, N, H, R, G, or W; and

(d) X_D is N, I, P, K, R, H, S, M, Q, D, T, L, A, Y, V, F, E, W, or G;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

199. The AAV particle of embodiment 198, wherein [N0] is or comprises:

(i) KTII (SEQ ID NO: 5565), KTFP (SEQ ID NO: 5566), KTEK (SEQ ID NO: 5567), KTVN (SEQ ID NO: 5568), KTFN (SEQ ID NO: 5569), KTIN (SEQ ID NO: 5570), TTIN (SEQ ID NO: 5571), KSIN (SEQ ID NO: 5572), KTER (SEQ ID NO: 5573), KELH (SEQ ID NO: 5574), KAIN (SEQ ID NO: 5575), KTDN (SEQ ID NO: 5576), KTFH (SEQ ID NO: 5577), KTSN (SEQ ID NO: 5578), ETIN (SEQ ID NO: 5579), NTIN (SEQ ID NO: 5580), KTEN (SEQ ID NO: 5581), KTSS (SEQ ID NO: 5582), KTCN (SEQ ID NO: 5583), KTEH (SEQ ID NO: 5584), KAEM (SEQ ID NO: 5585), KATN (SEQ ID NO: 5586), KAIK (SEQ ID NO: 5587), KTDK (SEQ ID NO: 5588), KTFK (SEQ ID NO: 5589), KSDQ (SEQ ID NO: 5590), KTEI (SEQ ID NO: 5591), KTID (SEQ ID NO: 5592), KNTN (SEQ ID NO: 5593), KTET (SEQ ID NO: 5594), KTEL (SEQ ID NO: 5595), KNIN (SEQ ID NO: 5596), KTEA (SEQ ID NO: 5597), KTAN (SEQ ID NO: 5598), NTIY (SEQ ID NO: 5599), KTFS (SEQ ID NO: 5600), KTES (SEQ ID NO: 5601), KTTN (SEQ ID NO: 5602), KTED (SEQ ID NO: 5603), KTNN (SEQ ID NO: 5604), KEVH (SEQ ID NO: 5605), KTIS (SEQ ID NO: 5606), KTVR (SEQ ID NO: 5607), KTDR (SEQ ID NO: 5608), ETIK (SEQ ID NO: 5609), KNHI (SEQ ID NO: 5610), KESD (SEQ ID NO: 5611), KTIK (SEQ ID NO: 5612), KTDL (SEQ ID NO: 5613), KTVP (SEQ ID NO: 5614), KTVI (SEQ ID NO: 5615), KAEH (SEQ ID NO: 5616), KNCL (SEQ ID NO: 5617), KTVK (SEQ ID NO: 5618), KNAD (SEQ ID NO: 5619), KTIT (SEQ ID NO: 5620), KNCV (SEQ ID NO: 5621), KNAL (SEQ ID NO: 5622), KVIN (SEQ ID NO: 5623), KTEF (SEQ ID NO: 5624), KTRE (SEQ ID NO: 5625), KQGE (SEQ ID NO: 5626), KSEK (SEQ ID NO: 5627), KNVN (SEQ ID NO: 5628), KGGE (SEQ ID NO: 5629), KEFV (SEQ ID NO: 5630), KSDK (SEQ ID NO: 5631), KTEQ (SEQ ID NO: 5632), KEVQ (SEQ ID NO: 5633), KTEY (SEQ ID NO: 5634), KNCW (SEQ ID NO: 5635), KTDV (SEQ ID NO: 5636), KSDI (SEQ ID NO: 5637), KNSI (SEQ ID NO: 5638), KNSL (SEQ ID NO: 5639), KEVV (SEQ ID NO: 5640), KTEP (SEQ ID NO: 5641), KSEL (SEQ ID NO: 5642), KTWQ (SEQ ID NO: 5643), KTEV (SEQ ID NO: 5644), KAVN (SEQ ID NO: 5645), KGVL (SEQ ID NO: 5646), KTEG (SEQ ID NO: 5647), KTRD (SEQ ID NO:

5648), KTGN (SEQ ID NO: 5649), KNAI (SEQ ID NO: 5650), KAEN (SEQ ID NO: 5651), KAET (SEQ ID NO: 5652), KTVH (SEQ ID NO: 5653), KETA (SEQ ID NO: 5654), KNNL (SEQ ID NO: 5655), EAIN (SEQ ID NO: 5656), KSLN (SEQ ID NO: 5657), KTIP (SEQ ID NO: 5658), or KTIH (SEQ ID NO: 5659);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

200. The AAV particle of embodiment 198 or 199, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3239-3526 or 3591-3605;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

201. The AAV particle of any one of embodiments 198-200, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTINGSGSPHSKAQNQQT (SEQ ID NO: 5660).

202. The AAV particle of any one of embodiments 198-200, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589).

203. An AAV particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6408), wherein:

(i) [N1] comprises X1, X2, and X3, wherein X2 is an amino acid other than S and X3 is an amino acid other than G;

(ii) [N2] comprises the amino acid sequence SPH; and

(iii) [N3] comprises X4, X5, and X6, wherein X4 is K.

204. The AAV particle of embodiment 203, wherein:

(i) X5 of [N3] is S, I, T, R, H, Y, L, or M; and

(ii) X6 of [N3] is G, A, L, E, V, R, W, N, Q, or K;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i) or (ii).

205. The AAV particle of embodiment 203 or 204, wherein X5 is S and/or X6 is G.

206. The AAV particle of any one of embodiments 203-205, wherein [N3] comprises KS, KI, KT, KR, KH, KY, KL, KM, SG, IG, TG, RG, SA, SL, SE, SV, SR, SW, SN, HG, YG, SQ, IV, SK, LW, MG, or MA.

207. The AAV particle of any one of embodiments 203-206, wherein [N3] is or comprises KSG, KIG, KTG, KRG, KSA, KSL, KSE, KSV, KSR, KSW, KSN, KHG, KYG, KSQ, KIV, KSK, KLW, KMG, or KMA.

208. The AAV particle of any one of embodiments 203-207, wherein [N3] is or comprises KSG.

209. The AAV particle of any one of embodiments 203-208, wherein [N2]-[N3] comprises SPHKS (SEQ ID NO: 4704), SPHKI (SEQ ID NO: 4713), SPHKT (SEQ ID NO: 4711), SPHKR (SEQ ID NO: 4717), NPHKS (SEQ ID NO: 5661), SPHKH (SEQ ID NO: 4728), SPHKY (SEQ ID NO: 4715), SPHKL (SEQ ID NO: 4714), or SPHKM (SEQ ID NO: 4729).

210. The AAV particle of any one of embodiments 203-209, wherein [N2]-[N3] is or comprises:

(i) SPHKSG (SEQ ID NO: 946), SPHKIG (SEQ ID NO: 958), SPHKTG (SEQ ID NO: 4738), SPHKRG (SEQ ID NO: 974), NPHKSG (SEQ ID NO: 5662), SPHKSA (SEQ ID NO: 977), SPHKSL (SEQ ID NO: 4740), SPHKSE (SEQ ID NO: 4741), SPHKSV (SEQ ID NO: 4742), SPHKSR (SEQ ID NO: 951), SPHKSW (SEQ ID NO: 4743), SPHKSN (SEQ ID NO: 4744), SPHKHG (SEQ ID NO: 4745), SPHKYG (SEQ ID NO: 966), SPHKSQ (SEQ ID NO: 4746), SPHKIV (SEQ ID NO: 5663), SPHKSK (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHKMG (SEQ ID NO: 4750), or SPHKMA (SEQ ID NO: 4751);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

211. The AAV particle of any one of embodiments 203-210, wherein [N2]-[N3] is or comprises SPHKSG (SEQ ID NO: 946).

212. The AAV particle of any one of embodiments 203-211, wherein the AAV capsid variant comprises an amino acid other than G at position 453 (e.g., A, K, W, R, L, I, M, N, T, E, Q, Y, H, F, or V), numbered according to SEQ ID NO: 138 or 981.

213. The AAV particle of any one of embodiments 203-212, wherein the AAV capsid variant comprises the amino acid G at position 453, numbered according to SEQ ID NO: 138 or 981.

214. The AAV particle of any one of embodiments 203-214, wherein:

(i) X1 of [N1] is G, A, K, W, R, L, I, M, N, T, E, Q, Y, H, F, or V;

(ii) X2 of [N1] is H, Y, R, Q, N, P, or D;

(iii) X3 of [N1] is D, E, G, V, or N;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i), (ii), or (iii).

215. The AAV particle of any one of embodiments 203-214, wherein X2 of [N1] is H and X3 of [N1] is D.

216. The AAV particle of any one of embodiments 203-215, wherein X1 of [N1] is G, X2 of [N1] is H and X3 of [N1] is D.

217. The AAV particle of any one of embodiments 203-216, wherein [N1] comprises GH, HD, GY, GR, GQ, AH, GN, KH, GP, WH, RH, LH, IH, MH, GD, NH, TH, EH, QH, YH, HH, FH, VH, YD, HE, RG, QD, RD, ND, PD, QV, DD, HN, or NG.

218. The AAV capsid variant of any one of embodiments 203-217, wherein [N1] is or comprises GHD, GYD, GHE, GRG, GQD, GRD, AHD, GND, KHD, GPD, WHD, RHD, LHD, GQV, IHD, MHD, GDD, GHN, NHD, THD, GNG, EHD, QHD, YHD, HHD, FHD, or VHD.

219. The AAV particle of any one of embodiments 203-218, wherein [N1] is or comprises GHD.

220. The AAV particle of any one of embodiments 203-219, wherein [N1]-[N2] comprises HDSPH (SEQ ID NO: 4703).

221. The AAV particle of any one of embodiments 203-220, wherein [N1]-[N2] is or comprises:

(i) GHDSPH (SEQ ID NO: 4784), GYDSPH (SEQ ID NO: 4829), GHESPH (SEQ ID NO: 4793), GRGSPH (SEQ ID NO: 4788), GHDNPH (SEQ ID NO: 5664), GQDSPH (SEQ ID NO: 4785), GRDSPH (SEQ ID NO: 4831), AHDSPH (SEQ ID NO: 5665), GNDSPH (SEQ ID NO: 4832), KHDSPH (SEQ ID NO: 5666), GPDSPH (SEQ ID NO: 4833), WHDSPH (SEQ ID NO: 5667), RHDSPH (SEQ ID NO: 5668), LHDSPH (SEQ ID NO: 5669), GQVSPH (SEQ ID NO: 4835), IHDSPH (SEQ ID NO: 5670), MHDSPH (SEQ ID NO: 5671), GDDSPH (SEQ ID NO: 4792), GHNSPH (SEQ ID NO: 4836), NHDSPH (SEQ ID NO: 5672), THDSPH (SEQ ID NO: 5673), GNGSPH (SEQ ID NO: 4805), EHDSPH (SEQ ID NO: 5674), QHDSPH (SEQ ID NO: 5675), YHDSPH (SEQ ID NO: 5676), HHDSPH (SEQ ID NO: 5677), FHDSPH (SEQ ID NO: 5678), or VHDSPH (SEQ ID NO: 5679);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

222. The AAV particle of any one of embodiments 203-221, wherein [N1]-[N2]-[N3] is or comprises:

(i) GHDSPHKSG (SEQ ID NO: 4698), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GHDNPHKSG (SEQ ID NO: 5680), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSA (SEQ ID NO: 4940), GHDSPHKSL (SEQ ID NO: 5001), GHDSPHKSE (SEQ ID NO: 5003), GRDSPHKSG (SEQ ID NO: 5004), AHDSPHKSG (SEQ ID NO: 5681), GNDSPHKSV (SEQ ID NO: 5005), AHDSPHKIG (SEQ ID NO: 5682), GHESPHKSA (SEQ ID NO: 4939), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GHDSPHKSR (SEQ ID NO: 4942), KHDSPHKSG (SEQ ID NO: 5683), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), WHDSPHKSG (SEQ ID NO: 5684), RHDSPHKSG (SEQ ID NO: 5685), GHDSPHKSN (SEQ ID NO: 5011), GHDSPHKRG (SEQ ID NO: 4937), GHDSPHKHG (SEQ ID NO: 5013), LHDSPHKSG (SEQ ID NO: 5686), GQVSPHKSG (SEQ ID NO: 5014), IHDSPHKSG (SEQ ID NO: 5687), MHDSPHKSG (SEQ ID NO: 5688), GDDSPHKSV (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), NHDSPHKSG (SEQ ID NO: 5689), THDSPHKSG (SEQ ID NO: 5690), GNGSPHKRG (SEQ ID NO: 5017), EHDSPHKSG (SEQ ID NO: 5691), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSQ (SEQ ID NO: 5019), QHDSPHKSG (SEQ ID NO: 5692), RHDSPHKIV (SEQ ID NO: 5693), YHDSPHKSG (SEQ ID NO: 5694), GNDSPHKIG (SEQ ID NO: 5020), HHDSPHKSG (SEQ ID NO: 5695), GHDSPHKSK (SEQ ID NO: 5021), FHDSPHKSG (SEQ ID NO: 5696), GHDSPHKLW (SEQ ID

NO: 5022), VHDSPHKSG (SEQ ID NO: 5697), GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GDDSPHKSG (SEQ ID NO: 4938);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, or 9 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

223. The AAV particle of any one of embodiments 203-222, wherein [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

224. The AAV particle of any one of embodiments 203-223, wherein the AAV capsid variant comprises an amino acid other than Q at position 456 (e.g., R, P, H, K, L, V, A, E, or I), an amino acid other than N at position 457 (e.g., I, K, S, H, R, T, D, Y, L, W, F, A, Q, or M), an amino acid other than Q at position 458 (e.g., R, V, K, P, Y, H, L, I, E, or M), an amino acid other than Q at position 459 (e.g., H, L, E, P, W, D, I, V, S, K, R, C, M, or N), and/or an amino acid other than T at position 460 (e.g., A, E, K, S, I, P, G, or N), numbered according to SEQ ID NO: 138.

225. The AAV particle of any one of embodiments 203-224, wherein the AAV capsid variant comprises an amino acid other than Q at position 462 (e.g., R, P, H, K, L, V, A, E, or I), an amino acid other than N at position 463 (e.g., I, K, S, H, R, T, D, Y, L, W, F, A, Q, or M), an amino acid other than Q at position 464 (e.g., R, V, K, P, Y, H, L, I, E, or M), an amino acid other than Q at position 465 (e.g., H, L, E, P, W, D, I, V, S, K, R, C, M, or N), and/or an amino acid other than T at position 466 (e.g., A, E, K, S, I, P, G, or N), numbered according to SEQ ID NO: 982.

226. The AAV particle of any one of embodiments 203-225, wherein the AAV capsid variant comprises the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, the amino acid Q at position 459, and/or the amino acid T at position 460, numbered according to SEQ ID NO: 138.

227. The AAV particle of any one of embodiments 203-226, wherein the AAV capsid variant comprises the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, the amino acid Q at position 465, and/or the amino acid T at position 466, numbered according to SEQ ID NO: 138.

228. The AAV particle of any one of embodiments 203-227, wherein the AAV capsid variant further comprises [N4], wherein [N4] comprises X7, X8, X9, X10, and X11, wherein:

(a) X7 is Q, R, P, H, L, K, I, G, S, M, or E;

(b) X8 is N, D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M;

(c) X9 is Q, R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, D;

(d) X10 is Q, H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G; and

(e) X11 is T, I, N, S, H, R, L, D, Y, A, Q;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

229. The AAV particle of embodiment 228, wherein [N4] is or comprises:

(i) QNQQT (SEQ ID NO: 5412), QIRQT (SEQ ID NO: 5698), QNQHA (SEQ ID NO: 5699), QKQQT (SEQ ID NO: 5543), QSVQT (SEQ ID NO: 5700), RSQQT (SEQ ID NO: 5701), QNKLE (SEQ ID NO: 5702), QNQQK (SEQ ID NO: 5703), QHQQA (SEQ ID NO: 5704), QIQHT (SEQ ID NO: 5705), PRQQT (SEQ ID NO: 5706), HTQQT (SEQ ID NO: 5707), QRQHT (SEQ ID NO: 5708), QSQQT (SEQ ID NO: 5418), QNQQS (SEQ ID NO: 5709), RNQET (SEQ ID NO: 5710), QTQLT (SEQ ID NO: 5478), KNQQT (SEQ ID NO: 5711), QDQQT (SEQ ID NO: 5432), HNQQT (SEQ ID NO: 5426), QNQLT (SEQ ID NO: 5423), QTQQT (SEQ ID NO: 5712), QTQQI (SEQ ID NO: 5713), QSKQA (SEQ ID NO: 5714), QNQPP (SEQ ID NO: 5715), QSPQT (SEQ ID NO: 5716), QNYQT (SEQ ID NO: 5493), QNHQT (SEQ ID NO: 5431), QNRQT (SEQ ID NO: 5446), QNQQG (SEQ ID NO: 5717), QNHLT (SEQ ID NO: 5482), QYQHT (SEQ ID NO: 5447), QNQWT (SEQ ID NO: 5503), QNQHT (SEQ ID NO: 5718), QTRQT (SEQ ID NO: 5719), QNLHT (SEQ ID NO: 5720), LNQQT (SEQ ID NO: 5471), QNQET (SEQ ID NO: 5721), QHLQT (SEQ ID NO: 5513), LNQPT (SEQ ID NO: 5722), QNQDT (SEQ ID NO: 5723), RNQQT (SEQ ID NO: 5724), QNLLT (SEQ ID NO: 5725), QLVIT (SEQ ID NO: 5726), RTQET (SEQ ID NO: 5727), QTHQT (SEQ ID NO: 5728), QNQPA (SEQ ID NO: 5729), QDQHT (SEQ ID NO: 5730), QSQHT (SEQ ID NO: 5731), RNQQI (SEQ ID NO: 5732), VRQQT (SEQ ID NO: 5733), QNQHS (SEQ ID NO: 5734), AWQQT (SEQ ID NO: 5735), QSVPT (SEQ ID NO: 5736), QNIQP (SEQ ID NO: 5737), QNHLN (SEQ ID NO: 5738), LDQQT (SEQ ID NO: 5739), PDQQS (SEQ ID NO: 5740), ESQQT (SEQ ID NO: 5741), QNKQT (SEQ ID NO: 5742), QRQLT (SEQ ID NO: 5743), QIIVT (SEQ ID NO: 5744), QKQST (SEQ ID NO: 5745), QSHQT (SEQ ID NO: 5746), QFVVT (SEQ ID NO: 5747), QNLQT (SEQ ID NO: 5428), QNQQI (SEQ ID NO: 5419), QSQPT (SEQ ID NO: 5748), QNEQT (SEQ ID NO: 5749), QSLQT (SEQ ID NO: 5516), RNRQT (SEQ ID NO: 5750), QSKQT (SEQ ID NO: 5751), QNPLT (SEQ ID NO: 5752), RDQKT (SEQ ID NO: 5753), HNQQN (SEQ ID NO: 5754), QWKRT (SEQ ID NO: 5755), QSQQI (SEQ ID NO: 5476), QAQQT (SEQ ID NO: 5462), QNHQI (SEQ ID NO: 5756), QNQQA (SEQ ID NO: 5757), QNQLN (SEQ ID NO: 5758), QTQPT (SEQ ID NO: 5759), INQQT (SEQ ID NO: 5560), QKQLT (SEQ ID NO: 5760), RNQLA (SEQ ID NO: 5761),

RNQQS (SEQ ID NO: 5762), ISIQT (SEQ ID NO: 5763), QNQQN (SEQ ID NO: 5764), QSQQS (SEQ ID NO: 5765), QTVCT (SEQ ID NO: 5766), QYQQI (SEQ ID NO: 5767), QQIMT (SEQ ID NO: 5768), QNEQS (SEQ ID NO: 5769), LNHQT (SEQ ID NO: 5770), QMIHT (SEQ ID NO: 5771), RNHQS (SEQ ID NO: 5772), QKMNT (SEQ ID NO: 5773), QSQQN (SEQ ID NO: 5774), QYQHA (SEQ ID NO: 5465);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

230. The AAV particle of embodiment 228 or 229, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 201 or 3160-3237;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

231. The AAV particle of any one of embodiments 228-230, wherein [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQT (SEQ ID NO: 201).

232. The AAV particle of any one of embodiments 203-231, wherein the AAV capsid variant comprises an amino acid other than K at position 449 (e.g., T), T at position 450 (e.g., A, S, I, V, N, E, Y, C, G, W, or Q), an amino acid other than I at position 451 (e.g., E, V, S, T, N, D, C, G, Q, L, P, A), and/or an amino acid other than N at position 452 (e.g., S, Y, I, K, F, T, D, E, G, V, L, A, M, Q, H, P, or R), numbered according to SEQ ID NO: 138 or 982.

233. The AAV particle of any one of embodiments 203-232, wherein the AAV capsid variant comprises the amino acid K at position 449, the amino acid T at position 450, the amino acid I at position 451, and/or the amino acid N at position 452, numbered according to SEQ ID NO: 138 or 982.

234. The AAV particle of any one of embodiments 203-233, wherein the AAV capsid variant further comprises [N0], wherein [N0] comprises X_A, X_B, X_C, and X_D, wherein:

(a) X_A is K or T;

(b) X_B is T, A, S, I, V, N, E, Y, C, G, W, or Q;

(c) X_C is I, E, V, S, T, N, D, C, G, Q, L, P, A; and

(d) X_D is N, S, Y, I, K, F, T, D, E, G, V, L, A, M, Q, H, P, or R;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

235. The AAV particle of embodiment 234, wherein [N0] is or comprises:

(i) KAIN (SEQ ID NO: 5575), KTIN (SEQ ID NO: 5570), KTES (SEQ ID NO: 5601), TTIN (SEQ ID NO: 5571), KSIN (SEQ ID NO: 5572), KTVN (SEQ ID NO: 5568), KSIY (SEQ ID NO: 5775), KTSN (SEQ ID NO: 5578), KTTN (SEQ ID NO: 5602), KIIN (SEQ ID NO: 5776), KTIS (SEQ ID NO: 5606), KAII (SEQ ID NO: 5777), KTIK (SEQ ID NO: 5612), KTEF (SEQ ID NO: 5624), KTIT (SEQ ID NO: 5620), KTNN (SEQ ID NO: 5604), KTID (SEQ ID NO: 5592), KAIS (SEQ ID NO: 5778), KTVD (SEQ ID NO: 5779), KTIE (SEQ ID NO: 5780), KTEG (SEQ ID NO: 5647), KVIN (SEQ ID NO: 5623), KAVN (SEQ ID NO: 5645), KTIY (SEQ ID NO: 5781), KTDN (SEQ ID NO: 5576), KTCN (SEQ ID NO: 5583), KNVV (SEQ ID NO: 5782), KTEL (SEQ ID NO: 5595), KTDA (SEQ ID NO: 5783), KTEV (SEQ ID NO: 5644), KSEL (SEQ ID NO: 5642), KTEM (SEQ ID NO: 5784), KTEQ (SEQ ID NO: 5632), KTII (SEQ ID NO: 5565), KIVN (SEQ ID NO: 5785), KTEK (SEQ ID NO: 5567), KTEN (SEQ ID NO: 5581), KIGN (SEQ ID NO: 5786), KEVM (SEQ ID NO: 5787), KYQV (SEQ ID NO: 5788), KTEA (SEQ ID NO: 5597), KATN (SEQ ID NO: 5586), KTEH (SEQ ID NO: 5584), KTVE (SEQ ID NO: 5789), KAID (SEQ ID NO: 5790), KTIM (SEQ ID NO: 5791), KEVG (SEQ ID NO: 5792), KSEM (SEQ ID NO: 5793), KAQQ (SEQ ID NO: 5794), KCGE (SEQ ID NO: 5795), KASN (SEQ ID NO: 5796), KTET (SEQ ID NO: 5594), KTIG (SEQ ID NO: 5797), KTDP (SEQ ID NO: 5798), KELV (SEQ ID NO: 5799), KELM (SEQ ID NO: 5800), KNEI (SEQ ID NO: 5801), KTPN (SEQ ID NO: 5802), KITN (SEQ ID NO: 5803), KTDI (SEQ ID NO: 5804), KTDQ (SEQ ID NO: 5805), KGIN (SEQ ID NO: 5806), KSEI (SEQ ID NO: 5807), KSEK (SEQ ID NO: 5627), KWSA (SEQ ID NO: 5808), KELA (SEQ ID NO: 5809), KQTQ (SEQ ID NO: 5810), KGAD (SEQ ID NO: 5811), KVGE (SEQ ID NO: 5812), KANE (SEQ ID NO: 5813), KTDT (SEQ ID NO: 5814), KTCI (SEQ ID NO: 5815), KELR (SEQ ID NO: 5816), KCQI (SEQ ID NO: 5817), KGVM (SEQ ID NO: 5818), KACD (SEQ ID NO: 5819), KNEL (SEQ ID NO: 5820), KAAE (SEQ ID NO: 5821), KGQN (SEQ ID NO: 5822), KNEF (SEQ ID NO: 5823), KTSI (SEQ ID NO: 5824), KAEH (SEQ ID NO: 5616), KCDQ (SEQ ID NO: 5825), KEIL (SEQ ID NO: 5826), KTER (SEQ ID NO: 5573), KNAI (SEQ ID NO: 5650), KTDK (SEQ ID NO: 5588), KTPD (SEQ ID NO: 5827), KTIH (SEQ ID NO: 5659), or KTEI (SEQ ID NO: 5591);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

236. The AAV particle of embodiment 234or 235, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3606-3836;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

237. The AAV particle of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTINGHDSPHKSGQNQQT (SEQ ID NO: 5828).

238. The AAV particle of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754).

239. The AAV particle of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTEKMSGSPHSKAQNQQT (SEQ ID NO: 3241).

240. The AAV particle of any one of embodiments 168-239, wherein [N1]-[N2]-[N3] is present in loop IV, e.g., numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

241. The AAV particle of any one of embodiments 198-202 or 234-240, wherein [N0] and [N4] are present in loop IV, e.g., numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

242. The AAV particle of any one of embodiments 198-202 or 234-241, wherein [N0] is present immediately subsequent to position 448, numbered according to the amino acid sequence of SEQ ID NO: 4, 36, 138, 981, or 982.

243. The AAV particle of any one of embodiments 198-202 or 234-242, wherein [N0] replaces positions 449-452 (e.g., K449, T450, I451, and N452), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

244. The AAV particle of any one of embodiments 198-202 or 234-243, wherein [N0] is present immediately subsequent to position 448 and wherein [N0] replaces positions 449-452 (e.g., K449, T450, I451, and N452), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

245. The AAV particle of any one of embodiments 198-202 or 234-244, wherein [N0] corresponds to positions 449-452 (e.g., K449, T450, I451, and N452) of any one of SEQ ID NOs: 4, 36, 138, 981, or 982.

246. The AAV particle of any one of embodiments 168-245, wherein [N1] is present immediately subsequent to position 452, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

247. The AAV particle of any one of embodiments 168-246, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

248. The AAV particle of any one of embodiments 168-246, wherein [N1] replaces position 453 (e.g., G453), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

249. The AAV particle of any one of embodiments 168-177, 179-181, 183-185, 187-193, 195-200, 202, or 240-246, wherein:

(i) X1 of [N1] replaces position 453 (e.g., G453);

(ii) X2 of [N1] corresponds to position 454 (e.g., S454); and

(iii) X3 of [N1] corresponds to position 455 (e.g., G455),

wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 981.

250. The AAV particle of any one of embodiments 168-176, 178-201, or 240-246, wherein:

(i) X1 of [N1] corresponds to position 453 (e.g., G453);

(ii) X2 of [N1] corresponds to position 454 (e.g., S454); and

(iii) X3 of [N1] corresponds to position 455 (e.g., G455);

wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 981.

251. The AAV particle of any one of embodiments 203-248, wherein:

(i) X1 of [N1] corresponds to position 453 (e.g., G453);

(ii) X2 of [N1] replaces position 454 (e.g., S454); and

(iii) X3 of [N1] replaces position 455 (e.g., G455),

wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

252. The AAV particle of any one of embodiments 203-248 or 251, wherein [N1] corresponds to positions 453-455 (e.g., G453, H454, D455) of SEQ ID NO 982.

253. The AAV particle of any one of embodiments 168-176, 178-201, 240-247, or 250, wherein [N1] corresponds to positions 453-455 (e.g., G453, S454, G455) of SEQ ID NO: 138 or 981.

254. The AAV particle of any one of embodiments 168-253, wherein [N2] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982.

255. The AAV particle of any one of embodiments 168-254, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, and H458) of SEQ ID NO: 981 or 982.

256. The AAV particle of any one of embodiments 168-254, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, and H458) of any one of SEQ ID NOs: 4 or 36-59.

257. The AAV particle of any one of embodiments 168-256, wherein [N2] is present immediately subsequent to [N1].

258. The AAV particle of any one of embodiments 168-202, 240-247, or 249-257, wherein [N3] corresponds to positions 459-460 (e.g., S459, K460, A461) of SEQ ID NO: 981.

259. The AAV particle of any one of embodiments 168-202, 240-247, or 249-257, wherein [N3] corresponds to positions 459-460 (e.g., S459, K460, A461) of SEQ ID NO: 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, or 59.

260. The AAV particle of any one of embodiments 168-259, wherein [N2]-[N3] is present immediately subsequent to position 455, numbered according to any one of SEQ ID NOs: 4, 36, 138, 981, or 982.

261. The AAV particle of any one of embodiments 168-259, wherein [N2]-[N3] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 981.

262. The AAV particle of any one of embodiments 168-261, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

263. The AAV particle of any one of embodiments 168-262, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of any one of SEQ ID NOs: 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, or 59.

264. The AAV particle of any one of embodiments 203-257 or 259-261, wherein [N3] corresponds to positions 459-460 (e.g., K459, S460, G461) of SEQ ID NO: 982.

265. The AAV particle of any one of embodiments 203-257 or 259-261, wherein [N3] corresponds to positions 459-460 (e.g., K459, S460, G461) of SEQ ID NO: 37.

266. The AAV particle of any one of embodiments 203-265, wherein [N2]-[N3] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 982.

267. The AAV particle of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-266, wherein [N3] replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

268. The AAV particle of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-267, wherein [N3] is present immediately subsequent to [N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

269. The AAV particle of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-268, wherein [N3] is present immediately subsequent to [N1]-[N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

270. The AAV particle of any one of embodiments 203-257, 260, 264-269, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

271. The AAV particle of any one of embodiments 203-257, 260, 264-270, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 37.

272. The AAV particle of any one of embodiments 191-202 or 228-271, wherein [N4] is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 138.

273. The AAV particle of any one of embodiments 191-202 or 228-272, wherein [N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

274. The AAV particle of any one of embodiments 191-202 or 228-273, wherein [N4] corresponds to positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466) of SEQ ID NO: 981 or 982.

275. The AAV particle of any one of embodiments 191-202 or 228-273, wherein [N4] corresponds to positions 462-466 of any one of SEQ ID NOs: 4 or 36-59.

276. The AAV particle of any one of embodiments 191-202 or 228-274, wherein [N4] corresponds to positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460) of SEQ ID NO: 138.

277. The AAV particle of any one of embodiments 191-202 or 228-276, wherein [N2]-[N3]-[N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

278. The AAV particle of any one of embodiments 191-202 or 228-277, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

279. The AAV particle of any one of embodiments 191-202 or 228-278, wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

280. The AAV particle of any one of embodiments 191-202 or 228-279, wherein [N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 452, and wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

281. The AAV particle of any one of embodiments 191-202, 240-247, 249, 250, 253-263, 266, or 272-280, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465, and T466) of SEQ ID NO: 981.

282. The AAV particle of any one of embodiments 168-202, 240-247, 249, 250, 253-263, 266, or 272-280, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

283. The AAV particle of any one of embodiments 228-257, 260, 261, 264-282, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 982.

284. The AAV particle of any one of embodiments 203-257, 260, 261, 264-283, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

285. The AAV particle of any one of embodiments 228-257, 260, 261, 264-282, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 of any one of SEQ ID NOs: 4 or 36-59.

286. The AAV particle of any one of embodiments 198-202 or 234-286, wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

287. The AAV particle of any one of embodiments 198-202 or 234-286, wherein [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 448, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered according to SEQ ID NO: 138.

288. The AAV particle of any one of embodiments 198-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, or 287 , wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 (e.g., K449, T450, I451, N452, G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 981.

289. The AAV particle of any one of embodiments 234-257, 260, 261, 264-284, 286, or 287, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 (e.g., K449, T450, I451, N452, G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 982.

290. The AAV particle of any one of embodiments 234-257, 260, 261, 264-284, 286, or 287, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 of any one of SEQ ID NOs: 4 or 36-59.

291. The AAV particle of any one of embodiments 191-202 or 228-290, wherein [N4] is present immediately subsequent to position 461, numbered according to SEQ ID NO: 4, 36, 981, or 982.

292. The AAV particle of any one of embodiments 191-202 or 228-291, wherein [N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), numbered according to SEQ ID NO: 4, 36, 981, or 982.

293. The AAV particle of any one of embodiments 191-202 or 228-292, wherein [N2]-[N3]-[N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), numbered according to SEQ ID NO: 4, 36, 981, or 982.

294. The AAV particle of any one of embodiments 191-202 or 228-293, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), numbered according to SEQ ID NO: 4, 36, 981, or 982.

295. The AAV particle of any one of embodiments 168-294, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N2]-[N3].

296. The AAV particle of any one of embodiments 168-295, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3].

297. The AAV particle of any one of embodiments 168-296, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3].

298. The AAV particle of any one of embodiments 168-297, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4].

299. The AAV particle of any one of embodiments 168-298, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

300. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises the formula [A]-[B] (SEQ ID NO: 4696), wherein:

(i) [A] comprises GSGSPH (SEQ ID NO: 4695); and

(ii) [B] comprises X1 X2, X3, X4, and X5, wherein:

(a) X1 is S, I, F, V, C, Y, W, R, P, L, Q, M, K, or G;

(b) X2 is K, M, R, F, V, C, P, Y, L, W, G, N, S, T, I, or A;

(c) X3 is A, Y, L, R, W, C, T, F, H, I, P, M, K, S, V, G, Q, or N;

(d) X4 is Q, M, F, K, H, R, C, W, P, V, L, G, S, Y, I, A, T, D, N, or E; and

(e) X5 is A, N, Y, R, K, L, I, M, Q, S, C, W, F, T, G, V, or P;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

301. The AAV particle of embodiment 300, wherein:

(a) X1 is S, L, R, V, or P;

(b) X2 is K, C, F, L, P, R, S, or V;

(c) X3 is A, C, F, I, K, L, M, P, R, T, W, or Y;

(d) X4 is Q, R, S, T, C, F, K, L, P or Y; and

(e) X5 is N, R, S, T, K, M, Q or Y;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

302. The AAV particle of embodiment 300 or 301, wherein [B] comprises SKA, SMY, SKL, SKR, SKW, SRC, SFT, SKF, IVW, SKY, SCH, FPW, SKI, VYY, SLY, SKP, SRF, SRM, SVK, SWA, SLW, SFR, SKK, SYA, SCS, SGA, SFP, SFF, SMC, SKT, SGK, FYR, CRV, YGI, VNC, SLA, WSY, RWL, PSC, SSW, SKG, VPW, SGC, STT, PKR, SKC, WVP, SFW, RIK, SKM, LRW, LPT, SYM, LLC, RCC, LCV, SYL, QGC, MAF, SFQ, SLC, RPW, RPR, SCP, SVR, SLP, VYH, SYT, LVY, YRY, SWL, CPA, SPP, RWT, PRK, PFV, SKS, WVA, SKV, CAL, SSC, SKN, LCT, STC, SKQ, KSG, SYY, SLT, SCQ, FPF, SVF, GRY, AQA, AQN, YMN, AFY, LKR, RHR, AQK, WRL, CRN, TCN, FFI, AQY, WQN, YFM, ARQ, HQN, IRR, YQN, YWN, AFS, FWN, AQC, MRN, KKN, APN, WKN, ARW, RPN, KVF, AFN, ACS, RLW, SRN, CPN, ACN, FRQ, PFN, FGN, CQN, LFW, TRK, KRN, RQN, VQN, IQN, AQR, PFR, AWN, RSY, LQN, WLN, RRA, AQT, GCT, RYT, TPN, ARM, CFL, PQN, WSN, FKN, KQN, APR, RYN, MIC, TQN, WKS, AAR, LTR, IRG, LVN, FQN, ACQ, WGL, ILR, QIN, ACI, ALR, AHA, CLN, AFV, AQF, RCN, MPC, KTS, PYN, AQS, TRN, LKN, AQM, CTN, PDN, RNY, ACR, CSV, ARI, LPK, SEQ, VRM, NSR, RKR, ARN, QRP, RVV, GQN, YSN, QSN, AKG, CTS, FEN, AKK, KAQ, MYM, KAF, KLK, KRH, KWR, RCR, FTC, KFF, VWQ, KYF, KAR, CHQ, PWQ, KIR, YYQ, LYW, KPK, RFW, RMR, VKK, WAP, LWK, FRP, KKV, YAF, KAC, KRL, CSR, RCP, GAC, KFR, FFG, MCQ, KLF, KTR, GKR, YRQ, RVQ, GIQ, NCQ, KPF, LAW, KRS, SYQ, WLQ, KRR, KGC, KRY, GCQ, FTP, TTC, KRQ, KCF, VPQ, FWS, KFK, IKQ, KAP, FRY, KMI, RWQ, PTQ, KWK, YMR, KAA, LCQ, CCQ, CVQ, KLT, KLC, YLV, AFQ, KWG, KIL, FQI, KAL, KAH, LCL, PRQ, CPQ, VRY, VRC, KMP, KKT, LPY, YHQ, YTR, VYQ, RYQ, WLK, PAQ, MCT, PPD, WTQ, RKQ, KCS, FVQ, KLP, KSE, VAQ, LYQ, KVR, ALQ, SCT, KNS, KRK, CTQ, TCL, YAR, KQR, KRV, SGQ, YYS, LTC, CQS, KAK, KPQ, PFQ, KCT, or VFE.

303. The AAV particle of any one of embodiments 300-302, wherein [B] comprises SKAQ (SEQ ID NO: 5829), SMYM (SEQ ID NO: 5830), SKAF (SEQ ID NO: 5831), SKLK (SEQ ID NO: 5832), SKRH (SEQ ID NO: 5833), SKWR (SEQ ID NO: 5834), SRCR (SEQ ID NO: 5835), SFTC (SEQ ID NO: 5836), SKFF (SEQ ID NO: 5837), IVWQ (SEQ ID NO: 5838), SKYF (SEQ ID NO: 5839), SKAR (SEQ ID NO: 5840), SCHQ (SEQ ID NO: 5841), FPWQ (SEQ ID NO: 5842), SKIR (SEQ ID NO: 5843), VYYQ (SEQ ID NO: 5844), SLYW (SEQ ID NO: 5845), SKPK (SEQ ID NO: 5846), SRFW (SEQ ID NO: 5847), SRMR (SEQ ID NO: 5848), SVKK (SEQ ID NO: 5849), SWAP (SEQ ID NO: 5850), SLWK (SEQ ID NO: 5851), SFRP (SEQ ID NO: 5852), SKKV (SEQ ID NO: 5853), SYAF (SEQ ID NO: 5854), SKAC (SEQ ID NO: 5855), SKRL (SEQ ID NO: 5856), SCSR (SEQ ID NO: 5857), SRCP (SEQ ID NO: 5858), SGAC (SEQ ID NO: 5859), SKFR (SEQ ID NO: 5860), SFPF (SEQ ID NO: 5861), SFFG (SEQ ID NO: 5862), SMCQ (SEQ ID NO: 5863), SKLF (SEQ ID NO: 5864), SKTR (SEQ ID NO: 5865), SGKR (SEQ ID NO: 5866), FYRQ (SEQ ID NO: 5867), CRVQ (SEQ ID NO: 5868), YGIQ (SEQ ID NO: 5869), VNCQ (SEQ ID NO: 5870), SKPF (SEQ ID NO: 5871), SLAW (SEQ ID NO: 5872), SKRS (SEQ ID NO: 5873), WSYQ (SEQ ID NO: 5874), RWLQ (SEQ ID NO: 5875), PSCQ (SEQ ID NO: 5876), SSWL (SEQ ID NO: 5877), SKRR (SEQ ID NO: 5878), SKGC (SEQ ID NO: 5879), VPWQ (SEQ ID NO: 5880), SKRY (SEQ ID NO: 5881), SGCQ (SEQ ID NO: 5882), SFTP (SEQ ID NO: 5883), STTC (SEQ ID NO: 5884), PKRQ (SEQ ID NO: 5885), SKCF (SEQ ID NO: 5886), WVPQ (SEQ ID NO: 5887), SFWS (SEQ ID NO: 5888), SKFK (SEQ ID NO: 5889), RIKQ (SEQ ID NO: 5890), SKAP (SEQ ID NO: 5891), SFRY (SEQ ID NO: 5892), SKMI (SEQ ID NO: 5893), LRWQ (SEQ ID NO: 5894), LPTQ (SEQ ID NO: 5895), SKWK (SEQ ID NO: 5896), SYMR (SEQ ID NO: 5897), SKAA (SEQ ID NO: 5898), LLCQ (SEQ ID NO: 5899), RCCQ (SEQ ID NO: 5900), LCVQ (SEQ ID NO: 5901), SKLT (SEQ ID NO: 5902), SKLC (SEQ ID NO: 5903), SYLV (SEQ ID NO: 5904), QGCQ (SEQ ID NO: 5905), MAFQ (SEQ ID NO: 5906), SKWG (SEQ ID NO: 5907), SKIL (SEQ ID NO: 5908), SFQI (SEQ ID NO: 5909), SKAL (SEQ ID NO: 5910), SKAH (SEQ ID NO: 5911), SLCL (SEQ ID NO: 5912), RPWQ (SEQ ID NO: 5913), RPRQ (SEQ ID NO: 5914), SCPQ (SEQ ID NO: 5915), SVRY (SEQ ID NO: 5916), SVRC (SEQ ID NO: 5917), SKMP (SEQ ID NO: 5918), SKKT (SEQ ID NO: 5919), SLPY (SEQ ID NO: 5920), VYHQ (SEQ ID NO: 5921), SYTR (SEQ ID NO: 5922), LVYQ (SEQ ID NO: 5923), YRYQ (SEQ ID NO: 5924), SWLK (SEQ ID NO: 5925), CPAQ (SEQ ID NO: 5926), SMCT (SEQ ID NO: 5927), SPPD (SEQ ID NO: 5928), SKRN (SEQ ID NO: 5929), RWTQ (SEQ ID NO: 5930), PRKQ (SEQ ID NO: 5931), SKCS (SEQ ID NO: 5932), PFVQ (SEQ ID NO: 5933), SKLP (SEQ ID NO: 5934), SKSE (SEQ ID NO: 5935), WVAQ (SEQ ID NO: 5936), SLYQ (SEQ ID NO: 5937), SKVR (SEQ ID NO: 5938), CALQ (SEQ ID NO: 5939), SSCT (SEQ ID NO: 5940), SKNS (SEQ ID NO: 5941), SKRK (SEQ ID NO: 5942), LCTQ (SEQ ID NO: 5943), STCL (SEQ ID NO: 5944), SYAR (SEQ ID NO: 5945), SKQR (SEQ ID NO: 5946), SKRV (SEQ ID NO: 5947), KSGQ (SEQ ID NO: 5948), SYYS (SEQ ID NO: 5949), SLTC (SEQ ID NO: 5950), SCQS (SEQ ID NO: 5951), SKAK (SEQ ID NO: 5952), SKPQ (SEQ ID NO: 5953), FPFQ (SEQ ID NO: 5954), SKCT (SEQ ID

NO: 5955), SVFE (SEQ ID NO: 5956), GRYQ (SEQ ID NO: 5957), KAQA (SEQ ID NO: 5958), KAQN (SEQ ID NO: 5959), MYMN (SEQ ID NO: 5960), KAFY (SEQ ID NO: 5961), KLKR (SEQ ID NO: 5962), KRHR (SEQ ID NO: 5963), KAQK (SEQ ID NO: 5964), KWRL (SEQ ID NO: 5965), RCRN (SEQ ID NO: 5966), FTCN (SEQ ID NO: 5967), KFFI (SEQ ID NO: 5968), KAQY (SEQ ID NO: 5969), VWQN (SEQ ID NO: 5970), KYFM (SEQ ID NO: 5971), KARQ (SEQ ID NO: 5972), CHQN (SEQ ID NO: 5973), PWQN (SEQ ID NO: 5974), KIRR (SEQ ID NO: 5975), YYQN (SEQ ID NO: 5976), LYWN (SEQ ID NO: 5977), KPKR (SEQ ID NO: 5978), KAFS (SEQ ID NO: 5979), RFWN (SEQ ID NO: 5980), KAQC (SEQ ID NO: 5981), RMRN (SEQ ID NO: 5982), VKKN (SEQ ID NO: 5983), WAPN (SEQ ID NO: 5984), LWKN (SEQ ID NO: 5985), KARW (SEQ ID NO: 5986), FRPN (SEQ ID NO: 5987), KKVF (SEQ ID NO: 5988), YAFN (SEQ ID NO: 5989), KACS (SEQ ID NO: 5990), KRLW (SEQ ID NO: 5991), CSRN (SEQ ID NO: 5992), RCPN (SEQ ID NO: 5993), GACN (SEQ ID NO: 5994), KFRQ (SEQ ID NO: 5995), FPFN (SEQ ID NO: 5996), FFGN (SEQ ID NO: 5997), MCQN (SEQ ID NO: 5998), KLFW (SEQ ID NO: 5999), KTRK (SEQ ID NO: 6000), GKRN (SEQ ID NO: 6001), YRQN (SEQ ID NO: 6002), RVQN (SEQ ID NO: 6003), GIQN (SEQ ID NO: 6004), KAQR (SEQ ID NO: 6005), NCQN (SEQ ID NO: 6006), KPFR (SEQ ID NO: 6007), LAWN (SEQ ID NO: 6008), KRSY (SEQ ID NO: 6009), SYQN (SEQ ID NO: 6010), WLQN (SEQ ID NO: 6011), SCQN (SEQ ID NO: 6012), SWLN (SEQ ID NO: 6013), KRRA (SEQ ID NO: 6014), KAQT (SEQ ID NO: 6015), KGCT (SEQ ID NO: 6016), KRYT (SEQ ID NO: 6017), GCQN (SEQ ID NO: 6018), FTPN (SEQ ID NO: 6019), TTCN (SEQ ID NO: 6020), KARM (SEQ ID NO: 6021), KRQN (SEQ ID NO: 6022), KCFL (SEQ ID NO: 6023), VPQN (SEQ ID NO: 6024), FWSN (SEQ ID NO: 6025), KFKN (SEQ ID NO: 6026), IKQN (SEQ ID NO: 6027), KAPR (SEQ ID NO: 6028), FRYN (SEQ ID NO: 6029), KMIC (SEQ ID NO: 6030), RWQN (SEQ ID NO: 6031), PTQN (SEQ ID NO: 6032), KWKS (SEQ ID NO: 6033), YMRN (SEQ ID NO: 6034), KAAR (SEQ ID NO: 6035), LCQN (SEQ ID NO: 6036), CCQN (SEQ ID NO: 6037), CVQN (SEQ ID NO: 6038), KLTR (SEQ ID NO: 6039), KLCT (SEQ ID NO: 6040), KIRG (SEQ ID NO: 6041), YLVN (SEQ ID NO: 6042), AFQN (SEQ ID NO: 6043), KACQ (SEQ ID NO: 6044), KWGL (SEQ ID NO: 6045), KILR (SEQ ID NO: 6046), FQIN (SEQ ID NO: 6047), KACI (SEQ ID NO: 6048), KALR (SEQ ID NO: 6049), KAHA (SEQ ID NO: 6050), LCLN (SEQ ID NO: 6051), KAFV (SEQ ID NO: 6052), PRQN (SEQ ID NO: 6053), CPQN (SEQ ID NO: 6054), KAQF (SEQ ID NO: 6055), VRYN (SEQ ID NO: 6056), VRCN (SEQ ID NO: 6057), KMPC (SEQ ID NO: 6058), KKTS (SEQ ID NO: 6059), LPYN (SEQ ID NO: 6060), YHQN (SEQ ID NO: 6061), KAQS (SEQ ID NO: 6062), YTRN (SEQ ID NO: 6063), VYQN (SEQ ID NO: 6064), RYQN (SEQ ID NO: 6065), WLKN (SEQ ID NO: 6066), KAQM (SEQ ID NO: 6067), PAQN (SEQ ID NO: 6068), MCTN (SEQ ID NO: 6069), PPDN (SEQ ID NO: 6070), KRNY (SEQ ID NO: 6071), WTQN (SEQ ID NO: 6072), KACR (SEQ ID NO: 6073), RKQN (SEQ ID NO: 6074), KCSV (SEQ ID NO: 6075), KARI (SEQ ID NO: 6076), FVQN (SEQ ID NO: 6077), KLPK (SEQ ID NO: 6078), KSEQ (SEQ ID NO: 6079), VAQN (SEQ ID NO: 6080), LYQN (SEQ ID NO: 6081), KVRM (SEQ ID NO: 6082), ALQN (SEQ ID NO: 6083), SCTN (SEQ

ID NO: 6084), KNSR (SEQ ID NO: 6085), KRKR (SEQ ID NO: 6086), CTQN (SEQ ID NO: 6087), TCLN (SEQ ID NO: 6088), YARN (SEQ ID NO: 6089), KQRP (SEQ ID NO: 6090), KRVV (SEQ ID NO: 6091), SGQN (SEQ ID NO: 6092), YYSN (SEQ ID NO: 6093), LTCN (SEQ ID NO: 6094), CQSN (SEQ ID NO: 6095), KAKG (SEQ ID NO: 6096), KPQN (SEQ ID NO: 6097), PFQN (SEQ ID NO: 6098), KCTS (SEQ ID NO: 6099), VFEN (SEQ ID NO: 6100), or KAKK (SEQ ID NO: 6101).

304. The AAV particle of any one of embodiments 300-303, wherein [B] is or comprises:

(i) SKAQA (SEQ ID NO: 6102), SKAQN (SEQ ID NO: 6103), SMYMN (SEQ ID NO: 6104), SKAFY (SEQ ID NO: 6105), SKLKR (SEQ ID NO: 6106), SKRHR (SEQ ID NO: 6107), SKAQK (SEQ ID NO: 6108), SKWRL (SEQ ID NO: 6109), SRCRN (SEQ ID NO: 6110), SFTCN (SEQ ID NO: 6111), SKFFI (SEQ ID NO: 6112), SKAQY (SEQ ID NO: 6113), IVWQN (SEQ ID NO: 6114), SKYFM (SEQ ID NO: 6115), SKARQ (SEQ ID NO: 6116), SCHQN (SEQ ID NO: 6117), FPWQN (SEQ ID NO: 6118), SKIRR (SEQ ID NO: 6119), VYYQN (SEQ ID NO: 6120), SLYWN (SEQ ID NO: 6121), SKPKR (SEQ ID NO: 6122), SKAFS (SEQ ID NO: 6123), SRFWN (SEQ ID NO: 6124), SKAQC (SEQ ID NO: 6125), SRMRN (SEQ ID NO: 6126), SVKKN (SEQ ID NO: 6127), SWAPN (SEQ ID NO: 6128), SLWKN (SEQ ID NO: 6129), SKARW (SEQ ID NO: 6130), SFRPN (SEQ ID NO: 6131), SKKVF (SEQ ID NO: 6132), SYAFN (SEQ ID NO: 6133), SKACS (SEQ ID NO: 6134), SKRLW (SEQ ID NO: 6135), SCSRN (SEQ ID NO: 6136), SRCPN (SEQ ID NO: 6137), SGACN (SEQ ID NO: 6138), SKFRQ (SEQ ID NO: 6139), SFPFN (SEQ ID NO: 6140), SFFGN (SEQ ID NO: 6141), SMCQN (SEQ ID NO: 6142), SKLFW (SEQ ID NO: 6143), SKTRK (SEQ ID NO: 6144), SGKRN (SEQ ID NO: 6145), FYRQN (SEQ ID NO: 6146), CRVQN (SEQ ID NO: 6147), YGIQN (SEQ ID NO: 6148), SKAQR (SEQ ID NO: 6149), VNCQN (SEQ ID NO: 6150), SKPFR (SEQ ID NO: 6151), SLAWN (SEQ ID NO: 6152), SKRSY (SEQ ID NO: 6153), WSYQN (SEQ ID NO: 6154), RWLQN (SEQ ID NO: 6155), PSCQN (SEQ ID NO: 6156), SSWLN (SEQ ID NO: 6157), SKRRA (SEQ ID NO: 6158), SKAQT (SEQ ID NO: 6159), SKGCT (SEQ ID NO: 6160), VPWQN (SEQ ID NO: 6161), SKRYT (SEQ ID NO: 6162), SGCQN (SEQ ID NO: 6163), SFTPN (SEQ ID NO: 6164), STTCN (SEQ ID NO: 6165), SKARM (SEQ ID NO: 6166), PKRQN (SEQ ID NO: 6167), SKCFL (SEQ ID NO: 6168), WVPQN (SEQ ID NO: 6169), SFWSN (SEQ ID NO: 6170), SKFKN (SEQ ID NO: 6171), RIKQN (SEQ ID NO: 6172), SKAPR (SEQ ID NO: 6173), SFRYN (SEQ ID NO: 6174), SKMIC (SEQ ID NO: 6175), LRWQN (SEQ ID NO: 6176), LPTQN (SEQ ID NO: 6177), SKWKS (SEQ ID NO: 6178), SYMRN (SEQ ID NO: 6179), SKAAR (SEQ ID NO: 6180), LLCQN (SEQ ID NO: 6181), RCCQN (SEQ ID NO: 6182), LCVQN (SEQ ID NO: 6183), SKLTR (SEQ ID NO: 6184), SKLCT (SEQ ID NO: 6185), SKIRG (SEQ ID NO: 6186), SYLVN (SEQ ID NO: 6187), QGCQN (SEQ ID NO: 6188), MAFQN (SEQ ID NO: 6189), SKACQ (SEQ ID NO: 6190), SKWGL (SEQ ID NO: 6191), SKILR (SEQ ID NO: 6192), SFQIN (SEQ ID NO: 6193), SKACI (SEQ ID NO: 6194), SKALR (SEQ ID NO: 6195),

SKAHA (SEQ ID NO: 6196), SLCLN (SEQ ID NO: 6197), SKAFV (SEQ ID NO: 6198), RPWQN (SEQ ID NO: 6199), RPRQN (SEQ ID NO: 6200), SCPQN (SEQ ID NO: 6201), SKAQF (SEQ ID NO: 6202), SVRYN (SEQ ID NO: 6203), SVRCN (SEQ ID NO: 6204), SKMPC (SEQ ID NO: 6205), SKKTS (SEQ ID NO: 6206), SLPYN (SEQ ID NO: 6207), VYHQN (SEQ ID NO: 6208), SKAQS (SEQ ID NO: 6209), SYTRN (SEQ ID NO: 6210), LVYQN (SEQ ID NO: 6211), YRYQN (SEQ ID NO: 6212), SWLKN (SEQ ID NO: 6213), SKAQM (SEQ ID NO: 6214), CPAQN (SEQ ID NO: 6215), SMCTN (SEQ ID NO: 6216), SPPDN (SEQ ID NO: 6217), SKRNY (SEQ ID NO: 6218), RWTQN (SEQ ID NO: 6219), SKACR (SEQ ID NO: 6220), PRKQN (SEQ ID NO: 6221), SKCSV (SEQ ID NO: 6222), SKARI (SEQ ID NO: 6223), PFVQN (SEQ ID NO: 6224), SKLPK (SEQ ID NO: 6225), SKSEQ (SEQ ID NO: 6226), WVAQN (SEQ ID NO: 6227), SLYQN (SEQ ID NO: 6228), SKVRM (SEQ ID NO: 6229), CALQN (SEQ ID NO: 6230), SSCTN (SEQ ID NO: 6231), SKNSR (SEQ ID NO: 6232), SKRKR (SEQ ID NO: 6233), LCTQN (SEQ ID NO: 6234), STCLN (SEQ ID NO: 6235), SYARN (SEQ ID NO: 6236), SKQRP (SEQ ID NO: 6237), SKRVV (SEQ ID NO: 6238), KSGQN (SEQ ID NO: 6239), SYYSN (SEQ ID NO: 6240), SLTCN (SEQ ID NO: 6241), SCQSN (SEQ ID NO: 6242), SKAKG (SEQ ID NO: 6243), SKPQN (SEQ ID NO: 6244), FPFQN (SEQ ID NO: 6245), SKCTS (SEQ ID NO: 6246), SVFEN (SEQ ID NO: 6247), SKAKK (SEQ ID NO: 6248), or GRYQN (SEQ ID NO: 6249);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

305. The AAV particle of any one of embodiments 300-304, wherein [A]-[B] is or comprises:

(i) GSGSPHSKAQA (SEQ ID NO: 6250), GSGSPHSKAQN (SEQ ID NO: 6251), GSGSPHSMYMN (SEQ ID NO: 6252), GSGSPHSKAFY (SEQ ID NO: 6253), GSGSPHSKLKR (SEQ ID NO: 6254), GSGSPHSKRHR (SEQ ID NO: 6255), GSGSPHSKAQK (SEQ ID NO: 6256), GSGSPHSKWRL (SEQ ID NO: 6257), GSGSPHSRCRN (SEQ ID NO: 6258), GSGSPHSFTCN (SEQ ID NO: 6259), GSGSPHSKFFI (SEQ ID NO: 6260), GSGSPHSKAQY (SEQ ID NO: 6261), GSGSPHIVWQN (SEQ ID NO: 6262), GSGSPHSKYFM (SEQ ID NO: 6263), GSGSPHSKARQ (SEQ ID NO: 6264), GSGSPHSCHQN (SEQ ID NO: 6265), GSGSPHFPWQN (SEQ ID NO: 6266), GSGSPHSKIRR (SEQ ID NO: 6267), GSGSPHVYYQN (SEQ ID NO: 6268), GSGSPHSLYWN (SEQ ID NO: 6269), GSGSPHSKPKR (SEQ ID NO: 6270), GSGSPHSKAFS (SEQ ID NO: 6271), GSGSPHSRFWN (SEQ ID NO: 6272), GSGSPHSKAQC (SEQ ID NO: 6273), GSGSPHSRMRN (SEQ ID NO: 6274), GSGSPHSVKKN (SEQ ID NO: 6275), GSGSPHSWAPN (SEQ ID NO: 6276), GSGSPHSLWKN (SEQ ID NO: 6277), GSGSPHSKARW (SEQ ID NO: 6278), GSGSPHSFRPN

(SEQ ID NO: 6279), GSGSPHSKKVF (SEQ ID NO: 6280), GSGSPHSYAFN (SEQ ID NO: 6281), GSGSPHSKACS (SEQ ID NO: 6282), GSGSPHSKRLW (SEQ ID NO: 6283), GSGSPHSCSRN (SEQ ID NO: 6284), GSGSPHSRCPN (SEQ ID NO: 6285), GSGSPHSGACN (SEQ ID NO: 6286), GSGSPHSKFRQ (SEQ ID NO: 6287), GSGSPHSFPFN (SEQ ID NO: 6288), GSGSPHSFFGN (SEQ ID NO: 6289), GSGSPHSMCQN (SEQ ID NO: 6290), GSGSPHSKLFW (SEQ ID NO: 6291), GSGSPHSKTRK (SEQ ID NO: 6292), GSGSPHSGKRN (SEQ ID NO: 6293), GSGSPHFYRQN (SEQ ID NO: 6294), GSGSPHCRVQN (SEQ ID NO: 6295), GSGSPHYGIQN (SEQ ID NO: 6296), GSGSPHSKAQR (SEQ ID NO: 6297), GSGSPHVNCQN (SEQ ID NO: 6298), GSGSPHSKPFR (SEQ ID NO: 6299), GSGSPHSLAWN (SEQ ID NO: 6300), GSGSPHSKRSY (SEQ ID NO: 6301), GSGSPHWSYQN (SEQ ID NO: 6302), GSGSPHRWLQN (SEQ ID NO: 6303), GSGSPHPSCQN (SEQ ID NO: 6304), GSGSPHSSWLN (SEQ ID NO: 6305), GSGSPHSKRRA (SEQ ID NO: 6306), GSGSPHSKAQT (SEQ ID NO: 6307), GSGSPHSKGCT (SEQ ID NO: 6308), GSGSPHVPWQN (SEQ ID NO: 6309), GSGSPHSKRYT (SEQ ID NO: 6310), GSGSPHSGCQN (SEQ ID NO: 6311), GSGSPHSFTPN (SEQ ID NO: 6312), GSGSPHSTTCN (SEQ ID NO: 6313), GSGSPHSKARM (SEQ ID NO: 6314), GSGSPHPKRQN (SEQ ID NO: 6315), GSGSPHSKCFL (SEQ ID NO: 6316), GSGSPHWVPQN (SEQ ID NO: 6317), GSGSPHSFWSN (SEQ ID NO: 6318), GSGSPHSKFKN (SEQ ID NO: 6319), GSGSPHRIKQN (SEQ ID NO: 6320), GSGSPHSKAPR (SEQ ID NO: 6321), GSGSPHSFRYN (SEQ ID NO: 6322), GSGSPHSKMIC (SEQ ID NO: 6323), GSGSPHLRWQN (SEQ ID NO: 6324), GSGSPHLPTQN (SEQ ID NO: 6325), GSGSPHSKWKS (SEQ ID NO: 6326), GSGSPHSYMRN (SEQ ID NO: 6327), GSGSPHSKAAR (SEQ ID NO: 6328), GSGSPHLLCQN (SEQ ID NO: 6329), GSGSPHRCCQN (SEQ ID NO: 6330), GSGSPHLCVQN (SEQ ID NO: 6331), GSGSPHSKLTR (SEQ ID NO: 6332), GSGSPHSKLCT (SEQ ID NO: 6333), GSGSPHSKIRG (SEQ ID NO: 6334), GSGSPHSYLVN (SEQ ID NO: 6335), GSGSPHQGCQN (SEQ ID NO: 6336), GSGSPHMAFQN (SEQ ID NO: 6337), GSGSPHSKACQ (SEQ ID NO: 6338), GSGSPHSKWGL (SEQ ID NO: 6339), GSGSPHSKILR (SEQ ID NO: 6340), GSGSPHSFQIN (SEQ ID NO: 6341), GSGSPHSKACI (SEQ ID NO: 6342), GSGSPHSKALR (SEQ ID NO: 6343), GSGSPHSKAHA (SEQ ID NO: 6344), GSGSPHSLCLN (SEQ ID NO: 6345), GSGSPHSKAFV (SEQ ID NO: 6346), GSGSPHRPWQN (SEQ ID NO: 6347), GSGSPHRPRQN (SEQ ID NO: 6348), GSGSPHSCPQN (SEQ ID NO: 6349), GSGSPHSKAQF (SEQ ID NO: 6350), GSGSPHSVRYN (SEQ ID NO: 6351), GSGSPHSVRCN (SEQ ID NO: 6352), GSGSPHSKMPC (SEQ ID NO: 6353), GSGSPHSKKTS (SEQ ID NO: 6354), GSGSPHSLPYN (SEQ ID NO: 6355), GSGSPHVYHQN (SEQ ID NO: 6356), GSGSPHSKAQS (SEQ ID NO: 6357), GSGSPHSYTRN (SEQ ID NO: 6358), GSGSPHLVYQN (SEQ ID NO: 6359), GSGSPHYRYQN (SEQ ID NO: 6360), GSGSPHSWLKN (SEQ ID NO: 6361), GSGSPHSKAQM (SEQ ID NO: 6362), GSGSPHCPAQN (SEQ ID NO: 6363), GSGSPHSMCTN (SEQ ID NO: 6364), GSGSPHSPPDN (SEQ ID NO: 6365), GSGSPHSKRNY (SEQ ID NO: 6366), GSGSPHRWTQN (SEQ ID NO: 6367), GSGSPHSKACR (SEQ ID NO: 6368), GSGSPHPRKQN (SEQ ID NO: 6369), GSGSPHSKCSV (SEQ ID NO: 6370), GSGSPHSKARI (SEQ ID NO: 6371),

GSGSPHPFVQN (SEQ ID NO: 6372), GSGSPHSKLPK (SEQ ID NO: 6373), GSGSPHSKSEQ (SEQ ID NO: 6374), GSGSPHWVAQN (SEQ ID NO: 6375), GSGSPHSLYQN (SEQ ID NO: 6376), GSGSPHSKVRM (SEQ ID NO: 6377), GSGSPHCALQN (SEQ ID NO: 6378), GSGSPHSSCTN (SEQ ID NO: 6379), GSGSPHSKNSR (SEQ ID NO: 6380), GSGSPHSKRKR (SEQ ID NO: 6381), GSGSPHLCTQN (SEQ ID NO: 6382), GSGSPHSTCLN (SEQ ID NO: 6383), GSGSPHSYARN (SEQ ID NO: 6384), GSGSPHSKQRP (SEQ ID NO: 6385), GSGSPHSKRVV (SEQ ID NO: 6386), GSGSPHKSGQN (SEQ ID NO: 6387), GSGSPHSYYSN (SEQ ID NO: 6388), GSGSPHSLTCN (SEQ ID NO: 6389), GSGSPHSCQSN (SEQ ID NO: 6390), GSGSPHSKAKG (SEQ ID NO: 6391), GSGSPHSKPQN (SEQ ID NO: 6392), GSGSPHFPFQN (SEQ ID NO: 6393), GSGSPHSKCTS (SEQ ID NO: 6394), GSGSPHSVFEN (SEQ ID NO: 6395), GSGSPHSKAKK (SEQ ID NO: 6396), or GSGSPHGRYQN (SEQ ID NO: 6397);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i)

306. The AAV particle of any one of embodiments 300-305, wherein [A]-[B] does not comprise the amino acid sequence of GSGSPHSKAQN (SEQ ID NO: 6251).

307. The AAV particle of any one of embodiments 300-306, wherein the AAV capsid variant comprises one, two, or all of an amino acid other than Q at position 458 (e.g., R, C, S, W, L, F, Y, H, I, V, A, or P), an amino acid other than Q at position 459 (e.g., K, I, R, L or S), and/or an amino acid other than T at position 460 (e.g., R), numbered according to SEQ ID NO: 138.

308. The AAV particle of any one of embodiments 300-307, wherein the AAV capsid variant comprises:

(i) the amino acid R at position 458;

(ii) the amino acid W at position 458;

(iii) the amino acid Y at position 458;

(iv) the amino acid F at position 458;

(v) the amino acid S at position 458;

(vi) the amino acid C at position 458;

(vii) the amino acid I at position 458;

(viii) the amino acid L at position 458;

(ix) the amino acid P at position 458;

(x) the amino acid I at position 459;
(xi) the amino acid H at position 458; or
(xii) the amino acid V at position 458;
wherein (i)-(xii) are numbered according to SEQ ID NO: 138.

309. The AAV particle of any one of embodiments 300-307, wherein the AAV capsid variant comprises:

(i) the amino acid R at position 458 and the amino acid K at position 459;
(ii) the amino acid C at position 458 and the amino acid I at position 459;
(iii) the amino acid S at position 458 and the amino acid R at position 459;
(iv) the amino acid L at position 458 and the amino acid K at position 459;
(v) the amino acid F at position 458 and the amino acid K at position 459;
(vi) the amino acid C at position 458 and the amino acid R at position 459;
(vii) the amino acid H at position 458 and the amino acid R at position 459;
(viii) the amino acid I at position 458 and the amino acid L at position 459;
(ix) the amino acid V at position 458 and the amino acid R at position 459;
(x) the amino acid A at position 458 and the amino acid K at position 459;
(xi) the amino acid I at position 458 and the amino acid K at position 459;
(xii) the amino acid C at position 458 and the amino acid S at position 459; or
(xiii) the amino acid C at position 458 and the amino acid L at position 459
wherein (i)-(xiii) are numbered according to SEQ ID NO: 138.

310. The AAV particle of any one of embodiments 300-307, wherein the AAV capsid variant comprises the amino acid F at position 458, the amino acid K at position 459, and the amino acid R at position 460, numbered according to SEQ ID NO: 138.

311. The AAV particle of any one of embodiments 300-310, wherein the AAV capsid variant comprises one, two, or all of an amino acid other than T at position 450 (e.g., Y, P, W, R, K, S, or F), an amino acid other than I at position 451 (e.g., R, S, Y, L, V, H, P, A, or F), and/or an amino acid other than N at position 452 (e.g., V, W, A, T, F, Y, L, R, H, S, or M), numbered according to SEQ ID NO: 138.

312. The AAV particle of any one of embodiments 300-311, wherein the AAV capsid variant comprises the amino acid V at position 452, numbered according to SEQ ID NO: 138.

313. The AAV particle of any one of embodiments 300-312, wherein the AAV capsid variant comprises the amino acid Y at position 450 and the amino acid V at position 452, numbered according to SEQ ID NO: 138.

314. The AAV particle of any one of embodiments 300-312, wherein the AAV capsid variant comprises the amino acid R at position 450 and the amino acid Y at position 451, numbered according to SEQ ID NO: 138.

315. The AAV particle of any one of embodiments 300-311, wherein the AAV capsid variant comprises:

(i) the amino acid P at position 450, the amino acid R at position 451, and the amino acid W at position 452;

(ii) the amino acid Y at position 450, the amino acid S at position 451, and the amino acid A at position 452;

(iii) the amino acid Y at position 450, the amino acid Y at position 451, and the amino acid T at position 452;

(iv) the amino acid P at position 450, the amino acid R at position 451, and the amino acid F at position 452;

(v) the amino acid W at position 450, the amino acid L at position 451, and the amino acid T at position 452;

(vi) the amino acid R at position 450, the amino acid S at position 451, and the amino acid Y at position 452;

(vii) the amino acid Y at position 450, the amino acid V at position 451, and the amino acid F at position 452;

(viii) the amino acid K at position 450, the amino acid H at position 451, and the amino acid L at position 452;

(ix) the amino acid P at position 450, the amino acid P at position 451, and the amino acid L at position 452;

(x) the amino acid P at position 450, the amino acid A at position 451, and the amino acid R at position 452;

(xi) the amino acid S at position 450, the amino acid R at position 451, and the amino acid R at position 452;

(xii) the amino acid F at position 450, the amino acid F at position 451, and the amino acid H at position 452;

(xiii) the amino acid R at position 450, the amino acid F at position 451, and the amino acid S at position 452;

(xiv) the amino acid Y at position 450, the amino acid S at position 451, and the amino acid M at position 452; or

(xv) the amino acid P at position 450, the amino acid F at position 451, and the amino acid L at position 452;

wherein (i)-(xv) is numbered according to SEQ ID NO: 138.

316. The AAV particle of any one of embodiments 300-315, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3849-3982, 2984-4010, 4681-4693;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

317. The AAV particle of any one of embodiments 300-316, wherein the AAV capsid variant does not comprise the amino acid sequence of GSGSPHSKAQNQQ (SEQ ID NO: 6415) or GSGSPHSKAQNQQT (SEQ ID NO: 200).

318. The AAV particle of any one of embodiments 300-317, wherein [A]-[B] is present in loop IV.

319. The AAV particle of any one of embodiments 300-318, wherein [A] is present immediately subsequent to position 452, numbered according to SEQ ID NO: 138 or 981.

320. The AAV particle of any one of embodiments 300-319, wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), numbered according to SEQ ID NO: 138 or 981.

321. The AAV particle of any one of embodiments 300-320, wherein [A] is present immediately subsequent to position 452, and wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), numbered according to SEQ ID NO: 138 or 981.

322. The AAV particle of any one of embodiments 300-321, wherein [B] is present immediately subsequent to [A].

323. The AAV particle of any one of embodiments 300-322, wherein [B] replaces positions 456 and 457 (e.g., Q456, N457), numbered according to SEQ ID NO: 138.

324. The AAV particle of any one of embodiments 300-323, wherein [A]-[B] replaces positions 453-457 (e.g., G453, S454, G455, Q456, N457), numbered according to SEQ ID NO: 138.

325. The AAV particle of any one of embodiments 300-324, wherein [A]-[B] is present immediately subsequent to position 452, and wherein [A]-[B] replaces positions 453-457 (e.g., G453, S454, G455, Q456, N457), numbered according to SEQ ID NO: 138.

326. The AAV particle of any one of embodiments 300-325, wherein the AAV capsid variant comprises, from N-terminus to C-terminus, [A][B].

327. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises at least one, at least two, at least three, or at least four (e.g., from 1-4 to 1-5) charged amino acid residues (e.g., acidic and/or basic amino acid residues) relative to SEQ ID NO: 138, which is present N-terminal to the amino acid sequence of SPH (e.g., within 1, 2, 3, 4, 5, or 6 amino acids from the start of the SPH amino acid sequence (e.g., within positions 450-455 numbered according to SEQ ID NO: 138)), optionally wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

328. The AAV particle of embodiment 327, wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

329. The AAV particle of embodiment 327 or 328, wherein the AAV capsid variant comprises less than four, less than three, less than two (e.g., two or one) charged amino acid residues (e.g., acidic and/or basic amino acid residues) relative to SEQ ID NO: 138.

330. The AAV particle of any one of embodiments 327-329, wherein the AAV capsid variant comprises one charged amino acid residues (e.g., an acidic or basic amino acid residue) relative to SEQ ID NO: 138, optionally at any one of positions 450-455 numbered relative to SEQ ID NO: 138.

331. The AAV particle of any one of embodiments 327-330, wherein the charged amino acid residue is an acidic amino acid (e.g., D or E).

332. The AAV particle of any one of embodiments 327-331, wherein the charged amino acid residue is a negatively charged amino acid (e.g., D or E).

333. The AAV particle of any one of embodiments 327-332, wherein the charged amino acid residue is D.

334. The AAV particle of any one of embodiments 327-333, wherein the charged amino acid residue is E.

335. The AAV particle of any one of embodiments 327-334, wherein the charged amino acid residue is a basic amino acid (e.g., K, R, or H).

336. The AAV particle of any one of embodiments 327-335, wherein the charged amino acid residue is a positively charged amino acid (e.g., K, R, or H).

337. The AAV particle of any one of embodiments 327-336, wherein the charged amino acid residue is H.

338. The AAV particle of any one of embodiments 327-337, wherein the charged amino acid residue is R.

339. The AAV particle of any one of embodiments 327-338, wherein the charged amino acid residue is K.

340. The AAV particle of any one of embodiments 327-339, wherein the AAV capsid variant comprises an acidic amino acid (e.g., E or D) and a basic amino acid (e.g., R, K, or H).

341. The AAV particle of any one of embodiments 327-340, wherein at least one, two, three or four charged amino acid residues is present within 1, 2, 3, 4, 5, or 6 (e.g., 1-6) amino acids from the start of the SPH amino acid sequence.

342. The AAV particle of any one of embodiments 327-341, wherein the AAV capsid variant comprises two charged amino acid residues immediately preceding the amino acid sequence of SPH (e.g., at positions 454 and 455, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982).

343. The AAV particle of any one of embodiments 327-342, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., E) within 1, 2, 3, 4, 5 (e.g., 5) amino acids from the start of the SPH amino acid sequence.

344. The AAV particle of any one of embodiments 327-343, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., E) at position 451, numbered according to any one of SEQ ID NO: 138, 981, or 982.

345. The AAV particle of any one of embodiments 327-344, wherein the AAV capsid variant comprises E at position 451, numbered according to any one of SEQ ID NOs: 138, 981, or 982.

346. The AAV particle of any one of embodiments 327-345, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., R or K) at position 452, numbered according to any one of SEQ ID NOs: 138, 981, or 982.

347. The AAV particle of any one of embodiments 327-346, wherein the AAV capsid variant comprises R at position 452, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

348. The AAV particle of any one of embodiments 327-347, wherein the AAV capsid variant comprises E at position 451 and R at position 452, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

349. The AAV particle of any one of embodiments 327-348, wherein the AAV capsid variant has decreased tropism for a liver cell or tissue, relative to the tropism of an AAV capsid comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981.

350. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises at least one, at least two, at least three, or at least four (e.g., from 1-4 to 1-5) charged amino acid residues (e.g., basic amino acid residues) relative to SEQ ID NO: 138, which is present C-terminal to the amino acid sequence of SPH (e.g., within 1, 2, 3, 4, 5, 6, or 7 amino acids from the end of the SPH amino acid sequence (e.g., within positions 459-465 numbered according to any one of SEQ ID NOs: 36-59, or 981)), optionally wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

351. The AAV particle of embodiment 350, wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

352. The AAV particle of embodiment 350 or 351, wherein the AAV capsid variant comprises less than four, less than three, less than two (e.g., two or one) charged amino acid residues (e.g., basic amino acid residues) relative to SEQ ID NO: 138.

353. The AAV particle of any one of embodiments 350-352, wherein the AAV capsid variant comprises one charged amino acid residues (e.g., a basic amino acid residue) relative to SEQ ID NO: 138, optionally at any one of positions 456-460 numbered relative to SEQ ID NO: 138 or at positions 462-466 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

354. The AAV particle of any one of embodiments 350-353, wherein the charged amino acid residue is a basic amino acid (e.g., R or K).

355. The AAV particle of any one of embodiments 350-354, wherein the charged amino acid residue is a positively charged amino acid (e.g., R or K).

356. The AAV particle of any one of embodiments 350-355, wherein the charged amino acid residue is R.

357. The AAV particle of any one of embodiments 350-355, wherein the charged amino acid residue is K.

358. The AAV particle of any one of embodiments 350-357, wherein at least one, two, three or four charged amino acid residues is present within 1, 2, 3, 4, 5, 6, 7 (e.g., 1-7) amino acids from the end of the SPH amino acid sequence.

359. The AAV particle of any one of embodiments 350-358, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., K or R) immediately after the SPH sequence (e.g., at position 459 numbered according to SEQ ID NO: 981).

360. The AAV particle of any one of embodiments 350-359, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., K or R) at position 459, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

361. The AAV particle of any one of embodiments 350-360, wherein the AAV capsid variant comprises K at position 459, numbered according to SEQ ID NO: 981.

362. The AAV particle of any one of embodiments 350-360, wherein the AAV capsid variant comprises R at position 459, numbered according to SEQ ID NO: 981.

363. The AAV particle of any one of embodiments 350-362, wherein the AAV capsid variant comprises a charged amino acid residue (e.g., R or K) at one, two three, four, five, or all of positions 460, 461, 462, 463, 464, and/or 465, numbered according to SEQ ID NO: 138 or 981.

364. The AAV particle of any one of embodiments 300-326 or 350-363, wherein the AAV capsid variant has increased tropism for a liver cell or tissue, relative to the tropism of an AAV capsid comprising the amino acid sequence of SEQ ID NO: 138.

365. The AAV particle of any one of embodiments 300-326 or 350-364, wherein the AAV capsid variant is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 150, 160, 170, 180, 190, or 200-fold, in the liver compared to an AAV capsid comprising SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

366. The AAV particle of any one of embodiments 300-326, 364, or 365, wherein the AAV capsid variant has reduced tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of an AAV capsid comprising the amino acid sequence of SEQ ID NO: 138.

367. The AAV particle of any one of embodiments 300-326 or 364-366, wherein the AAV capsid variant shows preferential transduction in a liver region relative to the transduction in the brain and/or dorsal root ganglia (DRG).

368. The AAV particle of any one of embodiments 300-326 or 364-367, wherein the AAV capsid variant shows preferential transduction in a liver region relative to the transduction in the heart and/or muscle (e.g., quadriceps).

369. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any of the sequences provided in Table 1, 2A, 2B, or 18-24;

(b) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, or at least 17 consecutive amino acids from any one of the sequences provided in Table 1, 2A, 2B, or 18-24; or

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to any one of the sequences provided in Table 1, 2A, 2B, or 18-24; or

(d) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of the sequences provided in Table 1, 2A, 2B, or 18-24.

370. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986;

(b) an amino acid sequence comprising at least 3, at least 4, or at least 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986; or

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986;

(d) an amino sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986.

371. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(b) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or

(d) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

372. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693;

(b) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16 or at least 17 consecutive amino acids from any one of SEQ ID NOs: 3849-4051 or 4681-4693;

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693; or

(d) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693.

373. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any one of SEQ ID NOs: 4052-4092;

(b) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16 or at least 17 consecutive amino acids from any one of SEQ ID NOs: 4052-4092;

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092; or

(d) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092.

374. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises:

(a) the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(b) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16 or at least 17 consecutive amino acids from any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(c) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097; or

(d) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097.

375. The AAV particle of embodiment 369 or 371, wherein the AAV capsid variant comprises an amino acid sequence comprising at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

376. The AAV particle of any one of embodiments 369-374, wherein the at least 3 consecutive amino acids comprise SPH.

377. The AAV particle of any one of embodiments 369-371 or 376, wherein the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700).

378. The AAV particle of any one of embodiments 369-371, 376, or 377, wherein the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701).

379. The AAV particle of any one of embodiments 369-371 or 376-378, wherein the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941).

380. The AAV particle of embodiment 369-371, wherein the at least 3 consecutive amino acids comprise HDS.

381. The AAV particle of any one of embodiments 369-371 or 380, wherein the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702).

382. The AAV particle of any one of embodiments 369-371, 380, or 381, wherein the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703).

383. The AAV particle of any one of embodiments 369-371 or 380-382, wherein the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2).

384. The AAV particle of any one of embodiments 369-371, wherein:

(i) the at least 3 consecutive amino acids comprise SPH;

(ii) the at least 4 consecutive amino acids comprise SPHK (SEQ ID NO: 6398);

(iii) the at least 5 consecutive amino acids comprise SPHKY (SEQ ID NO: 4715); and/or

(iv) the at least 6 consecutive amino acids comprise SPHKYG (SEQ ID NO: 966).

385. The AAV particle of embodiment 369 or 371, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

386. The AAV particle of any one of embodiments 369, 371, or 385, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

387. The AAV particle of any one of embodiments 369, 371, or 385, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

388. The AAV particle of any one of embodiments 369-371, 384, or 385, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966).

389. The AAV particle of embodiment 370, wherein the AAV capsid variant comprises:

(i) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications, relative to the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589);

(ii) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications, relative to the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754)

(iii) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications, relative to the amino acid sequence of KTEKMSGSPHSKAQNQQT (SEQ ID NO: 3241);

(iv) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications, relative to the amino acid sequence of KTINGHDSPHSKAQNLQT (SEQ ID NO: 4100); or

(v) an amino acid sequence comprising at least one, at least two, or at least three but no more than four modifications, relative to the amino acid sequence of KTVNGHDSPHSKAQNQQT (SEQ ID NO: 4062).

390. The AAV particle of embodiment 369 or 371, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four

different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

391. The AAV particle of any one of embodiments 369, 371, or 390, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

392. The AAV particle of any one of embodiments 369, 371, or 390, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

393. The AAV particle of any one of embodiments 369, 371, 384, or 390, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966).

394. The AAV particle of embodiment 369, wherein the AAV capsid variant comprises:

(i) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589);

(ii) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754);

(iii) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of KTEKMSGSPHSKAQNQQT (SEQ ID NO: 3241);

(iv) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of KTINGHDSPHSKAQNLQT (SEQ ID NO: 4100); or

(v) an amino acid sequence comprising at least one, at least two, or at least three but no more than four different amino acids relative to the amino acid sequence of KTVNGHDSPHSKAQNQQT (SEQ ID NO: 4062).

395. The AAV particle of any one of embodiments 1-129, 269, 271, 375-388, or 390-394, wherein the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

396. The AAV particle of any one of embodiments 295-297, 301-305, 313, 314, 318, 319, or 323, wherein the AAV capsid variant comprises the amino acid sequence of ERVSGSPHSKA (SEQ ID NO: 6399), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N542, G453, S454, G455), numbered according to SEQ ID NO: 138.

397. The AAV particle of any one of embodiments 369-371, 375-379, 385, 386, 389-391, or 394-396, wherein the AAV capsid variant comprises the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

398. The AAV particle of any one of embodiments 269-371, 375, 380-383, 385, 387, 389, 390, 393, or 394, wherein the AAV capsid variant comprises the amino acid sequence of AEIGHDSPHKSG (SEQ ID NO: 6400), optionally wherein the amino acid sequence is present immediately subsequent to position 449 and replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

399. The AAV particle of any one of embodiments 369-371, 375, 380-383, 385, 387, 389, 390, 393, 394, or 398, wherein the AAV capsid variant comprises the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

400. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of EKMSGSPHSKA (SEQ ID NO: 6401), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

401. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of KTEKMSGSPHSKAQNQQT (SEQ ID NO: 3241), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

402. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of HDSPHSKAQNL (SEQ ID NO: 6402), optionally wherein the amino acid sequence is present immediately subsequent to position 453 and replaces positions 456-458 (e.g., Q456, N457, Q458), numbered according to SEQ ID NO: 138.

403. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of KTINGHDSPHSKAQNLQT (SEQ ID NO: 4100), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

404. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of VNGHDSPHSKA (SEQ ID NO: 6403), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

405. The AAV particle of any one of embodiments 369-371, 375-379, 390, 391, or 395, wherein the AAV capsid variant comprises the amino acid sequence of KTVNGHDSPHSKAQNQQT (SEQ ID NO: 4062), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

406. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, or 395, wherein the AAV capsid variant comprises an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942.

407. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, or 395, wherein the

AAV capsid variant comprises an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

408. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, or 406, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942.

409. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, or 407, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

410. The AAV particle of any one of embodiments 369-409, wherein the amino acid sequence is present in loop IV, e.g., relative to the amino acid sequence of SEQ ID NO: 138.

411. The AAV particle of any one of embodiments 369-410, wherein the amino acid sequence is present immediately subsequent to position 448, 449, 450, 451, 452, 453, 454, or 455, numbered according to SEQ ID NO: 138.

412. The AAV particle of any one of embodiments 369-411, wherein the amino acid sequence replaces amino acids 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, and/or 460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and/or T460), numbered according to SEQ ID NO: 138.

413. The AAV particle of any one of embodiments 369-412, wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

414. The AAV particle of any one of embodiments 369-413, wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138.

415. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, or 410-413, wherein the AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, according to SEQ ID NO: 138.

416. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, or 415, wherein the AAV capsid variant the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 981.

417. The AAV particle of embodiment 415 or 416, wherein the AAV capsid variant further comprises an amino acid other than I at position 451, an amino acid other than N at position 452, and an amino acid other than G at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

418. The AAV particle of any one of embodiments 415-417, wherein the AAV capsid variant further comprises E at position 451, R at position 452, and V at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

419. The AAV particle of any one of embodiments 415-418, wherein the AAV capsid variant further comprises the substitutions I451E, N452R, and G453V, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

420. The AAV particle of any one of embodiments 415-419, wherein the AAV capsid variant comprises:

(i) E at position 451, R at position 452, and V at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to any one of SEQ ID NOs: 36, 138, or 981 (at amino acids 456-461, 36 or 981).

421. The AAV particle of embodiment 415 or 416, wherein the AAV capsid variant further comprises an amino acid other than I at position 451, an amino acid other than N at position 452, and/or G at position 453, numbered according to SEQ ID NO: 39 or 138.

422. The AAV particle of any one of embodiments 415, 416, or 421, wherein the AAV capsid variant further comprises E at position 451, K at position 452, and/or M at position 453, numbered according to SEQ ID NO: 138 or 39.

423. The AAV particle of any one of embodiments 415, 416, 421, or 422, wherein the AAV capsid variant further comprises the substitutions I451E, N452K, and G453M, numbered according to SEQ ID NO: 39 or 138.

424. The AAV particle of any one of embodiments 415, 416, or 421-423, wherein the AAV capsid variant comprises:

(i) E at position 451, K at position 452, and M at position 453, numbered according to SEQ ID NO: 39 or 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 39 or 138.

425. The AAV particle of embodiment 415 or 416, wherein the AAV capsid variant further comprises an amino acid other than S at position 454, an amino acid other than G at position 455, and/or Q at position 458, numbered according to SEQ ID NO: 138.

426. The AAV particle of any one of embodiments 415, 416, or 425, wherein the AAV capsid variant further comprises H at position 454, D at position 455, and/or L at position 458, numbered according to SEQ ID NO: 138.

427. The AAV particle of any one of embodiments 415, 416, 425, or 426, wherein the AAV capsid variant further comprises the substitutions S454H, G455D, and Q458L, numbered according to SEQ ID NO: 138.

428. The AAV particle of any one of embodiments 415, 416, or 425-427, wherein the AAV capsid variant comprises:

(i) H at position 454, D at position 455, and/or L at position 458, numbered according to SEQ ID NO: 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

429. The AAV particle of embodiment 415 or 416, wherein the AAV capsid variant further comprises an amino acid other than I at position 451, an amino acid other than S at position 454, and/or an amino acid other than G at position 455, numbered according to SEQ ID NO: 52 or 138.

430. The AAV particle of any one of embodiments 415, 416, or 429, wherein the AAV capsid variant further comprises V at position 451, H at position 454, and/or D at position 455, numbered according to SEQ ID NO: 52 or 138.

431. The AAV particle of any one of embodiments 415, 416, 429, or 430, wherein the AAV capsid variant further comprises the substitutions I451V, S454H, and/or G455D, numbered according to SEQ ID NO: 52 or 138.

432. The AAV particle of any one of embodiments 415, 416, or 429-431, wherein the AAV capsid variant comprises:

(i) V at position 451, H at position 454, and/or D at position 455, numbered according to SEQ ID NO: 52 or 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 52 or 138.

433. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, or 414, wherein the AAV capsid variant the amino acid sequence of HDSPHK (SEQ ID NO: 2),

wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 138.

434. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, or 433, comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982.

435. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433, or 434, wherein the AAV capsid variant the amino acid sequence of SPHKSG (SEQ ID NO: 946), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 982.

436. The AAV particle of any one of embodiments 369-435, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of HDSPHSKA (SEQ ID NO: 4486), which is present immediately subsequent to position 453; and

(ii) a deletion of amino acids SG at position 454 and 455;

wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

437. The AAV particle of any one of embodiments 369-436, wherein the AAV capsid variant comprises the amino acids HD at position 454 and 455, and further comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), which is present immediately subsequent to position 455, numbered relative to SEQ ID NO: 138.

438. The AAV particle of any one of embodiments 433-435, wherein the AAV capsid variant further comprises an amino acid other than T at position 450, an amino acid other than I at position 451, and an amino acid other than N at position 452, numbered according to SEQ ID NO: 138 or 982.

439. The AAV particle of any one of embodiments 433-435 or 438, wherein the AAV capsid variant further comprises A at position 450, E at position 451, and I at position 452, numbered according to SEQ ID NO: 138 or 982.

440. The AAV particle of any one of embodiments 433-435, 438, or 439, wherein the AAV capsid variant further comprises the substitutions T450A, I451E, and N452I, numbered according to SEQ ID NO: 138 or 982.

441. The AAV particle of any one of embodiments 433, 434, or 438-440, wherein the AAV capsid variant comprises:

(i) A at position 450, E at position 451, and I at position 452, numbered according to SEQ ID NO: 138 or 982; and

(ii) the amino acid sequence of HDSPHK (SEQ ID NO: 2), which is present immediately subsequent to positions 453, numbered according to SEQ ID NO: 138 or 982.

442. The AAV particle of any one of embodiments 1-22, 25-27, 31, 34-42, 45-50, 53-63, 69, 79, 83-86, 91-98, 102, 103, 110, 111, 118-129, 369-371, 384, 385, 390, 393, 395, 410-413, wherein the AAV capsid variant the amino acid sequence of SPHKYG (SEQ ID NO: 966), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 138.

443. An adeno-associated virus (AAV) particle comprising an AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982, wherein the AAV particle further comprises a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein).

444. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 981.

445. An adeno-associated virus (AAV) particle comprising an AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 37, and optionally further comprising:

(i) one, two, or all of an amino acid other than T at position 450, an amino acid other than I at position 541, and/or an amino acid other than N at position 452, numbered according to SEQ ID NO: 138 or 37;

(ii) one, two, or all of A at position 450, E at position 451, and/or I at position 452, numbered according to SEQ ID NO: 138 or 37;
wherein the AAV particle further comprises a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein).

446. An adeno-associated virus (AAV) particle comprising an AAV capsid variant comprising the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of any one of SEQ ID NO: 36, 38-55, 57, or 59, wherein the AAV particle further comprises a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein).

447. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant further comprises:

(i) a modification in loop I, II, VI and/or VIII; and/or

(ii) a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138.

448. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, not more than 20, or not more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138.

449. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than 30, not more than 20, or not more than 10 different amino acids relative to the amino acid sequence of SEQ ID NO: 138.

450. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: an amino acid sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 138.

451. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid sequence with at least 98% identity to SEQ ID NO: 138.

452. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises an amino acid sequence encoded by a sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 137.

453. The AAV particle of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant comprises a sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 137.

454. The AAV particle of any one of the preceding embodiments, wherein the AAV capsid variant comprises a VP1 protein, a VP2 protein, a VP3 protein, or a combination thereof.

455. The AAV particle of any one of embodiments 1-454, wherein the AAV capsid variant comprises the amino acid sequence corresponding to positions 138-742, e.g., a VP2, of SEQ ID NO: 981, 982, 36, or 4, or a sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

456. The AAV particle of any one of embodiments 1-455, wherein the AAV capsid variant comprises the amino acid sequence corresponding to positions 203-742, e.g., a VP3, of SEQ ID NO: 981, 982, 36, or 4, or a sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

457. The AAV particle of any one of embodiments 1-456, wherein the AAV capsid variant comprises an amino acid sequence corresponding to positions 138-736, e.g., a VP2, of SEQ ID NO: 138, or a sequence with at least 80% (e.g., at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 138.

458. The AAV particle of any one of embodiments 1-457, wherein the AAV capsid variant comprises an amino acid sequence . e.g., a VP3, of SEQ ID NO: with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 138.

459. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-458, wherein the AAV capsid variant comprises an amino acid sequence comprising at least 3,

at least 4, at least 5, or at least 6 consecutive amino acids from the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein:

(i) the at least 3 consecutive amino acids comprise SPH;

(ii) the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700);

(iii) the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701); or

(iv) the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941);

wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 981; (b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 981; (c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 981; or (d) an amino acid sequence with at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to any of the amino acid sequences in (a)-(c).

460. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-459, wherein the AAV capsid variant comprises an amino acid sequence comprising at least 3, at least 4, at least 5, or at least 6 consecutive amino acids from the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein:

(i) the at least 3 consecutive amino acids comprise SPH;

(ii) the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700);

(iii) the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701); or

(iv) the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941);

wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) to the amino acid sequence of SEQ ID NO: 981.

461. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-460, wherein the AAV capsid variant comprises one or two, but no more than three substitutions relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the AAV capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 981;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 981;

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 981; or

(d) an amino acid sequence with at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to any of the amino acid sequences in (a)-(c).

462. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-461, wherein the AAV capsid variant comprises one or two, but no more than three substitutions relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical to the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981.

463. The AAV particle of any one of embodiments 459-462, wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138 or 981.

464. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, or 447-458, wherein the AAV capsid variant an amino acid sequence comprising at least 3, at least 4, at least 5, or at least 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein:

(i) the at least 3 consecutive amino acids comprise HDS;

(ii) the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702);

(iii) the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); or

(iv) the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2);

wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982; (c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982; or (d) an amino acid sequence with at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to any of the amino acid sequences in (a)-(c).

465. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261,

264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464, wherein the AAV capsid variant comprises an amino acid sequence comprising at least 3, at least 4, at least 5, or at least 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein:

(i) the at least 3 consecutive amino acids comprise HDS;

(ii) the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702);

(iii) the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); or

(iv) the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2);

wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical to the amino acid sequence of SEQ ID NO: 982.

466. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464, or 465, wherein the AAV capsid variant comprises one or two, but no more than three substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982;

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982; or

(d) an amino acid sequence with at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to any of the amino acid sequences in (a)-(c).

467. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464-466, wherein the AAV capsid variant comprises one or two, but no more than three substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical to the amino acid sequence of SEQ ID NO: 982.

468. The AAV particle of any one of embodiments 464-468, wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138 or 982.

469. The AAV particle of any one of embodiments 1-468, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 981 or 982, or an amino acid sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%. at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

470. The AAV particle of any one of embodiments 1-469, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, not more than 20 or not more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981 or 982.

471. The AAV particle of any one of embodiments, 1-470, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three, but not more than 30, not more than 20 or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981 or 982.

472. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-471, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 981, or an amino acid sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

473. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-472, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, not more than 20 or not more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981.

474. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 240-247, 249, 250, 253-263, 266, 272-281, 286,

288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-473, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three, but not more than 30, not more than 20 or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981.

475. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464-471, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982, or an amino acid sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

476. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, or 475, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, not more than 20 or not more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 982.

477. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, 475, or 476, wherein the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two or at least three, but not more than 30, not more than 20 or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 982.

478. The AAV particle of any one of embodiments 1-477, wherein the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

479. The AAV particle of any one of embodiments 1-478, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NOs: 983 or 984, or a nucleotide

sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

480. The AAV particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, 469-474, 478, or 479, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

481. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, or 475-479, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

482. The AAV particle of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant is codon optimized.

483. An adeno-associated virus (AAV) particle of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, 469-474, 478-480, or 482, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 981.

484. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 981.

485. The AAV particle of embodiment 483 or 484, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence at least 90%, at least 95%, or at least 99% identical thereto.

486. The AAV particle of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, 475-479, 481, or 482, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 982.

487. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982.

488. The AAV particle of embodiment 486 or 487, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence at least 90%, at least 95%, or at least 99% identical thereto.

489. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NOs: 983 or 984, or a nucleotide sequence at least 95% identical thereto.

490. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 4 or 36-59, optionally wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 4 or 36.

491. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a nucleic acid encoding a frataxin (FXN) protein (e.g., a human FXN protein), wherein the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence at least 95% identical thereto.

492. The AAV particle of 490 or 491, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence at least 95% identical thereto.

493. The AAV particle of any one of embodiments 1-299, 369-371, or 375-492, which has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of an AAV particle comprising a capsid comprising the amino acid sequence of SEQ ID NO: 138.

494. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-493, which transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or at least 65-fold greater as compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2.

495. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-494, which transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or at least 65-fold greater as compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2.

496. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-495, which is enriched at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10-fold, in the brain compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1.

497. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-496, which is enriched at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80 or at least 85-fold, in the brain compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1.

498. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-497, which is enriched in the brain of at least two to at least three species, e.g., a non-human primate and rodent (e.g., mouse), e.g., as compared to an AAV particle comprising a capsid of SEQ ID NO: 138.

499. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-498, which is enriched at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, at least 100, at least 105, at least 115, at least 120, at least 125, at least 130, at least 135, at least 140, at least 145, at least 150, at least 155, at least 160, at least 165, at least 170, at least 175, at least 180, at least 190, at least 200, at least 205, or at least 210-fold, in the brain of at least two to at

least three species, e.g., a non-human primate and rodent (e.g., mouse), compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1 or 5.

500. The AAV particle of embodiment 498 or 499, wherein the at least two to at least three species are *Macaca fascicularis*, *Chlorocebus sabaeus*, *Callithrix jacchus*, and/or mouse (e.g., BALB/c mice, C57Bl/6 mice, and/or CD-1 outbred mice).

501. The AAV particle of any one of embodiments 130-146, 369, 410-414, 447-454, 457, 458, 482, or 493, which is enriched at least 2, at least 2.5, at least 3, at least 3.5, at least 4, at least 4.5, at least 5, at least 5.5, at least 6, at least 6.5, at least 7, at least 7.5, or at least 8-fold, in the brain compared to an AAV particle comprising a capsid of SEQ ID NO: 981, e.g., when measured by an assay as described in Example 3.

502. The AAV particle of any one of embodiments 147-167, 369, 410-414, 447-454, 457, 458, 482, or 493, which is enriched at least 2, at least 2.5, at least 3, at least 3.5, at least 4, at least 4.5, at least 5, or at least 5.5-fold, in the brain compared to an AAV particle comprising a capsid of SEQ ID NO: 982, e.g., when measured by an assay as described in Example 3.

503. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, or 375-500, which delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 10, at least 12, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, or at least 70-fold, as compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8).

504. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503, which delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, at least 10, at least 15, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50-fold, as compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8).

505. The AAV particle of embodiment 503 or 504, wherein the brain region is a midbrain region (e.g., the hippocampus or thalamus), frontal cortex, temporal cortex, motor cortex, cerebral cortex, caudate, putamen, dentate nucleus, substantia nigra, or the brainstem.

506. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-505, which is enriched at least 4, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35-fold, in the spinal cord compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1 or 8, optionally wherein the region of the spinal cord is a thoracic spinal cord region, cervical spinal cord region, C5 ventral horn region, lumbar spinal cord region, or L5 ventral horn region.

507. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-506, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

508. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-507, which shows preferential transduction in a brain region relative to the liver.

509. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-508, which shows preferential transduction in a brain region relative to the transduction in the heart.

510. The AAV particle of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-509, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG) and the heart.

511. The AAV particle of any one of the preceding embodiments, which is capable of transducing non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes).

512. The AAV particle of embodiment 511, wherein the non-neuronal cells comprise glial cells, oligodendrocytes (e.g., Olig2 positive oligodendrocytes), or astrocytes (e.g., Olig2 positive astrocytes).

513. The AAV particle of any one of the preceding embodiments, which is capable of transducing Olig2 positive cells, e.g., Olig2 positive astrocytes or Olig2 positive oligodendrocytes.

514. The AAV particle of any one of embodiments 369, 373, 447-454, 457, 458, or 482, which has increased tropism for a heart cell or tissue, e.g., a heart ventricle or heart atrium, relative to the tropism of an AAV particle comprising a capsid of SEQ ID NO: 138.

515. The AAV particle of any one of embodiments 369, 373, 447-454, 457, 458, 482, or 514, which is enriched at least 4, at least 5, at least 8, at least 10, at least 11, at least 12, at least 13, at least 14, at

least 18, at least 19, at least 20, at least 21, at least 22, at least 24, at least 25, at least 27, at least 31, at least 33, or at least 34-fold, in the heart compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

516. The AAV particle of any one of embodiments 369, 374, 447-454, 457, 458, 482, which has an increased tropism for a muscle cell or tissue (e.g., a quadriceps cell or a quadriceps tissue), relative to the tropism of an AAV particle comprising a capsid comprising the amino acid sequence of SEQ ID NO: 138.

517. The AAV particle of any one of embodiments 369, 374, 447-454, 457, 458, 482, which is enriched at least 4, at least 5, at least 8, at least 12, at least 17, at least 18, at least 20, at least 26, at least 27, at least 28, at least 30, or at least 36-fold, in the muscle compared to an AAV particle comprising a capsid of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

518. The AAV particle of embodiment 516 or 517, wherein the muscle cell or tissue is a heart muscle (e.g., a heart ventricle or a heart atrium, or both), a quadriceps muscle, or both.

519. The AAV particle of any one of the preceding embodiments, which is isolated and/or recombinant.

[Embodiments 520-585 are intentionally absent.]

586. The AAV particle of any one of the preceding embodiments, wherein the viral genome comprises a promoter operably linked to the FXN-encoding sequence (e.g., encoding human FXN protein).

587. The AAV particle of embodiment 586, wherein the promoter is human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA), CAG, CAG, FXN, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca2+/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof.

[Embodiments 588 and 589 are intentionally absent.]

590. The AAV particle of any one of embodiments 586-589, wherein the viral genome further comprises a polyadenylation (polyA) sequence.

591. The AAV particle of any one of embodiments 586-590, wherein the viral genome further comprises an inverted terminal repeat (ITR) sequence.

592. The AAV particle of any one of embodiments 586-591, wherein the viral genome comprises an ITR sequence positioned 5' relative to the FXN-encoding sequence (e.g., encoding human FXN protein).

593. The AAV particle of any one of embodiments 586-592, wherein the viral genome comprises an ITR sequence positioned 3' relative to the FXN-encoding sequence (e.g., encoding human FXN protein).

594. The AAV particle of any one of embodiments 586-593, wherein the viral genome comprises an ITR sequence positioned 5' relative to the FXN-encoding sequence (e.g., encoding human FXN protein) and an ITR sequence positioned 3' relative to the FXN-encoding sequence (e.g., encoding human FXN protein).

595. The AAV particle of any one of embodiments 586-594, wherein the viral genome further comprises an enhancer, a Kozak sequence, an intron region, and/or an exon region.

596. The AAV particle of any one of embodiments 586-594, wherein the viral genome further comprises a nucleotide sequence encoding a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the FXN protein encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.

597. The AAV particle of embodiment 596, wherein the encoded miRNA binding site is fully complementary or partially complementary to a miRNA expressed in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof.

598. The AAV particle of embodiment 596 or 597, wherein the encoded miR binding site modulates, e.g., reduces, expression of the encoded antibody molecule in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof.

599. The AAV particle of any one of embodiments 586-598, wherein the viral genome comprises at least 1-5 copies of the encoded miR binding site, e.g., at least 1, at least 2, at least 3, at least 4, or at least 5 copies.

600. The AAV particle of any one of embodiments 586-599, wherein the viral genome comprises at least 3 copies of an encoded miR binding sites, optionally wherein all three copies comprise the same miR binding site, or at least one, at least two, at least three, or all of the copies comprise a different miR binding site.

601. The AAV particle of embodiment 600, wherein the 3 copies of the encoded miR binding sites are continuous (e.g., not separated by a spacer).

[Embodiments 602-603 are intentionally absent.]

604. The AAV particle of any one of embodiments 596-601, wherein the encoded miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-1 binding site, a miR-142-3p, or a combination thereof,

optionally wherein the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1827, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto; or a nucleotide sequence having at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1827.

605. The AAV particle of any one of embodiments 586-604, wherein the viral genome comprises an encoded miR122 binding site.

606. The AAV particle of any one of embodiments 586-605, wherein the viral genome comprises at least 1-5 copies, e.g., 1, 2, or 3 copies of a miR122 binding site, optionally wherein each copy is continuous.

607. The AAV particle of embodiment 605 or 606, wherein the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1827, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto; or a nucleotide

sequence having at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1827.

608. The AAV particle of any one of embodiments 586-607, wherein the viral genome comprises an miR122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 1826.

[Embodiments 609-613 are intentionally absent.]

614. The AAV particle of any one of embodiments 586-608, wherein the viral genome is single stranded.

615. The AAV particle of any one of embodiments 586-613, wherein the viral genome self-complementary.

616. The AAV particle of any one of embodiments 586-615, wherein the viral genome further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

617. The AAV particle of any one of embodiments 586-615, wherein the AAV particle further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

618. The AAV particle of embodiment 616 or 617, wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

619. The AAV particle of any one of embodiments 586-618, wherein the viral genome further comprises a nucleic acid sequence encoding the AAV capsid variant of the AAV particle of any one of embodiments 1-519, 566, or 574.

620. The AAV particle of any one of embodiments 575-519, wherein the AAV particle is an isolated and/or recombinant AAV particle.

[Embodiment 621 is intentionally absent.]

622. A cell, e.g., a host cell, comprising the AAV particle of any one of the preceding embodiments.

623. The cell of embodiment 622, wherein the cell is a mammalian cell or an insect cell.

624. The cell of embodiment 622 or 623, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the brain stem, hippocampus, or thalamus.

625. The cell of any one of embodiments 622-624, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, oligodendrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

[Embodiment 626 is intentionally absent.]

627. A method of making an AAV particle, comprising

(i) providing a host cell comprising a viral genome; and

(ii) incubating the host cell under conditions suitable to encapsulate the viral genome in the AAV capsid variant as described in any one of embodiments 1-519, 566, or 574;

thereby making the AAV particle.

628. The method of embodiment 627, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the host cell.

629. The method of embodiment 628, wherein the host cell comprises a second nucleic acid encoding the capsid variant.

630. The method of embodiment 629, wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.

631. A pharmaceutical composition comprising the AAV particle of any one of embodiments 1-519, 566, or 574-620, and a pharmaceutically acceptable excipient.

632. A method of delivering FXN to a cell or tissue (e.g., a CNS cell or CNS tissue), comprising administering an effective amount of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620.

633. The method of embodiment 632, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, cerebellar cortex, cerebral cortex, brain stem, hippocampus, or thalamus.

634. The method of embodiment 632 or 633, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, or an oligodendrocyte.

[Embodiment 635 is intentionally absent.]

636. The method of any one of embodiments 632-634, wherein the cell or tissue is within a subject.

637. The method of embodiment 636, wherein the subject has, has been diagnosed with having, or is at risk of having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder.

638. The method of embodiment 636 or 637, wherein the subject has, has been diagnosed with having, or is at risk of having a neurological, e.g., a neurodegenerative disorder.

[Embodiment 639 is intentionally absent.]

640. The method of embodiment 636 or 637, wherein the subject has, has been diagnosed with having, or is at risk of having a muscular disorder or a neuromuscular disorder.

641. A method of treating a subject having or diagnosed with having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620.

642. A method of treating a subject having or diagnosed with having a neurological disorder, e.g., a neurodegenerative disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620.

643. A method of treating a subject having or diagnosed with having a muscular disorder or a neuromuscular disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620.

[Embodiment 644 is intentionally absent.]

645. The method of any one of embodiments 637-645, wherein the genetic disorder, neurological disorder, neurodegenerative disorder, muscular disorder, neuromuscular disorder, or neuro-oncological disorder is Friedreich's ataxia (FA).

646. The method of any one of embodiments 641-645, where treating comprises prevention of progression of the disease or disorder in the subject.

647. The method of embodiment 636-646, wherein the subject is a human.

648. The method of any one of embodiments 636-647, wherein the AAV particle is administered to the subject intravenously, via intra-cisterna magna injection (ICM), intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, intraarterially, or intramuscularly, or a combination thereof.

649. The method of any one of embodiments 636-648, wherein the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

650. The method of any one of embodiments 636-649, wherein the AAV particle is administered to the subject intravenously.

651. The method of any one of embodiments 636-650, wherein the AAV particle is administered to the subject via intra-cisterna magna injection (ICM).

652. The method of any one of embodiments 636-651, wherein the AAV particle is administered to the subject intracerebrally or intracerebroventricularly.

[Embodiment 653 is intentionally absent.]

654. The method of any one of embodiments 648-652, wherein administration of the AAV particle results in an increased presence, level, and/or activity of a frataxin gene, mRNA, protein, or a combination thereof.

655. The pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620 for use in a method of delivering a payload (e.g., a frataxin-encoding sequence) to a cell or tissue.

656. The pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620 for use in a method of treating a genetic disorder, a neurological disorder, a neurodegenerative disorder, a muscular disorder, or a neuromuscular disorder (optionally Friedreich's ataxia).

657. The pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620 for use in the manufacture of a medicament.

658. Use of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620 in the manufacture of a medicament.

659. Use of the pharmaceutical composition of embodiment 631 or the AAV particle of any one of embodiments 1-519, 566, or 574-620 in the manufacture of a medicament for treating a genetic disorder, a neurological disorder, or a neurodegenerative disorder, a muscular disorder, or a neuromuscular disorder (optionally Friedreich's ataxia).

660. The AAV particle, pharmaceutical composition, cell, method, or use of any one of the preceding embodiments, wherein the encoded frataxin protein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1824, or an amino acid sequence at least 70% (e.g., at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto.

661. The AAV particle, pharmaceutical composition, cell, method, or use of any one of the preceding embodiments, wherein the nucleotide sequence encoding the frataxin protein is at least 90% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to the nucleotide sequence of SEQ ID NO: 1824.

662. The AAV particle of embodiment 660 or embodiment 661, wherein the nucleotide sequence encoding the frataxin protein comprises a nucleotide sequence at least 95% identical to SEQ ID NO: 1824.

663. The AAV particle of any one of embodiments 660-662, wherein the nucleotide sequence encoding the frataxin protein comprises the nucleotide sequence of SEQ ID NO: 1824.

664. The AAV particle of any one of embodiments 660-662, wherein the nucleotide sequence encoding the frataxin protein consists of the nucleotide sequence of SEQ ID NO: 1824.

665. The AAV particle of any one of embodiments 660-664, wherein the AAV capsid variant comprises (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982; or (c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982; or wherein the AAV capsid variant is encoded by the nucleotide sequence of SEQ ID NO: 984 or a sequence at least 90% identical thereto.

666. The AAV particle of any one of embodiments 660-664, wherein the AAV capsid variant comprises no more than three amino acid substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 982.

667. The AAV particle of any one of the preceding embodiments, wherein viral genome further comprises a nucleic acid encoding a miR binding site that modulates, e.g., reduces, expression of the encoded FXN protein in a cell or tissue of the DRG, liver, hematopoietic lineage, or a combination thereof.

[Embodiments 668-671 are intentionally absent.]

663. The AAV particle of embodiment 586, wherein the promoter comprises a CMV promoter.

664. The AAV particle of embodiment 586, wherein the promoter comprises a CBA promoter.

[Embodiment 665 is intentionally absent.]

666. The AAV particle of embodiment 586, wherein the promoter is or comprises a truncated CBA promoter.

667. The AAV particle of embodiment 666, wherein the truncated CBA promoter is 100-332 nucleotides in length.

668. The AAV particle of embodiment 667, wherein the truncated CBA promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 1738, 1740, or 1742, or a nucleotide sequence that is at least 95% identical to any one of SEQ ID NOs: 1738, 1740, or 1742.

669. The AAV particle of embodiment 586, wherein the promoter comprises a truncated CMV promoter.

670. The AAV particle of embodiment 669, wherein the truncated CMV promoter is 109 nucleotides in length.

671. The AAV particle of any one of embodiment 670, wherein the truncated CMV promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1750 or a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1750.

672. The AAV particle of any one of embodiments 660-671, wherein the viral genome further comprises a miRNA (miR) binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the FXN protein encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.

673. The AAV particle of embodiment 672, wherein the miR binding site is fully or partially complementary to a miRNA expressed in a cell or tissue of the liver.

674. The AAV particle of embodiment 672 or embodiment 673, wherein the viral genome comprises at least 1, at least 2, at least 3, at least 4, or at least 5 copies of the miR binding site.

675. The AAV particle of embodiment 674, wherein the viral genome comprises at least 3 copies of the miR binding site, optionally wherein the viral genome has 3 copies of the miR binding site.

676. The AAV particle of embodiment 675, wherein the 3 copies of the miR binding site are continuous.

677. The AAV particle of any one of embodiments 672-676, wherein the viral genome comprises a miR-122 binding site.

678. The AAV particle of any one of embodiments 660-671, wherein the viral genome encodes at least 1-5 copies, e.g., at least 3 copies, of the miR-122 binding site.

679. The AAV particle of embodiment 678, wherein each copy of the miR-122 binding site is continuous, wherein, optionally, each copy of the miR-122 binding site comprises or consists of the nucleotide sequence of SEQ ID NO: 1827, wherein, further optionally, the viral genome comprises a miR122 binding site series comprising or consisting of the nucleotide sequence of SEQ ID NO: 1826.

680. The AAV particle of any one of embodiments 660-679, wherein the viral genome further comprises at least one inverted terminal repeat (ITR) region.

681. The AAV particle of embodiment 680, wherein the at least one ITR region is 141 nucleotides in length.

682. The AAV particle of embodiment 680 or embodiment 681, wherein the at least one ITR region is an AAV2 ITR.

683. The AAV particle of embodiment 680, wherein the viral genome comprises a 5' ITR region and/or a 3' ITR region, optionally wherein each of the 5'ITR and/or 3'ITR region is 141 nucleotides in length, further optionally wherein each of the 5'ITR and/or 3'ITR is an AAV2 ITR.

684. The AAV particle of any one of embodiments 660-683, wherein the viral genome further comprises an intron region.

685. The AAV particle of embodiment 684, wherein the intron region comprises an immediate-early 1 (ie1) intron region and/or a hemoglobin-beta (HB) intron region.

686. The AAV particle of any one of embodiments 660-685, wherein the viral genome further comprises an exon region.

687. The AAV particle of embodiment 686, wherein the exon region comprises an ie1 exon region and/or an HB exon region.

688. The AAV particle of any one of embodiments 660-687, wherein the viral genome further comprises a polyadenylation (polyA) region.

689. The AAV particle of embodiment 688, wherein the polyA region comprises a human growth hormone (hGH) polyA region.

690. The AAV particle of any one of embodiments 660-689, wherein the viral genome encodes a human frataxin protein.

691. The AAV particle of any one of embodiments 660-662, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 1797.

692. The AAV particle of any one of embodiments 660-662, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 1801.

693. The AAV particle of any one of embodiments 660-662, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 1808.

694. The AAV particle of any one of embodiments 660-662, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 1809.

695. The AAV particle of any one of embodiments 667-794, wherein the viral genome is single-stranded.

696. The AAV particle of any one of embodiments 667-794, wherein the viral genome is self-complementary.

696a. The AAV particle of any one of the preceding embodiments, comprising a viral genome that comprises:

(i) a promoter; and

(ii) a FXN protein-encoding sequence comprising the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NO: 1824.

696b. The AAV particle of embodiment 696a, wherein the viral genome further comprises a 5' inverted terminal repeat (ITR) and a 3' ITR.

696c. The AAV particle of embodiment 696b, wherein the viral genome comprises:

(i) a 5' ITR;

(ii) a promoter;

(iii) a FXN protein-encoding sequence comprising the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(iv) at least one miR-122 binding site; and

(v) a 3' ITR.

696d. The AAV particle of embodiment 696c, wherein the viral genome comprises:

(i) a 5' ITR;

(ii) a promoter;

(iii) an intron and/or exon region;

(iv) a FXN protein-encoding sequence comprising the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(v) at least one miR-122 binding site; and

(vi) a 3' ITR.

696e. The AAV particle of embodiment 696c, wherein the viral genome comprises:

(i) a 5' ITR;

(ii) a promoter;

(iii) an intron and/or exon region;

(iv) a FXN protein-encoding sequence comprising the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(v) at least one miR-122 binding site;

(vi) a polyadenylation (polyA) region; and

(vi) a 3' ITR.

696f. The AAV particle of embodiment 696e, wherein:

(i) the 5' ITR comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1742 or a sequence that is at least 90% identical thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical thereto;

(iv) the FXN protein-encoding region comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 80% identical thereto;

(v) the at least one miR-122 binding site comprises a miR-122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a sequence that is at least 90% identical thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical thereto; and/or

(vii) the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical thereto;

optionally wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1841 or a sequence that is at least 90% identical thereto, further optionally wherein the filler region is positioned 3' to the polyA region and 5' to the 3' ITR.

696g. The AAV particle of embodiment 696e, wherein:

(i) the 5' ITR comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1750 or a sequence that is at least 90% identical thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical thereto;

(iv) the FXN protein-encoding region comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 80% identical thereto;

(v) the at least one miR-122 binding site comprises a miR-122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a sequence that is at least 90% identical thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical thereto; and/or

(vii) the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical thereto;

optionally wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1840 or a sequence that is at least 90% identical thereto, further optionally wherein the filler region is positioned 3' to the polyA region and 5' to the 3' ITR.

696h. The AAV particle of embodiment 696e, wherein:

(i) the 5' ITR comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1738 or a sequence that is at least 90% identical thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical thereto;

(iv) the FXN protein-encoding region comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 80% identical thereto;

(v) the at least one miR-122 binding site comprises a miR-122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a sequence that is at least 90% identical thereto:

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical thereto; and/or

(vii) the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical thereto;

optionally wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1838 or a sequence that is at least 90% identical thereto, further optionally wherein the filler region is positioned 3' to the polyA region and 5' to the 3' ITR.

696i. The AAV particle of embodiment 696e, wherein:

(i) the 5' ITR comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1740 or a sequence that is at least 90% identical thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical thereto;

(iv) the FXN protein-encoding region comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 80% identical thereto;

(v) the at least one miR-122 binding site comprises a miR-122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a sequence that is at least 90% identical thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical thereto; and/or

(vii) the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical thereto;

optionally wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1839 or a sequence that is at least 90% identical thereto, further optionally wherein the filler region is positioned 3' to the polyA region and 5' to the 3' ITR.

697. An adeno-associated virus (AAV) particle comprising an AAV capsid variant and a viral genome, wherein the AAV capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to SEQ ID NO: 982;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 138-742 of SEQ ID NO: 982; and/or

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 982; and

wherein the viral genome encodes a frataxin protein and comprises the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1797.

698. An AAV particle comprising an AAV capsid variant and a viral genome, wherein the capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and/or

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and

wherein the viral genome encodes a frataxin protein and comprises the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1801.

699. An AAV particle comprising an AAV capsid variant and a viral genome, wherein the capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and/or

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and

wherein the viral genome encodes a frataxin protein and comprises the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1808.

700. An AAV particle comprising an AAV capsid variant and a viral genome, wherein the capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and/or

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or a nucleotide sequence that is at least 90% identical thereto; and

wherein the viral genome encodes a frataxin protein and comprises the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1809.

701. The AAV particle of any one of embodiments 697-700, wherein the AAV capsid variant comprises

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982;

(b) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982; and/or

(c) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982.

702. The AAV particle of embodiment 701, wherein the AAV capsid variant is encoded by the nucleotide sequence of SEQ ID NO: 984.

703. The AAV particle of any one of embodiments 660-702, further comprising a nucleic acid encoding a Rep protein, wherein the Rep protein comprises a Rep78 protein, a Rep68 protein, a Rep52 protein, and/or a Rep40 protein.

704. The AAV particle of embodiment 703, wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

705. A vector encoding the AAV particle of any one of embodiments 660-704.

706. A cell comprising the AAV particle of any one of embodiments 660-704 or the vector of embodiment 705.

707. The cell of embodiment 706, which is a mammalian cell, e.g., an HEK293 cell, an insect cell, e.g., an Sf9 cell, or a bacterial cell.

708. A method of making a recombinant AAV particle, the method comprising

(i) providing a host cell comprising a viral genome comprising any one of the nucleotide sequences of SEQ ID NOs: 1797, 1801, 1808, or 1809, or a nucleotide sequence at least 90% identical to any one of the nucleotide sequences of SEQ ID NOs: 1797, 1801, 1808, or 1809; and

(ii) incubating the cell under conditions suitable to encapsulate the viral genome in a capsid variant comprising the amino acid sequence of SEQ ID NO: 982;

thereby making the recombinant AAV particle.

709. The method of embodiment 708, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the cell.

710. The method of embodiment 708 or embodiment 709, wherein the cell comprises a second nucleic acid encoding the capsid variant.

711. The method of embodiment 708, further comprising introducing the second nucleic acid into the cell, optionally wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.

712. The method of any one of embodiments 708-711, wherein the cell comprises a mammalian cell, e.g., an HEK293 cell, an insect cell, e.g., an Sf9 cell, or a bacterial cell.

713. A pharmaceutical composition comprising the AAV particle of any one of embodiments 660-704 and a pharmaceutically acceptable excipient.

714. A method of delivering a FXN protein to a subject comprising administering an effective amount of the pharmaceutical composition of embodiment 713 or the AAV particle of any one of embodiments 660-704.

715. The method of embodiment 714, wherein the subject has, has been diagnosed with having, or is at risk of having Friedreich's Ataxia (FA).

716. A method of treating FA in a subject in need thereof comprising administering an effective amount of the pharmaceutical composition of embodiment 713 or the AAV particle of any one of embodiments 660-704.

717. The method of any one of embodiments 714-716, wherein the subject has a reduced level of FXN protein or gene expression as compared to a healthy individual.

718. The method of any one of embodiments 714-717, wherein the administration results in a 0.5-3x increase in the subject's FXN protein level as compared to baseline.

719. The method of any one of embodiments 714-718, wherein the administration results in amelioration of at least one symptom of FA.

720. The method of embodiment 719, wherein the at least one symptom of FA includes impaired sensory functions, impaired motor function, e.g., ataxia and/or involuntary movements, fatigue, chronic pain, seizures, impaired speech, sleep disturbances, metabolic disorders, e.g., diabetes, and increased spasticity.

721. The method of any one of embodiments 714-718, wherein the administration stabilizes, slows the progression of, or improves the subject's FA as determined by the modified Friedreich Ataxia Rating Scale (mFARS), the Scale for the Assessment and Rating of Ataxia (SARA), and/or the International Cooperative Ataxia Rating Scale (ICARS).

722. The method of any one of embodiments 714-718, wherein the administration slows the subject's progression of FA by 50% as measured by mFARS, SARA, or ICARS relative to a comparator group.

723. The method of any one of embodiments 714-722, wherein the subject is a human.

724. The method of any one of embodiments 714-723, wherein the AAV particle is administered to the subject intravenously, intracerebrally (IC), via intrathalamic (ITH) administration, intramuscularly, intrathecally, intracerebroventricularly, via intraparenchymal administration, via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration, or via intra-cisterna magna injection (ICM).

725. The method of any one of embodiments 714-724, wherein the AAV particle is delivered to a cell, tissue, or region of the CNS, e.g., a region of the brain or spinal cord, e.g., the parenchyma, the cortex, substantia nigra, caudate cerebellum, striatum, corpus callosum, cerebellum, brain stem caudate-putamen, thalamus, superior colliculus, the spinal cord, or a combination thereof.

726. The method of any one of embodiments 714-725, further comprising evaluating, e.g., measuring, the level of FXN expression, e.g., FXN gene, FXN mRNA, and/or FXN protein expression, in the subject, e.g., in a cell, tissue, or fluid, of the subject, optionally wherein the level of FXN protein is measured by an assay described herein, e.g., an enzyme-linked immunosorbent assay (ELISA), a Western blot, an immunohistochemistry assay, or a frataxin biofluid assay.

727. The method of embodiment 726, wherein measuring the level of FXN expression is performed prior to, during, or subsequent to treatment with the AAV particle.

728. The method of embodiment 726 or embodiment 727, wherein the cell or tissue is a cell or tissue of the central nervous system (e.g., parenchyma) or a peripheral cell or tissue (e.g., the liver, heart, and/or spleen).

729. The method of any one of embodiments 714-728, wherein the administration results in an increase in at least one, at least two, or all of:

(i) the level of FXN protein or gene expression in a cell, tissue, (e.g., a cell or tissue of the CNS, e.g., the cortex, striatum, thalamus, cerebellum, and/or brainstem), and/or fluid (e.g., CSF and/or serum), of the subject, wherein the level of FXN protein or gene expression is increased by 0.5-3x as compared to baseline; and/or

(ii) the level of viral genomes (VG) per cell in a CNS tissue (e.g., the cortex, striatum, thalamus, cerebellum, brainstem, and/or spinal cord) of the subject, optionally wherein the VG level is increased by greater than 50 VGs per cell, as compared to a peripheral tissue.

730. The method of any one of embodiments 714-729, further comprising administration of an additional therapeutic agent and/or therapy suitable for treating a disease associated with FXN deficiency, e.g., Friedreich's ataxia.

731. The method of embodiment 730, wherein the additional therapeutic agent comprises omaveloxolone or idebenone.

732. The pharmaceutical composition of embodiment 713 or the AAV particle of any one of embodiments 660-704 for use in the treatment of a disease associated with FXN deficiency, e.g., Friedreich's ataxia.

733. Use of an effective amount of the pharmaceutical composition of embodiment 713 or the AAV particle of any one of embodiments 660-704 in the manufacture of a medicament for the treatment of a disease associated with FXN deficiency, e.g., Friedreich's ataxia.

[066] The details of various aspects or embodiments of the present disclosure are set forth below. Other features, objects, and advantages of the disclosure will be apparent from the description and the claims. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the

same meaning as commonly understood by one of ordinary skill in the art in the field of this disclosure. In the case of conflict, the present description will control.

BRIEF DESCRIPTION OF THE DRAWINGS

[067] **FIG. 1** depicts biodistribution (VG/cell) in the motor cortex, frontal cortex, putamen, substantia nigra, dentate nucleus, cervical spinal cord ventral horn, DRG, liver, and heart in cynomolgus monkeys at 28 days post-IV injection of TTM-002.GBA_VG17-HA, AAV9.GBA_VG17-HA, or vehicle control.

[068] **FIG. 2** depicts mRNA expression of the GBA1 transgene in the motor cortex, frontal cortex, putamen, substantia nigra, dentate nucleus, cervical spinal cord ventral horn, DRG, liver, and heart in cynomolgus monkeys at 28 days post-IV injection of TTM-002.GBA_VG17-HA, AAV9.GBA_VG17-HA, or vehicle control.

[069] **FIGs. 3A-3D** depict frataxin expression and the number of vector genome per cell in the heart (FIG. 3A); cerebellum (FIG. 3B); lumbar and DRG (FIG. 3C); and liver (FIG. 3D).

[070] **FIG. 4A** is a graph showing the percentage of HA positive cells (percent of cells transduced by the indicated capsid variant) in the cortex in mice on the Y axis at the indicated doses on the X-axis (from highest dose to lowest dose: 1e14 vg/kg, 3.2e13 vg/kg, 1e13 vg/kg, 3.2e12 vg/kg, or 1e12 vg/kg) at 28 days post-intravenous administration of AAV particles comprising the TTM-002 or TTM-027 AAV capsid variant. **FIG. 4B** is a graph showing the mRNA transgene expression relative to the housekeeping gene in the brains of the mice on the Y axis at the indicated doses on the X-axis (from highest to lowest dose: 1e14 vg/kg, 3.2e13 vg/kg, 1e13 vg/kg, 3.2e12 vg/kg, or 1e12 vg/kg) at 28 days post-intravenous administration of AAV particles comprising the TTM-002 or TTM-027 AAV capsid variant.

[071] **FIG. 5A** is a graph showing the percentage of transduced cells having HA+ nuclei as measured by co-localization of nuclear H2B-HA staining and hematoxylin (%HA+ cells) in the indicated brain regions (temporal cortex, caudate, thalamus, or hippocampus) of African green monkeys. Measurements are at day 28 post-intravenous injection of AAV particles comprising the TTM-002 capsid variant or the AAV9 capsid control and a self-complementary genome encoding a histone 2B protein with an HA-tag at a dose of 1e13 VG/kg. **FIG. 5B** is a graph showing the percentage of HA+ cells among cells positive for the indicated marker (NeuN+ neurons, SM311+ Neurons, GFAP+ astrocytes, or Sox9+ astrocytes) in the indicated brain regions (temporal cortex, caudate, thalamus, or hippocampus) of African green monkeys. Measurements are at day 28 post-intravenous injection of AAV particles comprising the TTM-002 capsid variant and a self-complementary genome encoding a histone 2B protein with an HA-tag at a dose of 1e13 VG/kg. Plotted data in **FIGs. 5A-5B** represent one slice per monkey (n=2). Quantitative image analysis was performed on 1e3 to 1e5 cells according to region size. All P values are derived from an unpaired two-tailed t-test.

[072] **FIGs. 6A-6D** are a series of graphs showing tropism of TTM-001 and TTM-002 relative to the AAV9 control in the brain and liver at 28 days post-intravenous administration in mice at a dose of 1e13 VG/kg. **FIG. 6A** shows the viral genomes (VG)/diploid genomes (DG) in the brain for the AAV9 control, TTM-001, or TTM-002; **FIG. 6B** shows brain RNA (fold vs AAV9) for the AAV9 control, TTM-001, or TTM-002; **FIG. 6C** shows the VG/DG in the liver for the AAV9 control, TTM-001, or TTM-002; and **FIG. 6D** shows the liver RNA (fold vs AAV9) for the AAV9 control, TTM-001, or TTM-002. Each data point represents an individual mouse and all plotted values represent mean ± SD (n=3). P values are derived from an unpaired two-tailed t-test.

DETAILED DESCRIPTION

Overview

[073] Described herein, *inter alia*, are compositions comprising an AAV capsid variant for delivery of a FXN protein, e.g., a human FXN protein. The AAV capsid variants described herein have enhanced CNS tropism compared to other cells or tissues in the body, e.g., liver and/or the DRG.

[074] AAVs have proven to be useful as a biological tool due to their relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. Engineered adeno-associated virus (AAV) capsids with improved brain tropism represent an attractive solution to the limitations of CNS delivery. AAV-derived vectors are promising tools for clinical gene transfer because of their non-pathogenic nature, their low immunogenic profile, low rate of integration into the host genome, and long-term transgene expression in non-dividing cells. However, the transduction efficiency of naturally occurring AAVs in certain organs is too low for clinical applications, and capsid neutralization by pre-existing neutralizing antibodies may prevent treatment of a large proportion of patients. For these reasons, considerable efforts have been devoted to obtaining capsid variants with enhanced properties. Of many approaches tested so far, significant advances have resulted from directed evolution of AAV capsids using in vitro or in vivo selection of capsid variants created by capsid sequence randomization using either error-prone PCR, shuffling of various parent serotypes, or insertion of fully randomized short peptides at defined positions.

[075] The genome of the virus may be modified to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload. The genome of the virus may encode a FXN protein, and the viral particle comprising said genome may be delivered to a target cell, tissue, or organism. In some embodiments, the genome encodes a human FXN protein, e.g., a wildtype FXN protein.. In some embodiments, the target cell is a CNS cell. In some embodiments, the target tissue is a CNS tissue. In some embodiments, The target CNS tissue is brain tissue.

[076] Gene therapy presents an alternative approach for treating FA. AAVs are commonly used in gene therapy approaches as a result of a number of advantageous features. Without wishing to be bound by theory, it is believed in some embodiments, that expression vectors, e.g., an adeno-associated viral vector (AAVs) or AAV particle, e.g., an AAV particle described herein, can be used to administer and/or deliver a FXN protein (e.g., a human FXN protein), in order to achieve sustained, high concentrations, allowing for longer lasting efficacy, fewer dose treatments, broad biodistribution, and/or more consistent levels of the FXN protein, relative to a non-AAV therapy.

[077] Provided herein are compositions and methods with improved features compared to prior AAV-mediated enzyme replacement approaches, including (i) increased biodistribution throughout the CNS (e.g., the cortex, striatum, thalamus, cerebellum, brainstem, and/or spinal cord), (ii) elevated payload expression, e.g., FXN mRNA expression, in multiple brain regions (e.g., cortex, thalamus, and brain stem); and (iii) reduced biodistribution in the liver and/or DRG, of the subject.

[078] Also provided herein are compositions comprising an AAV capsid variant, e.g., an AAV wild-type AAV9, including (i) increased penetrance through the blood brain barrier following intravenous administration, (ii) wider distribution throughout the multiple brain regions, e.g., frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus, and/or (iii) elevated payload expression in multiple brain regions. Without being that these advantages may be due, in part, to the dissemination of the AAV capsid variants through the brain vasculature. In some embodiments, the AAV capsids described herein enhance the delivery of a payload to multiple regions of the brain including for example, the frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[079] Thus, the compositions and methods described herein can be used in the treatment of Friedreich's Ataxia (FA). In some embodiments, the disclosure provides an AAV particle comprising one of the AAV capsid variants disclosed herein and an AAV viral genome comprising a nucleotide sequence comprising a truncated promoter region and a sequence encoding a FXN protein (e.g., comprising the nucleotide sequence of any one of SEQ ID NOs: 1797, 1801, 1808, 1809) for use in treating FA.

I. Compositions

Adeno-associated viral (AAV) Particles

[080] AAVs have a genome of about 5,000 nucleotides in length and contain two open reading frames encoding the proteins responsible for replication (Rep) and the structural protein of the capsid (Cap). The open reading frames are flanked by two Inverted Terminal Repeat (ITR) sequences, which serve as the origin of replication of the viral genome. The wild-type AAV viral genome comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are important for

replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In some embodiments, with reference to the amino acid sequence of SEQ ID NO: 982, 36, or 4, VP1 comprises amino acids 1-742, VP2 comprises amino acids 138-742, and VP3 comprises amino acids 203-742. In other words, VP1 is the full-length capsid protein sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region are also changes to VP1 and VP2; however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid. While not wishing to be bound by theory, the AAV capsid typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3.

[081] The AAV particle typically requires a co-helper (*e.g.*, adenovirus) to undergo productive infection in cells. In the absence of such helper functions, the AAV virions essentially enter host cells but do not integrate into the cells' genome.

[082] AAV particles have been investigated for delivery of gene therapeutics because of several unique features. Non-limiting examples of the features include (i) the ability to infect both dividing and non-dividing cells; (ii) a broad host range for infectivity, including human cells; (iii) wild-type AAV has not been associated with any disease and has not been shown to replicate in infected cells; (iv) the lack of cell-mediated immune response against the particle, and (v) the non-integrative nature in a host chromosome thereby reducing potential for long-term genetic alterations. Moreover, infection with AAV particles has minimal influence on changing the pattern of cellular gene expression (Stilwell and Samulski *et al.*, Biotechniques, 2003, 34, 148, the contents of which are herein incorporated by reference in their entirety).

[083] Typically, AAV vectors for FXN protein delivery may be recombinant viral particles which are replication defective as they lack sequences encoding functional Rep and Cap proteins within the viral genome. In some cases, the replication defective AAV particles may lack most or all coding sequences and essentially only contain one or two AAV ITR sequences and a nucleic acid sequence encoding a FXN protein.

[084] In some embodiments, the AAV particles of the present disclosure may be introduced into mammalian cells.

[085] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles of the present disclosure can be packaged efficiently and can be used to successfully

infect the target cells at high frequency and with minimal toxicity.

[086] In other embodiments, AAV particles of the present disclosure may be used to deliver FXN protein to the central nervous system (see, *e.g.*, U.S. Pat. No. 6,180,613; the contents of which are herein incorporated by reference in their entirety) or to specific tissues of the CNS.

[087] It is understood that the compositions described herein may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

[088] In some embodiments, an AAV capsid variant disclosed herein comprises a modification in loop IV of AAV9. e.g., at positions between 449-460, e.g., at position 454 and/or 456, numbered relative to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, loop (e.g., loop IV) is used interchangeably herein with the term variable region (e.g., variable region IV), or VR (e.g., VR-IV). In some embodiments loop IV comprises positions 449-475 (e.g., amino acids KTINGSGQNQQTLKFSVAGPSNMAVQG (SEQ ID NO: 6404)), numbered according to SEQ ID NO: 138. In some embodiments loop IV comprises positions 449-460 (e.g., amino acids KTINGSGQNQQT (SEQ ID NO: 6405)), numbered according to SEQ ID NO: 138. In some embodiments, loop IV or variable region IV (VR-IV) is as described in DiMattia et al. "Structural Insights into the Unique Properties of the Adeno-Associated Virus Serotype 9," *Journal of Virology*, 12(86):6947-6958 (the contents of which are hereby incorporated by reference in their entirety), e.g., comprising positions 452-460 (e.g., NGSGQNQQT (SEQ ID NO: 4487)), numbered according to SEQ ID NO: 138.

[089] The AAV particles and payloads of the disclosure may be delivered to one or more target cells, tissues, organs, or organisms. In some embodiments, the AAV particles demonstrate enhanced tropism for a target cell type, tissue or organ. As a non-limiting example, the AAV particle may have enhanced tropism for cells and tissues of the central or peripheral nervous systems (CNS and PNS, respectively). In some embodiments, an AAV particle may, in addition, or alternatively, have decreased tropism for a cell-type, tissue or organ.

[090] In some embodiments, AAV particles are used as a biological tool due to a relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload.

[091] In some embodiments, the AAV particle is a recombinant AAV particle. In some embodiments, the wild-type AAV viral genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. In some embodiments, inverted terminal repeats (ITRs) cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. In some embodiments, an AAV viral genome comprises two ITR sequences. In some embodiments, the ITRs have a characteristic T-shaped hairpin structure defined by a self-

complementary region (145nt in wild-type AAV) at the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. In some embodiments, the double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[092] In some embodiments, the wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are used for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid polypeptide, e.g., an AAV capsid variant. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In some embodiments, for any one of the amino acid sequences of SEQ ID NO: 981 or 982, VP1 comprises amino acids 1-742, VP2 comprises amino acids 138-742, and VP3 comprises amino acids 203-742. In other words, VP1 is the full-length capsid sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region, are also changes to VP1 and VP2, however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid protein. While not wishing to be bound by theory, the AAV capsid protein typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3.

[093] AAV particles of the present disclosure may be produced recombinantly and may be based on AAV reference sequences. In addition to single-stranded AAV viral genomes (e.g., ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) viral genomes. scAAV viral genomes contain DNA strands that anneal together to form double-stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the transduced cell. In some embodiments, the AAV particle of the present disclosure is an scAAV. In some embodiments, the AAV particle of the present disclosure is an ssAAV.

[094] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV particles (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[095] As described herein, the AAV particles of the disclosure comprising an AAV capsid variant, and a viral genome, have enhanced tropism for a cell-type or a tissue, e.g., a CNS cell-type, region, or tissue.

AAV Capsid Variants

[096] Disclosed herein are AAV particles comprising an AAV capsid variant comprising one or more modifications (e.g., comprising one or more insertions and/or substitutions relative to a wildtype AAV capsid) for enhanced or improved transduction of a target tissue (e.g., cells, regions, and/or tissues of the CNS and/or PNS). In some embodiments, the one or more modifications comprises a peptide insertion and/or amino acid substitution relative to a wildtype AAV capsid. In some embodiments, the one or more modifications is present in a capsid protein of the AAV particle. In some embodiments, the one or more modification is present in a VP1, VP2, and/or VP3 protein of the AAV particle.

[097] In some embodiments, the one or more modifications (e.g., the peptide insertion relative to a wildtype AAV capsid) is in loop IV of the AAV capsid variant. In some embodiments, the AAV capsid variant is an AAV9 capsid variant.

[098] In some embodiments, the variant is an insertional variant. As used herein, the term "insertional variant" refers to a polypeptide comprising one or more amino acids inserted, e.g., "immediately adjacent" or "immediately subsequent" to a position in a reference amino acid sequence. "Immediately adjacent" or "immediately subsequent" to an amino acid refers to the insertion sequence being connected to either the alpha-carboxy or alpha-amino functional group of the amino acid. In some embodiments, the variant is a deletion variant. As used herein, the term "deletion variant" refers to a polypeptide comprising one or more amino acids removed from a reference amino acid sequence. In some embodiments, the variant is a substitution variant. As used herein, the term "substitution variant" refers to a polypeptide comprising one or more amino acid changes from a reference amino acid sequence. In some embodiments, the variant is an insertional variant and a substitution variant.

[099] In some embodiments, the one or more modifications in the AAV capsid may increase distribution of an AAV particle to a cell, region, or tissue of the CNS. The cell of the CNS may be, but is not limited to, neurons (e.g., excitatory, inhibitory, motor, sensory, autonomic, sympathetic, parasympathetic, Purkinje, Betz, etc.), glial cells (e.g., microglia, astrocytes, oligodendrocytes) and/or supporting cells of the brain such as immune cells (e.g., T cells). The tissue of the CNS may be, but is not limited to, the cortex (e.g., frontal, parietal, occipital, and/or temporal), thalamus, hypothalamus, striatum, putamen, caudate nucleus, hippocampus, entorhinal cortex, basal ganglia, or deep cerebellar nuclei.

[0100] In some embodiments, the one or more modifications may increase distribution of an AAV particle to the CNS (e.g., the cortex) after intravenous administration. In some embodiments, the one

or more modifications may increase distribution of an AAV particle to the CNS (e.g., the cortex) following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0101] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence as set forth in Table 1. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence as set forth in Table 2A or Table 2B. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence set forth in Table 20. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence as set forth in Table 21.

Table 1. Exemplary Sequences

Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:
GSGSPHSKAQNQQT	200	GSLHHDNHGQNQQT	385	GSVFGVPSGQNQQT	570	GSIAMTSHGQNQQT	755
GHDSPHKSGQNQQT	201	GIMARDSSGQNQQT	386	GSGLPDRNLQNQQT	571	GSPGVSPSGQNQQT	756
GSGSPHARMQNQQT	202	GVVHITNSGQNQQT	387	GSGTHNSAIQNQQT	572	GSGQNQQTGSSSRV	757
GSGSPHVKSQNQQT	203	GSGQNQHSAPFNQT	388	GSGMIIASMQNQQT	573	GSGQHLPLLGNQQT	758
GQDSPHKSGQNQQT	204	GSGQTSGLKQNQQT	389	GGITWTDSGQNQQT	574	GSDHSHRGGQNQQT	759
GSGSPHASRQNQQT	205	GSGQNQQTSLSNTA	390	GSGQNQQASGRQQT	575	GSGIVTKLGQNQQT	760
GSGSPHASRQNKQT	206	GSGQNQAVHNKSQT	391	GSGQNQQPHLKSLT	576	GSGQDVTKTGNQQT	761
GSGSPHVKIQNQQT	207	GVHTHLPSGQNQQT	392	GPPQHMTSGQNQQT	577	GSGQNQQSHGRIGT	762
GSGSPHSKAKNQQT	208	GHLTMHNSGQNHQT	393	GSGQNQQASLPSRT	578	GSGQNQQINHRSPT	763
GSGSPHKKNQNQQT	209	GSGSSSRPYQNQQT	394	GSGQIVSTQTNQQT	579	GSGDDSRVGQNQQT	764
GSGSPHVRMQNQQT	210	GILLATPSGQNQQT	395	GSGKGHSAGQNQQT	580	GSGQSTLKRINQQT	765
GSGSPHASRQKQQT	211	GSGQNAGSFPNQQT	396	GSGQNTRLQLGQQT	581	GSGSQHSKAQNQQT	766
GHSSPHRSGQNQQT	212	GSRDGIITVGQNQQT	397	GSVGSRPVGQNQQT	582	GSGQNQQHASSNNT	767
GMRTYHLSGQNQQT	213	GSLLISTSGQNQQT	398	GSSHTLALGQNQQT	583	GSRTYQVSGQNQQT	768
GSGSPHTRGQNQQT	214	GSGAMPSHGQNQQT	399	GMYEYSQSGQNQQT	584	GSGQNQGLLSSPQT	769
GSGIIPVSSQNQQT	215	GALVSPISGQNQQT	400	GNGQNQQHSILHGT	585	GSGGGLQHNQNQQT	770
GSEYGHKSGQNQQT	216	GSLSSHGVGQNQQT	401	GSGYNQPHLQNQQT	586	GSGQNQQTTAATRM	771
GRGQNVSSVHRQQT	217	GSGQNQQASLAMRT	402	GPLVNASSGQNQQT	587	GSGQNQRASILVQT	772
GSSHRFYGGQNQQT	218	GPGLGSHSGQNQQT	403	GSGQNQQVLTTART	588	GSGQNLGLLGAQQT	773
GYFVAAWSGQNQQT	219	GHDSQHKSGQNQQT	404	GSGQNQHSVHNDQT	589	GSLDLGRSGQNQQT	774
GSVLHSHAAQNQQT	220	GSGLTLSATQNQQT	405	GAGLIMHSGQNQQT	590	GNSQVKVSGQNQQT	775
GSGDLVVSTQNQQT	221	GSGQVVAHVGNQQT	406	GMGRHSASGQNQQT	591	GSSGSHQYGQNQQT	776
GSYGMAASGQNQQT	222	GSGLRTMTTQNQQT	407	GSHSQSGHGQNQQT	592	GSGQNQQQRDGTLT	777
GLNHFGASGQNQQT	223	GSGQVGRLLQNQQT	408	GSSTTIVSGQNHQT	593	GRGQHVSVANNQQT	778

GSTGSHSAGQNQHT	224	GSGQLSHQSVNQQT	409	GRHLVTASGQNQQT	594	GDSSSRISGQNQQT	779
GLAGHTVSGQNQQT	225	GSGDRYQTLQNQQT	410	GSGQNQQHANLNQT	595	GSGQNQQHSLSSQT	780
GIILGASSGQNQQT	226	GSGQNQQLKSSAQT	411	GSGSTHSKAQNQQT	596	GSLMDVHRGQNQQT	781
GSGVSTYNIQNQQT	227	GSGQNQYSIPVAQT	412	GSGQNKQMLSGNTT	597	GSIQYQSSGQNQQT	782
GSLVSVQTGQNQQT	228	GSGERLHLTQNQQT	413	GSGQVHNPTQNQQT	598	GLGSKNPSGQNQQT	783
GQSSPHRSGQNQQT	229	GSGHNQQVRTAPNT	414	GSGQNQQIPIIVIIQT	599	GSGQLVLTLQNQQT	784
GREYGHKSGQNQQT	230	GGLSIIVMSGQNQQT	415	GSLHAGLSGQNQQT	600	GSGQNQQTSQPLPG	785
GHTLTLSSGQNQQT	231	GSGQSHRDVLNQQT	416	GPAQHGTSGQNQQT	601	GSGQNQQNLGKLNT	786
GSITLIPSGQNQQT	232	GSGQNLAGRMDQQT	417	GEKAVTSSGQNQQT	602	GTTAHQPSGQNQQT	787
GSNGFTALGQNQQT	233	GSGQNQQTNRGNPM	418	GSGQNQQTMANGQR	603	GSGQNRAQIGTQQT	788
GSGHSSHSVQNQQT	234	GSGQSYQRDHNQQT	419	GSGSPHSKDQNQQT	604	GSGQYVHVSSNQQT	789
GSGIPQRSGKNQQT	235	GSLLSAGMGQNQHT	420	GSFSMGYGGQNQQT	605	GSGQNQQTAHAFNI	790
GSGDTLHMLQNQQT	236	GSGQNQQTAIYRNI	421	GSGTHLVSLQNQQT	606	GSGQNQRTMVATQT	791
GERHTVLSGQNQQT	237	GSGQNQQTSGTTNC	422	GSGQMQPHVQNQQT	607	GSGQNPIRGAMQQT	792
GSGMPQSHIQNQQT	238	GMTSHSVSGQNQQT	423	GSGQNQQVAGLNNT	608	GSGYVITGSQNQQT	793
GSGQLSGIGGNQQT	239	GSSQSTGYQPNQQT	424	GSSQNQQHDMRLRT	609	GRGPKQSNIQNQQT	794
GSGQNRKPASFAQT	240	GSLKPTTLGQNQQT	425	GPASLPISGQNQQT	610	GSGQNQQTMLGKPC	795
GSGSVSQLGQNQQT	241	GRMFSLGSGQNQQT	426	GSGQNQQPPLATRT	611	GSGQNQQVGSTVRT	796
GSDFLGTHGQNQQT	242	GSGQNQQTALGVKC	427	GSSRVPVSGQNQQT	612	GNVTTQKSGQNQQT	797
GQIVQNPSGQNQQT	243	GAMVSHSSGQNQQT	428	GSGQNQQTNLGHTT	613	GSGNPVSHLQNQQT	798
GSGTQIPSQQNQQT	244	GSGQNQQRNSDSVT	429	GSGQNQQLVSRVQT	614	GSLSHMESGQNQQT	799
GSGQNQQSAREGLT	245	GSGQSMTLHLNQQT	430	GPNSYPVSGQKQQT	615	GRAPTNLSGQNQQT	800
GSGLGMSTGQNQQT	246	GSGQVHQAEVNQQT	431	GHAHYQASGQNQQT	616	GSGQNQQTVMTARA	801
GSGLPVLSGQNQQT	247	GSGQNQSQNHLQQT	432	GSGQALLSTGNQQT	617	GSGMPASRLQNQQT	802
GSGHSIRTDQNQQT	248	GSLLTTASGQNQQT	433	GSGQLPRQMTNQQT	618	GVVRNHQSGQNQQT	803
GSGQSVQTVVNQQT	249	GSGLIRTAAQNQQT	434	GSGFPKSTEQNQQT	619	GSGQNQHSVQVRQT	804
GSGQNRAQSRFQQT	250	GSGQNQQTVSRQST	435	GSRETSLSGQNQQT	620	GSGQNTGHLTMQQT	805
GGGDLGRSSQNQQT	251	GSGQYANHGINQQT	436	GSGQNQQGTGVSHT	621	GSGQNQQYAGKILT	806
GGGTKMDSGQNQQT	252	GSRSTGPSGQNQQT	437	GSRTVPVYGQNQQT	622	GSGNPHVRNQNQQT	807
GSGSPHPSRQNQQT	253	GRGVQQKLQQNQQT	438	GSNAQSAHGQNQQT	623	GSGQNGGSSNRQQT	808
GSGQFTNAGMNQQT	254	GSGQNQQVHLSTGT	439	GAFHLAASGQNQQT	624	GSGQRLSQGVNHQT	809
GGRNGHTVGQNQQT	255	GSGQNQQLSAKSST	440	GSGQYRSSSDNQQT	625	GSGQNAHAKEGQQT	810
GSGFGPQTGQNQQT	256	GSGYKAARPQNQQT	441	GSGQVYISTPNQQT	626	GSSPAPNSGQNQQT	811
GRTDSHTSGQNQQT	257	GSAGISPSGQNQQT	442	GSGVSTQLLQNQQT	627	GLAHKTSSGQNQQT	812
GYEVLGSSGQNQQT	258	GSGQNRAHAFLQQT	443	GSGQLGLSVTNQQT	628	GSGQNQQTPGAHKT	813
GSVHLSVTGQNQQT	259	GSGLSGITMQNQQT	444	GSGSNMRLSQNQQT	629	GSGQNQQSLSGSFT	814

GFMSYKGSGQNQQT	260	GPGSAHSSGQNQQT	445	GSGQNLHSGLPQQT	630	GSGQNQQSTGTSRT	815
GNIAGSVSGQNQQT	261	GSSHTQALGQNQQT	446	GSSHTLALGQNKQT	631	GSGQNQQTVQSNLV	816
GSGSHRDVSQNQQT	262	GSGVHGVSSQNQQT	447	GSGQNQHSLPAHRT	632	GSGQNQQLGSRQCT	817
GGLGSMSSGQNQQT	263	GSSGRDMGGQNQQT	448	GSGQNQGTVYPNQT	633	GSGQNQYLRLELQT	818
GSGHLPQSAQNQQT	264	GERAFPTSGQNQQT	449	GSGQNQQPSLRQST	634	GSGQNQQTSPRLQT	819
GGVLVGGSGQNQQT	265	GGRIVSLSGQNQQT	450	GSGQNARLKDNQQT	635	GSGQNQQTTSSNMT	820
GTHPYTSSGQNQQT	266	GSGQNSYSHTSQQT	451	GHAGSTGSGQNQQT	636	GTASTYNSGQNQQT	821
GSGQNQQLKENRST	267	GLGYPGSSGQNQQT	452	GSGQALSSSGNQQT	637	GSGQNQQTMPQHKI	822
GSGQNQQTSPHNHT	268	GSGPQSHTGQNQQT	453	GSGASESHRQNQQT	638	GSGQSHLHTGNQQT	823
GSGTLYPQSQNQQT	269	GSGQNQQLSRDAST	454	GVGVITSSGQNQQT	639	GVKGVGHSGQNQQT	824
GSGQNQQSNWITKT	270	GSGQILHSVPNQQT	455	GSLYGQSLGQNQQT	640	GSGKVTKQSQNQQT	825
GSGYTSLFLQNQQT	271	GSGFHTDSRQNQQT	456	GSGQMSDVHGNQQT	641	GSGQNQQTALEKSL	826
GSGVMTHVLQNQQT	272	GSGQSHSLATNQQT	457	GSGQNQQHSSKATT	642	GSGYKDTYGQNQQT	827
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GTGSPHSKAQNHQ	1852	GSGSPHSKAQMPS	1962	GSGSPHSKWLLQQ	2072	GNGSPHSKAQNQE	2182
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GNGSPHSKAQNPL	1860	GSGSPHSKAQVPS	1970	GSGSPHSKSRRQQ	2080	GHDSPHKSGQNQL	2190
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GSGSPHSKGQNRQ	1863	GGGSPHSKAQYQH	1973	GSGSPHSKASKRQ	2083	GNGSPHKRGQNQQ	2193
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GHDSPHKSGQNHLT	3114	GHESPHKSGQNIQP	3155	HHDSPHKSGQNQQT	3197	GHDSPHKRGPDQQS	3158
GHDSPHKSGQYQHT	3115	GHDSPHKSVQNHLN	3156	GHDSPHKSGQTQQI	3198	GHDSPHKSGRDQKT	3200
GNDSPHKSVQNHQT	3116	GHDSPHKIGLDQQT	3157	GQDSPHKSGQNPLT	3199	GHDSPHKSVHNQQN	3201
GHDSPHKSVQNQHT	3118	GHDSPHKSGESQQT	3159	KTISKRGSPHSKAQNQQT	4098	KGLGGSGSPHSKAQNQQT	4099
KTINGHDSPHSKAQNLQT	4100	KTINGSGSPHSKTCIQQT	4196	KEIYGSGSPHSKAQNQQT	4292	KTINGSGSPHKRGQKQQT	4388
KTINGHDSPHSKAQNQQI	4101	KTINGSGSPHSKWLTQQT	4197	KELSGSGSPHSKAQNQQT	4293	KTINGSGSPHKRGQNQET	4389
KTINGSGSPHFTRQNQQT	4102	KTINGSGSPHSKWVVQQT	4198	KETIGSGSPHSKAQNQQT	4294	KTINGSGSPHKRGQNQLT	4390
KTINGSGSPHSLPWNQQT	4103	KTINGSGSPHSKYRLQQT	4199	KEVLGSGSPHSKAQNQQT	4295	KTINGSGSPHKRGRNQQT	4391
KTINGHDSPHSKAQNHQT	4104	KTINGSGSPHSKYSKQQT	4200	KFALGHDSPHKSGQKQQT	4296	KTINGSGSPHKSGGNQQT	4392
KTMNGHDSPHSKAQNQQT	4105	KTINGSGSPHSKYSRQQT	4201	KIINGHDSPHKSGQNLVL	4297	KTINGSGSPHKSGHNQET	4393
KPYKGSGSPHSKAQNQQT	4106	KTINGSGSPHSLKRNQQT	4202	KIINGHDSPHKSGQRNYT	4298	KTINGSGSPHKSGHNQLT	4394
KRLWGSGSPHSKAQNQQT	4107	KTINGSGSPHSLWFNQQT	4203	KIINGHDSPHSKAQNQQT	4299	KTINGSGSPHKSGHNQQN	4395
KRMRGSGSPHSKAQNQQT	4108	KTINGSGSPHSLWPNQQT	4204	KLNPGHDSPHKSGQTQQT	4300	KTINGSGSPHKSGLNQLT	4396
KRTYGSGSPHSKAQNQQT	4109	KTINGSGSPHSLWTNQQT	4205	KLNRGHDSPHKSGQNQQS	4301	KTINGSGSPHKSGPNQQT	4397
KTINCLRSPHSKAQNQQT	4110	KTINGSGSPHSMRRNQQT	4206	KLSSGHDSPHKSGQNQQN	4302	KTINGSGSPHKSGQGQQT	4398
KTINFSRSPHSKAQNQQT	4111	KTINGSGSPHSPCLNQQT	4207	KNINGHDSPHSKAQNQQT	4303	KTINGSGSPHKSGQHLQT	4399
KTINGLRSPHFKAQNQQT	4112	KTINGSGSPHSQWQNQQT	4208	KNNDGSGSPHSKAQNQQT	4304	KTINGSGSPHKSGQHQQT	4400
KTINGNRSPHNKAQNQQT	4113	KTINGSGSPHSRCANQQT	4209	KNVMGSGSPHSKAQNQQT	4305	KTINGSGSPHKSGQKHQT	4401
KTINGPRSPHYKAQNQQT	4114	KTINGSGSPHSRIRNQQT	4210	KPINGHDSPHKSGQNKLS	4306	KTINGSGSPHKSGQKQQS	4402
KTINGQASPHWKAQNQQT	4115	KTINGSGSPHSRKSNQQT	4211	KPINGHDSPHKSGQNLSS	4307	KTINGSGSPHKSGQNEQT	4403
KTINGRCSPHSKAQNQQT	4116	KTINGSGSPHSRLWNQQT	4212	KPINGHDSPHSKAQNQQT	4308	KTINGSGSPHKSGQNHQT	4404
KTINGRHSPHSKAQNQQT	4117	KTINGSGSPHSRRFNQQT	4213	KRINGHDSPHSKAQNQQT	4309	KTINGSGSPHKSGQNKQT	4405
KTINGRKSPHRKAQNQQT	4118	KTINGSGSPHSRRPNQQT	4214	KSCSGHDSPHKSGQNQQS	4310	KTINGSGSPHKSGQNKTS	4406

KTINGRLSPHWKAQNQQT	4119	KTINGSGSPHSRSCNQQT	4215	KSINGHDSPHKSGQNLAS	4311	KTINGSGSPHKSGQNQEA	4407
KTINGRLSPHYKAQNQQT	4120	KTINGSGSPHSRSKNQQT	4216	KSINGHDSPHKSGQNLFL	4312	KTINGSGSPHKSGQNQET	4408
KTINGRPSPHMKAQNQQT	4121	KTINGSGSPHSRTKNQQT	4217	KSINGHDSPHKSGQNLLM	4313	KTINGSGSPHKSGQNQKT	4409
KTINGRSSPHWKAQNQQT	4122	KTINGSGSPHSRWLNQQT	4218	KSINGHDSPHKSGQNLLQ	4314	KTINGSGSPHKSGQNQQI	4410
KTINGRWSPHSKAQNQQT	4123	KTINGSGSPHSSVCNQQT	4219	KSINGHDSPHKSGQNSLG	4315	KTINGSGSPHKSGQNQQR	4411
KTINGSGSPHAPCQNQQT	4124	KTINGSGSPHSSWRNQQT	4220	KSINGHDSPHKSGQNTLQ	4316	KTINGSGSPHKSGQNQRT	4412
KTINGSGSPHAWAQNQQT	4125	KTINGSGSPHSVCQNQQT	4221	KSINGHDSPHKSSSNQQT	4317	KTINGSGSPHKSGQNQYT	4413
KTINGSGSPHCMRQNQQT	4126	KTINGSGSPHSVLCNQQT	4222	KSINGHDSPHKYKLNQQT	4318	KTINGSGSPHKSGQRQQT	4414
KTINGSGSPHFCSQNQQT	4127	KTINGSGSPHSVRRNQQT	4223	KSINGSGSPHKSGQKQQT	4319	KTINGSGSPHKSGQSQQT	4415
KTINGSGSPHFLFQNQQT	4128	KTINGSGSPHSVSCNQQT	4224	KSINGSGSPHKSGQNQQT	4320	KTINGSGSPHKSGQYQRT	4416
KTINGSGSPHFWAQNQQT	4129	KTINGSGSPHSWALNQQT	4225	KSINGSGSPHSKAQGLST	4321	KTINGSGSPHKSGRNQQA	4417
KTINGSGSPHLCAQNQQT	4130	KTINGSGSPHSWITNQQT	4226	KSINGSGSPHSKAQLLGT	4322	KTINGSGSPHKSRHNQQT	4418
KTINGSGSPHLRYQNQQT	4131	KTINGSGSPHSWPMNQQT	4227	KSINGSGSPHSKTSWQQT	4323	KTINGSGSPHKSRQYQQT	4419
KTINGSGSPHLYYQNQQT	4132	KTINGSGSPHSWRSNQQT	4228	KSMNGHDSPHSKAQNQQT	4324	KTINGSGSPHRKAQAPGT	4420
KTINGSGSPHPLCQNQQT	4133	KTINGSGSPHSYFLNQQT	4229	KSTLGSGSPHSKAQNQHT	4325	KTINGSGSPHSKAAMKQT	4421
KTINGSGSPHRIRQNQQT	4134	KTINGSGSPHSYTYNQQT	4230	KSTLGSGSPHSKAQNQQN	4326	KTINGSGSPHSKAGRQQT	4422
KTINGSGSPHRLFQNQQT	4135	KTINGSGSPHSYWQNQQT	4231	KSTVGSGSPHSKAQTQQT	4327	KTINGSGSPHSKAGRTQT	4423
KTINGSGSPHSCGQNQQT	4136	KTINGSGSPHTLCQNQQT	4232	KTCKESGSPHSKAQNQQT	4328	KTINGSGSPHSKAKSNQT	4424
KTINGSGSPHSCLRNQQT	4137	KTINGSGSPHWLRQNQQT	4233	KTCKGSGSPHSKAQNQQT	4329	KTINGSGSPHSKALKTQT	4425
KTINGSGSPHSCLSNQQT	4138	KTINGSGSPHWPSQNQQT	4234	KTCKSSGSPHSKAQNQQT	4330	KTINGSGSPHSKAPRTQT	4426
KTINGSGSPHSCRLNQQT	4139	KTINGSGSPHYLRQNQQT	4235	KTDMGSGSPHSKAQNQQT	4331	KTINGSGSPHSKAQAART	4427
KTINGSGSPHSCSLNQQT	4140	KTINGSGSPHYTRQNQQT	4236	KTDNGIGSPHSKAQNQQT	4332	KTINGSGSPHSKAQAILT	4428
KTINGSGSPHSKACTLQT	4141	KTINGSLSPHLWAQNQQT	4237	KTEGGSGSPHSKAQNQQT	4333	KTINGSGSPHSKAQCRGT	4429
KTINGSGSPHSKAFRAQT	4142	KTINGSPSPHCQAQNQQT	4238	KTEHHSGSPHSKAQNQQT	4334	KTINGSGSPHSKAQGLRT	4430
KTINGSGSPHSKAIRKQT	4143	KTINGSRSPHLCAQNQQT	4239	KTEKDSGSPHSKAQNQQT	4335	KTINGSGSPHSKAQKGVL	4431
KTINGSGSPHSKAQASRT	4144	KTINGSRSPHWRAQNQQT	4240	KTELGHDSPHKRGQNQQT	4336	KTINGSGSPHSKAQKSNT	4432
KTINGSGSPHSKAQFELT	4145	KTINGSVSPHWLAQNQQT	4241	KTESVSGSPHSKAQNQQT	4337	KTINGSGSPHSKAQNNKF	4433
KTINGSGSPHSKAQIVIT	4146	KTINGTFSPHRKAQNQQT	4242	KTETNSGSPHSKAQNQQT	4338	KTINGSGSPHSKAQNRRT	4434
KTINGSGSPHSKAQLART	4147	KTINGWTSPHRKAQNQQT	4243	KTETYSGSPHSKAQNQQT	4339	KTINGSGSPHSKAQPKQT	4435
KTINGSGSPHSKAQLQRT	4148	KTINRGISPHSKAQNQQT	4244	KTEWLSGSPHSKAQNQQT	4340	KTINGSGSPHSKAQRAPT	4436
KTINGSGSPHSKAQNARR	4149	KTINTVRSPHSKAQNQQT	4245	KTFNGSGSPHKSGQNQQT	4341	KTINGSGSPHSKAQREHT	4437
KTINGSGSPHSKAQNCPR	4150	KTKLRSGSPHSKAQNQQT	4246	KTGLRHDSPHKSGQKQQT	4342	KTINGSGSPHSKAQRFGT	4438
KTINGSGSPHSKAQNMRR	4151	KTRLRSGSPHSKAQNQQT	4247	KTGLRHDSPHKSGQNQQS	4343	KTINGSGSPHSKAQRPCT	4439
KTINGSGSPHSKAQNRRV	4152	KWLLGSGSPHSKAQNQQT	4248	KTGVTHDSPHKSGQKQQT	4344	KTINGSGSPHSKAQRQAT	4440
KTINGSGSPHSKAQPSRT	4153	KWSQGSGSPHSKAQNQQT	4249	KTIDGHESPHSKAQNQQT	4345	KTINGSGSPHSKAQRQPT	4441
KTINGSGSPHSKAQQVKT	4154	KWYLGSGSPHSKAQNQQT	4250	KTIEGHDSPHKSGQTQQT	4346	KTINGSGSPHSKAQTKLT	4442

KTINGSGSPHSKAQQ VRT	4155	KYHSGSGSPHSKAQ NQQT	4251	KTIHGHDSPHSK AQNQQT	4347	KTINGSGSPHSK AQTTHT	4443
KTINGSGSPHSKAQR LKT	4156	KYLPGSGSPHSKAQ NQQT	4252	KTIHGHESPHSK AQNQQT	4348	KTINGSGSPHSK AQVQRT	4444
KTINGSGSPHSKAQR RAT	4157	KAINGGGSPHSKTQ NQQT	4253	KTIIGHDSPHKSG QNRSS	4349	KTINGSGSPHSK AQVVRT	4445
KTINGSGSPHSKAQR RGT	4158	KAINGHDSPHKRSPN QQT	4254	KTIIGHDSPHKSG QRLGT	4350	KTINGSGSPHSK AQWPNT	4446
KTINGSGSPHSKAQR RRT	4159	KAINGHDSPHKSFSP QQT	4255	KTIIGSGSPHKSG QNQQT	4351	KTINGSGSPHSK AQYPST	4447
KTINGSGSPHSKAQR TRT	4160	KAINGHDSPHKSGE NQQP	4256	KTIKGHDSPHKS GQNMLF	4352	KTINGSGSPHSK ARALQT	4448
KTINGSGSPHSKAQR VHT	4161	KAINGHDSPHKSGQ LART	4257	KTILGSGSPHSK AQNLQT	4353	KTINGSGSPHSK ARDQHT	4449
KTINGSGSPHSKAQT YRT	4162	KAINGHDSPHKSGQ NAFL	4258	KTINGCSSPHWK AQNQQT	4354	KTINGSGSPHSK ARFQQT	4450
KTINGSGSPHSKAQV RKT	4163	KAINGHDSPHKSGQ NAYT	4259	KTINGGGSTHSK AQNQQT	4355	KTINGSGSPHSK ARRTQT	4451
KTINGSGSPHSKARG RQT	4164	KAINGHDSPHKSGQ NFAS	4260	KTINGHDSPHKA GQSQQT	4356	KTINGSGSPHSK ARSLQT	4452
KTINGSGSPHSKARL CQT	4165	KAINGHDSPHKSGQ NLAS	4261	KTINGHDSPHKR GQNVPS	4357	KTINGSGSPHSK ARVIQT	4453
KTINGSGSPHSKARL KQT	4166	KAINGHDSPHKSGQ NLGS	4262	KTINGHDSPHKR GRSYQT	4358	KTINGSGSPHSK AWYLQT	4454
KTINGSGSPHSKARN SQT	4167	KAINGHDSPHKSGQ NLKF	4263	KTINGHDSPHKT GQNPPT	4359	KTINGSGSPHSK GGGQQT	4455
KTINGSGSPHSKARW VQT	4168	KAINGHDSPHKSGQ NLLK	4264	KTINGHDSPHSK AENQQT	4360	KTINGSGSPHSK GSRQQT	4456
KTINGSGSPHSKAVR WQT	4169	KAINGHDSPHKSGQ NLSR	4265	KTINGHDSPHSK ALSLQT	4361	KTINGSGSPHSK LQRQQT	4457
KTINGSGSPHSKAYT RQT	4170	KAINGHDSPHKSGQ NLSS	4266	KTINGHDSPHSK AQGQQT	4362	KTINGSGSPHSK MLRQQT	4458
KTINGSGSPHSKCQS QQT	4171	KAINGHDSPHKSGQ NSLG	4267	KTINGHDSPHSK AQHQQT	4363	KTINGSGSPHSK SSIKQT	4459
KTINGSGSPHSKFLR QQT	4172	KAINGHDSPHKSGQ NTLQ	4268	KTINGHDSPHSK AQIQQT	4364	KTINGSGSPHSK VRFQQT	4460
KTINGSGSPHSKFRF QQT	4173	KAINGHDSPHKSGQ NTSL	4269	KTINGHDSPHSK AQKQQT	4365	KTINGSGSPHSV VWNQQT	4461
KTINGSGSPHSKFRL QQT	4174	KAINGHDSPHKSGQ RLGT	4270	KTINGHDSPHSK AQNLSS	4366	KTINGSTSPHKL AQNQQP	4462
KTINGSGSPHSKFRR QQT	4175	KAINGHDSPHKSGQ RNYT	4271	KTINGHDSPHSK AQNPQT	4367	KTINRHDSPHKS GQRPST	4463
KTINGSGSPHSKGMK QQT	4176	KAINGHDSPHKSGQ RPST	4272	KTINGHDSPHSK AQNQET	4368	KTINRIMSPHSK AQNQQT	4464
KTINGSGSPHSKKLR QQT	4177	KAINGHDSPHKSGQ RPVT	4273	KTINGHDSPHSK AQNQHT	4369	KTINTARSPHSK AQNQQT	4465
KTINGSGSPHSKKRP QQT	4178	KAINGHDSPHKSGQ VPST	4274	KTINGHDSPHSK AQNQLT	4370	KTISGHDSPHSK AQNQQT	4466
KTINGSGSPHSKKSR QQT	4179	KAINGHDSPHKSLSN QQT	4275	KTINGHDSPHSK AQNQPT	4371	KTISGSGSPHKS GQNQQT	4467
KTINGSGSPHSKLYR QQT	4180	KAINGHDSPHKSVLS QQT	4276	KTINGHDSPHSK AQNQQA	4372	KTITGHDSPHKS GQRLGT	4468
KTINGSGSPHSKLYW QQT	4181	KAINGHDSPHKTLQ NQQT	4277	KTINGHDSPHSK AQNTGS	4373	KTITGSGSPHKS GQNQQT	4469
KTINGSGSPHSKPRM QQT	4182	KAINGHNSPHSKAQ NQQT	4278	KTINGHDSPHSK AQSQQT	4374	KTIYGHDSPHKS GQRLGT	4470
KTINGSGSPHSKRFP QQT	4183	KAINGLDSPHSKAQ NQQT	4279	KTINGHDSPHSK AQTQQT	4375	KTLNGHDSPHKS GQNLFL	4471
KTINGSGSPHSKRFR QQT	4184	KAINGSGSPHKSGQN QQT	4280	KTINGHDSPHSK AQYQQT	4376	KTLNGHDSPHKS GQNLSS	4472
KTINGSGSPHSKRPY QQT	4185	KAINGSGSPHSKAQG QQT	4281	KTINGHDSPHSK ARNQQT	4377	KTLSFHDSPHKS GQNQQS	4473
KTINGSGSPHSKRRM QQT	4186	KAINGSGSPHSKAQL SGT	4282	KTINGHDSPHSK LPGQQT	4378	KTSNGSGSPHSK AQNTMT	4474
KTINGSGSPHSKRSK QQT	4187	KAINGSGSPHSKAQN GSL	4283	KTINGHDSPHSK SPNQQT	4379	KTTNGHDSPHSK AQNQQT	4475
KTINGSGSPHSKRSR QQT	4188	KAINGSGSPHSKAQN SLL	4284	KTINGHESPHKS GQNAFL	4380	KTVNGGGSPHS KAQNQQT	4476
KTINGSGSPHSKRTM QQT	4189	KAINGSGSPHSKAVG LQT	4285	KTINGIGSPHSKA PNEQT	4381	KTVNGHDSPHK SGQNVSL	4477
KTINGSGSPHSKRTR QQT	4190	KAINGSGSPHSKSLL QQT	4286	KTINGQDSPHKS GQNLHM	4382	KTVNGHDSPHK SGQRPST	4478

KTINGSGSPHSKRVR QQT	4191	KAINGSGSPHSKSLP QQT	4287	KTINGRGSPHSK AQIGMT	4383	KTVNGHDSPHK SGQTQQA	4479
KTINGSGSPHSKRYI QQT	4192	KAINGSGSPHSKSTF QQT	4288	KTINGRGSPHSK AQNQVL	4384	KTVNGHESPHSK AQNQQT	4480
KTINGSGSPHSKRYN QQT	4193	KAITGHDSPHSKAQ NQQT	4289	KTINGRGSPHSK AQSPTT	4385	KTVNGSGSPHSK AQGLST	4481
KTINGSGSPHSKRYP QQT	4194	KDVMGSGSPHSKAQ NQQT	4290	KTINGRGSPHSK ATSFQT	4386	KTVNGSGSPHSK AQNVTS	4482
KTINGSGSPHSKRYS QQT	4195	KEIVGSGSPHSKAQN QQT	4291	KTINGSGSPHFV VQNQQT	4387	KTVPASGSPHSK AQNQQT	4483
NTINGSGSPHSKAIN QQT	4484	TTINGGGSPHSKAQN QQT	4485				

Table 2A. Exemplary Sequences

SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Nucleotide Sequence
941	SPHSKA	942	AGCCCACACAGCAAAGCA
943	HDSPHKSG	944	CACGACAGCCCACACAAAAGCGGA
2	HDSPHK	3	CACGACAGCCCACACAAA

Table 2B. Exemplary Sequences

Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:
SPIISKA	945	SPIIKKN	954	SPIIKTS	963	SPIITRG	972
SPHKSG	946	SPHVRM	955	SPHKTT	964	SPHVRG	973
SPHARM	947	SPHRKA	956	SPHKTY	965	SPHKRG	974
SPHVKS	948	SPHKFG	957	SPHKYG	966	SPHGAR	975
SPHASR	949	SPHKIG	958	SPHSKD	967	SPHRSG	976
SPHVKI	950	SPHKLG	959	SPHSKP	968	SPHKSA	977
SPHKSR	951	SPHSKL	960	SPHSRA	969	SPHSKR	978
SPHSLR	952	SPHSRG	961	SPHSSR	970	SPHFLR	979
SPHSKW	953	SPHSKS	962	SPHWKA	971	SPHVRR	980
STHASR	985	SQHKSG	986	HDSPHK	2	HDSPHSKA	4486

[0102] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence having the formula [N1]-[N2]-[N3], wherein [N2] comprises the amino acid sequence of SPH and [N3] comprises amino acids X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R. In some embodiments, X4 of [N2] is K. In some embodiments, X5 of [N2] is K.

[0103] In some embodiments, the AAV capsid variant comprises an amino acid sequence having the formula [N1]-[N2]-[N3], wherein: [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G; [N2] comprises the amino acid sequence of SPH; and [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R; wherein [N1]-[N2]-[N3] is present in hypervariable loop IV; and wherein the AAV capsid variant comprises an amino acid sequence at least 95% identical to the amino acid sequence corresponding to positions 203-736 of SEQ ID NO: 138.

[0104] In some embodiments, [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G. In some embodiments, X1 of [N1] is G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C. In some embodiments, X2 of [N1] is: S, V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q. In some embodiments, X3 of [N1] is: G, C, L, D, E, Y, H, V, A, N, P, or S. In some embodiments, [N1] comprises GS, SG, GH, HD, GQ, QD, VS, CS, GR, RG, QS, SH, MS, RN, TS, IS, GP, ES, SS, GN, AS, NS, LS, GG, KS, GT, PS, RS, GI, WS, DS, ID, GL, DA, DG, ME, EN, KN, KE, AI, NG, PG, TG, SV, IG, LG, AG, EG, SA, YD, HE, HG, RD, ND, PD, MG, QV, DD, HN, HP, GY, GM, GD, or HS. In some embodiments, [N1] comprises GS, SG, GH, or HD. In some embodiments [N1] is or comprises GSG, GHD, GQD, VSG, CSG, GRG, CSH, GQS, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GQV, GHN, GHP, or GHS. In some embodiments, [N1] is or comprises GSG. In some embodiments, [N1] is or comprises GHD. In some embodiments, [N1]-[N2] comprises SGSPH (SEQ ID NO: 4752), HDSPH (SEQ ID NO: 4703), QDSPH (SEQ ID NO: 4753), RGSPH (SEQ ID NO: 4754), SHSPH (SEQ ID NO: 4755), QSSPH (SEQ ID NO: 4756), DDSPH (SEQ ID NO: 4757), HESPH (SEQ ID NO: 4758), NYSPH (SEQ ID NO: 4759), VGSPH (SEQ ID NO: 4760), SCSPH (SEQ ID NO: 4761), LLSPH (SEQ ID NO: 4762), NGSPH (SEQ ID NO: 4763), PGSPH (SEQ ID NO: 4764), GGSPH (SEQ ID NO: 4765), TGSPH (SEQ ID NO: 4766), SVSPH (SEQ ID NO: 4767), IGSPH (SEQ ID NO: 4768), DGSPH (SEQ ID NO: 4769), LGSPH (SEQ ID NO: 4770), AGSPH (SEQ ID NO: 4771), EGSPH (SEQ ID NO: 4772), SASPH (SEQ ID NO: 4773), YDSPH (SEQ ID NO: 4774), HGSPH (SEQ ID NO: 4775), RDSPH (SEQ ID NO: 4776), NDSPH (SEQ ID NO: 4777), PDSPH (SEQ ID NO: 4778), MGSPH (SEQ ID NO: 4779), QVSPH (SEQ ID NO: 4780), HNSPH (SEQ ID NO: 4781), HPSPH (SEQ ID NO: 4782), or HSSPH (SEQ ID NO: 4783); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications relative to any one of the aforesaid amino acid sequences; or an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695), GHDSPH (SEQ ID NO: 4784), GQDSPH (SEQ ID NO: 4785), VSGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791), GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807),

LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications relative to any one of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695). In some embodiments, [N1]-[N2] is or comprises GHDSPH (SEQ ID NO: 4784).

[0105] In some embodiments, X4, X5, or both of [N3] are K. In some embodiments, X4, X5, or X6 of [N3] is R. In some embodiments, X4 of [N3] is: A, K, V, S, T, G, F, W, V, N, or R. In some embodiments, X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R. In some embodiments, X6 of [N3] is: G, R, A, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S. In some embodiments, [N3] comprises SK, KA, KS, AR, RM, VK, AS, SR, VK, KR, KK, KN, VR, RS, RK, KT, TS, KF, FG, KI, IG, KL, LG, TT, TY, KY, YG, KD, KP, TR, RG, VR, GA, SL, SS, FL, WK, SA, RA, LR, KW, RR, GK, TK, NK, AK, KV, KG, KH, KM, TG, SE, SV, SW, SN, HG, SQ, LW, MG, MA, or SG. In some embodiments, [N3] comprises SK, KA, KS, or SG. In some embodiments, [N3] is or comprises SKA, KSG, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLG, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG, KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG. In some embodiments, [N3] is or comprises SKA. In some embodiments, [N3] is or comprises KSG. In some embodiments, [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), SPHAR (SEQ ID NO: 4705), SPHVK (SEQ ID NO: 4706), SPHAS (SEQ ID NO: 4707), SPHKK (SEQ ID NO: 4708), SPHVR (SEQ ID NO: 4709), SPHRK (SEQ ID NO: 4710), SPHKT (SEQ ID NO: 4711), SPHKF (SEQ ID NO: 4712), SPHKI (SEQ ID NO: 4713), SPHKL (SEQ ID NO: 4714), SPHKY (SEQ ID NO: 4715), SPHTR (SEQ ID NO: 4716), SPHKR (SEQ ID NO: 4717), SPHGA (SEQ ID NO: 4718), SPHSR (SEQ ID NO: 4719), SPHSL (SEQ ID NO: 4720), SPHSS (SEQ ID NO: 4721), SPHFL (SEQ ID NO: 4722), SPHWK (SEQ ID NO: 4723), SPHGK (SEQ ID NO: 4724), SPHTK (SEQ ID NO: 4725),

SPHNK (SEQ ID NO: 4726), SPHAK (SEQ ID NO: 4727), SPHKH (SEQ ID NO: 4728), SPHKM (SEQ ID NO: 4729), or SPHRS (SEQ ID NO: 4730). In some embodiments [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701) or SPHKS (SEQ ID NO: 4704). In some embodiments, [N2]-[N3] is or comprises SPHSKA (SEQ ID NO: 941), SPHKSG (SEQ ID NO: 946), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLG (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHSKD (SEQ ID NO: 967), SPHSKP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID NO: 973), SPHKRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKSA (SEQ ID NO: 977), SPHKSR (SEQ ID NO: 951), SPHSKL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHSKR (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSSR (SEQ ID NO: 970), SPHFLR (SEQ ID NO: 979), SPHSKW (SEQ ID NO: 953), SPHSKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVRR (SEQ ID NO: 980), SPHSKT (SEQ ID NO: 4731), SPHSKG (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHSKN (SEQ ID NO: 4735), SPHAKA (SEQ ID NO: 4736), SPHSKV (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKSL (SEQ ID NO: 4740), SPHKSE (SEQ ID NO: 4741), SPHKSV (SEQ ID NO: 4742), SPHKSW (SEQ ID NO: 4743), SPHKSN (SEQ ID NO: 4744), SPHKHG (SEQ ID NO: 4745), SPHKSQ (SEQ ID NO: 4746), SPHKSK (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPHKMG (SEQ ID NO: 4750), SPHKMA (SEQ ID NO: 4751), or SPHRSG (SEQ ID NO: 976). In some embodiments, [N2]-[N3] is or comprises SPHSKA (SEQ ID NO: 941). In some embodiments, [N2]-[N3] is or comprises SPHKSG (SEQ ID NO: 946).

[0106] In some embodiments, [N1]-[N2]-[N3] comprises SGSPHSK (SEQ ID NO: 4839), HDSPHKS (SEQ ID NO: 4840), SGSPHAR (SEQ ID NO: 4841), SGSPHVK (SEQ ID NO: 4842), QDSPHKS (SEQ ID NO: 4843), SGSPHKK (SEQ ID NO: 4844), SGSPHVR (SEQ ID NO: 4845), SGSPHAS (SEQ ID NO: 4846), SGSPHRK (SEQ ID NO: 4847), SGSPHKT (SEQ ID NO: 4848), SHSPHKS (SEQ ID NO: 4849), QSSPHRS (SEQ ID NO: 4850), RGSPHAS (SEQ ID NO: 4851), RGSPHSK (SEQ ID NO: 4852), SGSPHKF (SEQ ID NO: 4853), SGSPHKI (SEQ ID NO: 4854), SGSPHKL (SEQ ID NO: 4855), SGSPHKY (SEQ ID NO: 4856), SGSPHTR (SEQ ID NO: 4857), SHSPHKR (SEQ ID NO: 4858), SGSPHGA (SEQ ID NO: 4859), HDSPHKR (SEQ ID NO: 4860), DDSPHKS (SEQ ID NO: 4861), HESPHKS (SEQ ID NO: 4862), NYSPHKI (SEQ ID NO: 4863), SGSPHSR (SEQ ID NO: 4864), SGSPHSL (SEQ ID NO: 4865), SGSPHSS (SEQ ID NO: 4866), VGSPHSK (SEQ ID NO: 4867), SCSPHRK (SEQ ID NO: 4868), SGSPHFL (SEQ ID NO: 4869), LLSPHWK (SEQ ID NO: 4870), NGSPHSK (SEQ ID NO: 4871), PGSPHSK (SEQ ID NO: 4872), GGSPHSK (SEQ ID NO: 4873), TGSPHSK (SEQ ID NO: 4874), SVSPHGK (SEQ ID NO: 4875), SGSPHTK (SEQ ID NO: 4876), IGSPHSK (SEQ ID NO: 4877), DGSPHSK (SEQ ID NO: 4878),

SGSPHNK (SEQ ID NO: 4879), LGSPHSK (SEQ ID NO: 4880), AGSPHSK (SEQ ID NO: 4881), EGSPHSK (SEQ ID NO: 4882), SASPHSK (SEQ ID NO: 4883), SGSPHAK (SEQ ID NO: 4884), HDSPHKI (SEQ ID NO: 4885), YDSPHKS (SEQ ID NO: 4886), HDSPHKT (SEQ ID NO: 4887), RGSPHKR (SEQ ID NO: 4888), HGSPHSK (SEQ ID NO: 4889), RDSPHKS (SEQ ID NO: 4890), NDSPHKS (SEQ ID NO: 4891), QDSPHKI (SEQ ID NO: 4892), PDSPHKI (SEQ ID NO: 4893), PDSPHKS (SEQ ID NO: 4894), MGSPHSK (SEQ ID NO: 4895), HDSPHKH (SEQ ID NO: 4896), QVSPHKS (SEQ ID NO: 4897), HNSPHKS (SEQ ID NO: 4898), NGSPHKR (SEQ ID NO: 4899), HDSPHKY (SEQ ID NO: 4900), NDSPHKI (SEQ ID NO: 4901), HDSPHKL (SEQ ID NO: 4902), HPSPHWK (SEQ ID NO: 4903), HDSPHKM (SEQ ID NO: 4904), or HSSPHRS (SEQ ID NO: 4905). In some embodiments, [N1]-[N2]-[N3] is GSGSPHSKA (SEQ ID NO: 4697), GHDSPHKSG (SEQ ID NO: 4698), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHSKA (SEQ ID NO: 4913), CSGSPHSKA (SEQ ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKSG (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHSKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKLG (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID NO: 4927), GSGSPHSKD (SEQ ID NO: 4928), GSGSPHSKP (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKSG (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGAR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKSG (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHSKL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSKR (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHSKA (SEQ ID NO: 4949), GSCSPHRKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSKW (SEQ ID NO: 4952), GSGSPHSKS (SEQ ID NO: 4953), GLLSPHWKA (SEQ ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSKV (SEQ ID NO: 4956), MSGSPHSKA (SEQ ID NO: 4957), RNGSPHSKA (SEQ ID NO: 4958), TSGSPHSKA (SEQ ID NO: 4959), ISGSPHSKA (SEQ ID NO: 4960), GPGSPHSKA (SEQ ID NO: 4961), GSGSPHSKT (SEQ ID NO: 4962), ESGSPHSKA (SEQ ID NO: 4963), SSGSPHSKA (SEQ ID NO: 4964), GNGSPHSKA (SEQ ID NO: 4965), ASGSPHSKA (SEQ ID NO: 4966), NSGSPHSKA (SEQ ID NO: 4967), LSGSPHSKA (SEQ ID NO: 4968), GGGSPHSKA (SEQ ID NO: 4969), KSGSPHSKA (SEQ ID NO: 4970), GGGSPHSKS (SEQ ID NO: 4971), GSGSPHSKG (SEQ ID NO: 4972), HSGSPHSKA (SEQ ID NO: 4973), GTGSPHSKA (SEQ ID NO: 4974), PSGSPHSKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHSKA (SEQ ID NO:

4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHSKA (SEQ ID NO: 4979), WSGSPHSKA (SEQ ID NO: 4980), DSGSPHSKA (SEQ ID NO: 4981), IDGSPHSKA (SEQ ID NO: 4982), GSGSPHNKA (SEQ ID NO: 4983), GLGSPHSKS (SEQ ID NO: 4984), DAGSPHSKA (SEQ ID NO: 4985), DGGSPHSKA (SEQ ID NO: 4986), MEGSPHSKA (SEQ ID NO: 4987), ENGSPHSKA (SEQ ID NO: 4988), GSASPHSKA (SEQ ID NO: 4989), GNGSPHSKS (SEQ ID NO: 4990), KNGSPHSKA (SEQ ID NO: 4991), KEGSPHSKA (SEQ ID NO: 4992), AIGSPHSKA (SEQ ID NO: 4993), GSGSPHSKN (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHSKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHSKA (SEQ ID NO: 4913), GRDSPHKSG (SEQ ID NO: 5004), GNDSPHKSV (SEQ ID NO: 5005), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), GHDSPHKSN (SEQ ID NO: 5011), GMGSPHSKT (SEQ ID NO: 5012), GHDSPHKHG (SEQ ID NO: 5013), GQVSPHKSG (SEQ ID NO: 5014), GDDSPHKSV (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), GNGSPHKRG (SEQ ID NO: 5017), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSQ (SEQ ID NO: 5019), GNDSPHKIG (SEQ ID NO: 5020), GHDSPHKSK (SEQ ID NO: 5021), GHDSPHKLW (SEQ ID NO: 5022), GHPSPHWKG (SEQ ID NO: 5023), GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GHSSPHRSG (SEQ ID NO: 5026); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications relative to any one of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3] is or comprises GSGSPHSKA (SEQ ID NO: 4697). In some embodiments, [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

[0107] In some embodiments, the AAV capsid variant comprising an amino acid sequence having the formula [N1]-[N2]-[N3] (e.g., in loop IV) further comprises [N4], which comprises X7 X8 X9 X10. In some embodiments, X7 of [N4] is W, Q, K, R, G, L, V, S, P, H, K, I, M, A, E, or F. In some embodiments, X8 of [N4] is N, Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L. In some embodiments, X9 of [N4] is Q, G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y. In some embodiments, X10 of [N4] is Q, H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V. In some embodiments [N4] is or comprises QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), QNQQ (SEQ ID NO: 5028), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO:

5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ (SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100), QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAQQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO: 5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGHH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168),

HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191), QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVP (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245), or any dipeptide or tripeptide thereof. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises: the amino acid sequence of any of SEQ ID NOs: 1800-2241; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHSKAQNQQ (SEQ ID NO: 6415). In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQ (SEQ ID NO: 1800).

[0108] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence having the formula [N1]-[N2]-[N3]; and further comprises [N0], which comprises X_A X_B and X_C. In some embodiments, X_A of [N0] is T, S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G. In some embodiments, X_B of [N0] is I, M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L. In some embodiments, X_C of [N0] is N, M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S. In some embodiments, [N0] is or comprises TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW,

ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEI, LEY, ADW, IEI, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI, VEY, IIN, TSN, IEV, MEM, AEV, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ, HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ, TEI, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN, TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA, NNL, or any dipeptide thereof. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises the amino acid sequence of any one of SEQ ID NOs: 2242-2886; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHSKAQNQQ (SEQ ID NO: 2242). In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGHDSPHKSGQNQQ (SEQ ID NO: 2243).

[0109] In some embodiments, [N3] is present immediately subsequent to [N2]. In some embodiments, the amino acid sequence comprises, from N-terminus to C-terminus, [N2]-[N3]. In some embodiments, the amino acid sequence comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]. In some embodiments, the amino acid sequence comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4]. In some embodiments, the amino acid sequence comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]. In some embodiments, the amino acid sequence comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

[0110] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence having the formula [A][B] (SEQ ID NO: 4694), wherein [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695) and [B] comprises X1 X2 X3 X4 X5 X6 X7. In some embodiments, X1 of [B] is S, C, F, or V. In some embodiments. X2 of [B] is K, L, R, I, E, Y, V, or S. In some embodiments, X3 of [B] is A, R, L, G, I, Y, S, F, or W. In some embodiments X4 of [B] is W, Q, R, G, L, V, S, or F. In some embodiments, X5 of [B] is N, Y, R, C, K, or L. In some embodiments, X6 of [B] is Q, G, K, R, T, L, or Y. In some embodiment. X7 of [B] is Q, L, R, or V. In some embodiments, [B] comprises SLLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259), CLAQNQQ (SEQ ID NO:

5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRL (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284), or any dipeptide, tripeptide, tetrapeptide, pentapeptide, or hexapeptide thereof. In some embodiments, [A][B] comprises GSGSPHSLLWNQQ (SEQ ID NO: 5285), GSGSPHSKAQYYV (SEQ ID NO: 2060), GSGSPHSKLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNQQ (SEQ ID NO: 5286), GSGSPHSKAGCGQ (SEQ ID NO: 2062), GSGSPHSRAQNQQ (SEQ ID NO: 2063), GSGSPHSKRLRQQ (SEQ ID NO: 2064), GSGSPHSLRRNQQ (SEQ ID NO: 2065), GSGSPHSRGRNQQ (SEQ ID NO: 2066), GSGSPHSEIVNQQ (SEQ ID NO: 5287), GSGSPHSSRRNQQ (SEQ ID NO: 2067), GSGSPHCLLQNQQ (SEQ ID NO: 5288), GSGSPHSKAFRLQ (SEQ ID NO: 2068), GSGSPHCLAQNQQ (SEQ ID NO: 5289), GSGSPHFLRQNQQ (SEQ ID NO: 2070), GSGSPHSLRFNQQ (SEQ ID NO: 2071), GSGSPHSYLRNQQ (SEQ ID NO: 5290), GSGSPHCSLQNQQ (SEQ ID NO: 5291), GSGSPHVLWQNQQ (SEQ ID NO: 5292), GSGSPHSKWLLQQ (SEQ ID NO: 2072), GSGSPHSLWSNQQ (SEQ ID NO: 5293), GSGSPHSKRRLQQ (SEQ ID NO: 2073), GSGSPHSVYLNQQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHSKAQRKL (SEQ ID NO: 2074), GSGSPHSKALRRQ (SEQ ID NO: 2075), GSGSPHSKAQRLR (SEQ ID NO: 2076), GSGSPHSKAQNQQ (SEQ ID NO: 6415), GSGSPHSKAQRRL (SEQ ID NO: 2077), GSGSPHSKARRQQ (SEQ ID NO: 2078), GSGSPHSKARRLQ (SEQ ID NO: 2079), GSGSPHSKSRRQQ (SEQ ID NO: 2080), GSGSPHSKARLRQ (SEQ ID NO: 2082), GSGSPHSKASKRQ (SEQ ID NO: 2083), GSGSPHVRRQNQQ (SEQ ID NO: 2084), GSGSPHSKAQLYR (SEQ ID NO: 2085), GSGSPHSLFRNQQ (SEQ ID NO: 5296), GSGSPHSKAQLTV (SEQ ID NO: 2086), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising, from N-terminus to C-terminus, [A][B].

[0111] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence having the formula [A][B] (SEQ ID NO: 4699), wherein [A] comprises X1 X2 X3 X4 X5 X6 and [B] comprises SPHKSG (SEQ ID NO: 946). In some embodiments, X1 of [A] is T, M, A, C, I, R, L, D, F, V, Q, N, or H. In some embodiments, X2 of [A] is I, P, E, N, D, S, A, T, M, or Q. In some embodiments, X3 of [A] is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L. In some

embodiments, X4 of [A] is G, D, R, or E. In some embodiments, X5 of [A] is H, Q, N, or D. In some embodiments, X6 of [A] is D or R. In some embodiments, [A] comprises TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGHD (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGHD (SEQ ID NO: 5306), ADYGHD (SEQ ID NO: 5307), IETGHD (SEQ ID NO: 5308), MEWGHD (SEQ ID NO: 5309), CEYGHD (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGHD (SEQ ID NO: 5312), LEYGHD (SEQ ID NO: 5313), ADWGHD (SEQ ID NO: 5314), IEIGHD (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGHD (SEQ ID NO: 5317), FEQGHD (SEQ ID NO: 5318), MEFGHD (SEQ ID NO: 5319), CDQGHD (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGHD (SEQ ID NO: 5323), AEIGHD (SEQ ID NO: 5324), VEYGHD (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGHD (SEQ ID NO: 5327), MEMGHD (SEQ ID NO: 5328), AEVGHD (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGHD (SEQ ID NO: 5331), AEQGHD (SEQ ID NO: 5332), LEWGHD (SEQ ID NO: 5333), MELGHD (SEQ ID NO: 5334), METGHD (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGHD (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGHD (SEQ ID NO: 5340), CEIGHD (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGHD (SEQ ID NO: 5344), ADQGHD (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347), IEMGHD (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGHD (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGHD (SEQ ID NO: 5352), IEGGHD (SEQ ID NO: 5353), or any dipeptide, tripeptide, tetrapeptide, or pentapeptide thereof. In some embodiments, [A][B] comprises TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370), ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS (SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390), MELGHDSPHKS (SEQ ID NO: 5391),

METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising, from N-terminus to C-terminus, [A][B].

[0112] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, or at least 17 consecutive amino acids from any one of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least 3, at least 4, or at least 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

[0113] In some embodiments, the at least 3 consecutive amino acids comprise SPH. In some embodiments, the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700). In some embodiments, the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701). In some embodiments, the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941).

[0114] In some embodiments, at least 3 consecutive amino acids comprise HDS. In some embodiments, the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702). In some embodiments, the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703). In some embodiments, the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2).

[0115] In some embodiments, the at least 3 consecutive amino acids comprise SPH. In some embodiments, the at least 4 consecutive amino acids comprise SPHK (SEQ ID NO: 6398). In some embodiments, the at least 5 consecutive amino acids comprise SPHKY (SEQ ID NO: 4715). In some embodiments, the at least 6 consecutive amino acids comprise SPHKYG (SEQ ID NO: 966).

[0116] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of any one of the sequences provided in Table 1, 2A, 2B, or 18-

24. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, relative to the amino acid sequence of any one of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids relative to the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids relative to the amino acid sequence of SEQ ID NO: 1754.

[0117] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the peptide comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

[0118] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2). In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least

two, or at least three, but no more than four different amino acids relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

[0119] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966). In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966).

[0120] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of any of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 941. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 943. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 2. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 3241. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 4100. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 4062. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) the amino acid sequence of SEQ ID NO: 4486.

[0121] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence described herein, e.g., a nucleotide sequence of Table 2A. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%,

at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto.

[0122] In some embodiments, the AAV capsid variant comprises (e.g., in loop IV) an amino acid sequence encoded by a nucleotide sequence described herein, e.g., a nucleotide sequence of Table 2A. In some embodiments, the nucleotide sequence is codon optimized. In some embodiments, the nucleotide sequence is an isolated nucleotide nucleotide sequence is a recombinant nucleotide sequence.

[0123] In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments the nucleic acid sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto.

[0124] In some embodiments, the nucleic acid encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 3. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3. In some embodiments, the nucleic acid encoding an AAV capsid variant comprises a nucleotide sequence

comprising the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto.

[0125] In some embodiments, the nucleic acid encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments the nucleic acid encoding an AAV capsid variant comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto.

[0126] Also provided herein are polynucleotide sequences encoding any of the AAV capsid variants described above, AAV particles, vectors, and cells comprising the same.

[0127] In some embodiments, [N1]-[N2]-[N3] is present in loop IV of the AAV capsid variant. In some embodiments [N0] and [N4] are present in loop IV of the AAV capsid variant. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is present in loop IV of the AAV capsid variant.

[0128] In some embodiments, [N0] is present immediately subsequent to amino acid 449, relative to a reference sequence of SEQ ID NO: 138 (i.e., at a sequence position corresponding to that in SEQ ID NO: 138). In some embodiments, [N0] is present immediately subsequent to amino acid 449, numbered according to SEQ ID NO: 4, 36, 981, or 982 (i.e., at a sequence position corresponding to that in SEQ ID NO: 4, 36, 981, or 982). In some embodiments, [N0] replaces amino acids 450, 451, and 452 (e.g., amino acids T450, I451, and N452), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N0] is present immediately subsequent to amino acid 449 and [N0] replaces amino acids 450-452 (e.g., T450, I451, and N452), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to amino acid 452, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N1] replaces amino acids 453- 455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to amino acid 452 and wherein [N1] replaces amino acids 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N2] is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N2]-[N3] is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments [N1]-[N2]-[N3] is present immediately

subsequent to amino acid 452, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N1]-[N2]-[N3] replaces amino acids 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to amino acid 452 and wherein [N1]-[N2]-[N3] replaces amino acids 453-455 (e.g., G453, S454, and G455), numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, [N4] is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 138. In some embodiments, [N4] replaces amino acids 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N4] is present immediately subsequent to amino acid 455, and [N4] replaces amino acids 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N2]-[N3]-[N4] replaces amino acids 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N2]-[N3]-[N4] is present immediately subsequent to amino acid 455, wherein [N2]-[N3]-[N4] replaces amino acids 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N1]-[N2]-[N3]-[N4] replaces amino acids 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N1]-[N2]-[N3]-[N4] is present immediately subsequent to amino acid 452, and [N1]-[N2]-[N3]-[N4] replaces amino acids 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] replaces amino acids 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to amino acid 449, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces amino acids 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), numbered according to SEQ ID NO: 138.

[0129] In some embodiments, [N3] is present immediately subsequent to [N2].

[0130] In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [N2]-[N3]. In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]. In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4]. In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]. In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

[0131] In some embodiments, an AAV capsid variant comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4694), wherein [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695) and [B] comprises X1 X2 X3 X4 X5 X6 X7. In some embodiments, X1 of [B] is S, C, F, or V. In some embodiments, X2 of [B] is K, L, R, I, E, Y, V, or S. In some embodiments, X3 of [B] is A, R, L, G, I, Y, S, F, or W. In some embodiments, X4 of [B] is W, Q, R, G, L, V, S, or F. In some embodiments, X5 of [B] is N, Y, R, C, K, or L. In some embodiments, X6 of [B] is Q, G, K, R, T, L, or Y. In some embodiments, X7 of [B] is Q, L, R, or V. In some embodiments, [B]

comprises SLLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259), CLAQNQQ (SEQ ID NO: 5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRL (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284), or any dipeptide, tripeptide, tetrapeptide, pentapeptide, or hexapeptide thereof. In some embodiments, [A][B] comprises GSGSPHSLLWNQQ (SEQ ID NO: 5285), GSGSPHSKAQYYV (SEQ ID NO: 2060), GSGSPHSKLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNQQ (SEQ ID NO: 5286), GSGSPHSKAGCGQ (SEQ ID NO: 2062), GSGSPHSRAQNQQ (SEQ ID NO: 2063), GSGSPHSKRLRQQ (SEQ ID NO: 2064), GSGSPHSLRRNQQ (SEQ ID NO: 2065), GSGSPHSRGRNQQ (SEQ ID NO: 2066), GSGSPHSEIVNQQ (SEQ ID NO: 5287), GSGSPHSSRRNQQ (SEQ ID NO: 2067), GSGSPHCLLQNQQ (SEQ ID NO: 5288), GSGSPHSKAFRLQ (SEQ ID NO: 2068), GSGSPHCLAQNQQ (SEQ ID NO: 5289), GSGSPHFLRQNQQ (SEQ ID NO: 2070), GSGSPHSLRFNQQ (SEQ ID NO: 2071), GSGSPHSYLRNQQ (SEQ ID NO: 5290), GSGSPHCSLQNQQ (SEQ ID NO: 5291), GSGSPHVLWQNQQ (SEQ ID NO: 5292), GSGSPHSKWLLQQ (SEQ ID NO: 2072), GSGSPHSLWSNQQ (SEQ ID NO: 5293), GSGSPHSKRRLQQ (SEQ ID NO: 2073), GSGSPHSVYLNQQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHSKAQRKL (SEQ ID NO: 2074), GSGSPHSKALRRQ (SEQ ID NO: 2075), GSGSPHSKAQRLR (SEQ ID NO: 2076), GSGSPHSKAQNQQ (SEQ ID NO: 1801), GSGSPHSKAQRRL (SEQ ID NO: 2077), GSGSPHSKARRQQ (SEQ ID NO: 2078), GSGSPHSKARRLQ (SEQ ID NO: 2079), GSGSPHSKSRRQQ (SEQ ID NO: 2080), GSGSPHSKARLRQ (SEQ ID NO: 2082), GSGSPHSKASKRQ (SEQ ID NO: 2083), GSGSPHVRRQNQQ (SEQ ID NO: 2084), GSGSPHSKAQLYR (SEQ ID NO: 2085), GSGSPHSLFRNQQ (SEQ ID NO: 5296), GSGSPHSKAQLTV (SEQ ID NO: 2086), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof.

[0132] In some embodiments, [A][B] is present in loop IV of the AAV capsid variant. In some embodiments, [A] is present immediately subsequent to amino acid 452, relative to a reference sequence of SEQ ID NO: 138 (i.e., at a sequence position corresponding to that in SEQ ID NO: 138).

In some embodiments, [A] replaces amino acids 453-455 (e.g., G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A] is present immediately subsequent to amino acid 452, and [A] replaces amino acids 453-455 (e.g., G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, [B] replaces amino acids 456-459 (e.g., Q456, N457, Q458, Q459), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A][B] replaces amino acids 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A][B] is present immediately subsequent to amino acid 452, and wherein [A][B] replaces amino acids 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises, from N-terminus to C-terminus, [A][B].

[0133] In some embodiments, an AAV capsid variant comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4699), wherein [A] comprises X1 X2 X3 X4 X5 X6 and [B] comprises SPHKSG (SEQ ID NO: 946). In some embodiments, X1 of [A] is T, M, A, C, I, R, L, D, F, V, Q, N, or H. In some embodiments, X2 of [A] is I, P, E, N, D, S, A, T, M, or Q. In some embodiments, X3 of [A] is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L. In some embodiments, X4 of [A] is G, D, R, or E. In some embodiments, X5 of [A] is H, Q, N, or D. In some embodiments, X6 of [A] is D or R. In some embodiments, [A] comprises TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGHD (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGHD (SEQ ID NO: 5306), ADYGHD (SEQ ID NO: 5307), IETGHD (SEQ ID NO: 5308), MEWGHD (SEQ ID NO: 5309), CEYGHD (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGHD (SEQ ID NO: 5312), LEYGHD (SEQ ID NO: 5313), ADWGHD (SEQ ID NO: 5314), IEIGHD (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGHD (SEQ ID NO: 5317), FEQGHD (SEQ ID NO: 5318), MEFGHD (SEQ ID NO: 5319), CDQGHD (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGHD (SEQ ID NO: 5323), AEIGHD (SEQ ID NO: 5324), VEYGHD (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGHD (SEQ ID NO: 5327), MEMGHD (SEQ ID NO: 5328), AEVGHD (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGHD (SEQ ID NO: 5331), AEQGHD (SEQ ID NO: 5332), LEWGHD (SEQ ID NO: 5333), MELGHD (SEQ ID NO: 5334), METGHD (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGHD (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGHD (SEQ ID NO: 5340), CEIGHD (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGHD (SEQ ID NO: 5344), ADQGHD (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347), IEMGHD (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGHD (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGHD (SEQ ID NO: 5352), IEGGHD (SEQ ID NO: 5353), or any dipeptide, tripeptide, tetrapeptide, or pentapeptide

thereof. In some embodiments, [A][B] comprises TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370), ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS (SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390), MELGHDSPHKS (SEQ ID NO: 5391), METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof.

[0134] In some embodiments, [A][B] is present in loop IV of the AAV capsid variant. In some embodiments, [A] is present immediately subsequent to amino acid 449, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A] replaces amino acids 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A] is present immediately subsequent to amino acid 449, and wherein [A] replaces amino acids 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, [A][B] replaces amino acids 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, [A][B] is present immediately subsequent to amino acid 449, and wherein [A][B] replaces amino acids 450-455 (e.g.,

T450, I451, N452, G453, S454, G455), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the peptide comprises, from N-terminus to C-terminus, [A][B].

[0135] In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 16, or at least 17 consecutive amino acids from any one of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least 3, at least 4, or at least 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 448, 452, 453, or 455, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982 (i.e., at a sequence position corresponding to that in SEQ ID NO: 4, 36, 138, 981, or 982). In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 982. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, numbered according to SEQ ID NO: 981. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of amino acids 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and 460 (e.g., T460), numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises one or more amino acid substitutions at amino acids 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and/or 460 (e.g., T460), numbered according to SEQ ID NO: 138.

[0136] In some embodiments, the at least 3 consecutive amino acids comprise SPH. In some embodiments, the at least 3 consecutive amino acids comprise SPH in an AAV9 variant. In some embodiments, the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700). In some embodiments, the at least 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700) in an AAV9 variant. In some embodiments, the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701). In some embodiments, the at least 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701) in an AAV9 variant. In some embodiments, the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941). in some embodiments, the at least 6 consecutive amino acids comprise SPHSKA (SEQ ID NO: 941) in an AAV9 variant.

[0137] In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461, numbered according to SEQ ID NO: 981. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461 of an AAV9 variant, numbered according to SEQ ID NO: 981. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461, numbered according to SEQ ID NO: 4. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461 of an AAV9 variant, numbered according to SEQ ID NO: 4. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461, numbered according to SEQ ID NO: 36. In some embodiments, the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present at amino acids 456-461 of an AAV9 variant, numbered according to SEQ ID NO: 36.

[0138] In some embodiments, the at least 3 consecutive amino acids comprise HDS. In some embodiments, the at least 3 consecutive amino acids comprise HDS in an AAV9 variant. In some embodiments, the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702). In some embodiments, the at least 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702) in an AAV9 variant. In some embodiments, the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703). In some embodiments, the at least 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703) in an AAV9 variant. In some embodiments, the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2). In some embodiments, the at least 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2) in an AAV9 variant.

[0139] In some embodiments, the amino acid sequence of HDSPHK (SEQ ID NO: 2) is present in at amino acids 454-459, numbered according to SEQ ID NO: 982. In some embodiments, the amino acid sequence of HDSPHK (SEQ ID NO: 2) is present in an AAV9 variant at amino acids 454-459, numbered according to SEQ ID NO: 982.

[0140] In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of any one of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, relative to the amino acid sequence of any one of the sequences provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to

the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids, from the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 448, 452, 453, or 455, numbered according to SEQ ID NO: 4, 36, 138, 981, or 982. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 982. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, numbered according to SEQ ID NO: 981, 4, or 36. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of amino acids 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and 460 (e.g., T460), numbered according to SEQ ID NO: 138.

[0141] In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids from the amino acid sequence of SPHSKA (SEQ ID NO: 941).

[0142] In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four modifications, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2). In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three, but no more than four different amino acids that relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

[0143] In some embodiments, the AAV capsid variant, comprises an amino acid sequence of provided in Table 1, 2A, 2B, or 18-24. In some embodiments, the amino acid sequence comprises any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 941. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 943. In some embodiments, the AAV capsid variant comprises the amino acid sequence

of SEQ ID NO: 3589. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 448, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 448 and replaces amino acids 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 449, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 450-460 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 449, and replaces amino acids 450-460 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 450, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 451-460 (e.g., I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 450 and replaces amino acids 451-460 (e.g., I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 451, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 452-460 (e.g., N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 451 and replaces amino acids 452-460 (e.g., N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 452, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 452, and replaces amino acids 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, and replaces amino acids 454 and 455 (e.g., S454

and G455), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces amino acids 454-460 (e.g., S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 453, and replaces amino acids 454-460 (e.g., S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 454, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 454, relative to a reference sequence of SEQ ID NO: 981. In some embodiments, the amino acid sequence replaces amino acids 455-460 (e.g., amino acids G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acids 454, and replaces amino acids 455-460 (e.g., amino acids G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, relative to a reference sequence of SEQ ID NO: 982. In some embodiments, the amino acid sequence replaces amino acids 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to amino acid 455, and replaces amino acids 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138.

[0144] In some embodiments, the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 942 or 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the AAV capsid variant described herein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 3 or 942, or a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequence of SEQ ID NO: 3 or 942. In some embodiments, the AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3 or 942.

[0145] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid

variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequences of SEQ ID NO: 942. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942.

[0146] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequences of SEQ ID NO: 3. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

[0147] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 5, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequences of SEQ ID NO: 5. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5.

[0148] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications, relative to the nucleotide sequences of SEQ ID NO: 12. In some embodiments, the nucleotide sequence encoding an AAV capsid variant comprises a nucleotide sequence comprising at least one,

at least two, at least three, at least four, at least five, at least six, or at least seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 12.

[0149] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to amino acid 455, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to amino acid 455, relative to a reference sequence of SEQ ID NO: 981.

[0150] In some embodiments, an AAV capsid variant comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to amino acid 453, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to amino acid 453, relative to a reference sequence of SEQ ID NO: 982.

[0151] In some embodiments, an AAV capsid variant comprises (i) the amino acid sequence of HDSPHSKA (SEQ ID NO: 4486), which is present immediately subsequent to amino acid 453; and (ii) a deletion of amino acids SG at amino acid 454 and 455; wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0152] In some embodiments, an AAV capsid variant comprises an amino acid other than S at amino acid 454 and/or an amino acid other than G at amino acid 455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid H at amino acid 454 and the amino acid D at amino acid 455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises: (i) the amino acid H at amino acid 454 and the amino acid D at amino acid 455, and (ii) the amino acid sequence SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence of SPHKSG (SEQ ID NO: 946) is present immediately subsequent to amino acid 455, wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0153] In some embodiments, an AAV capsid variant comprises a modification, e.g., substitution, relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification, e.g., substitution, at amino acid S454 and/or G455, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a S454H substitution and/or G455D substitution, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a S454H substitution and a G455D substitution, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises: (i) a S454H substitution and a G455D substitution, and (ii) the amino acid sequence SPHKSG (SEQ ID NO: 946),

wherein the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present immediately subsequent to amino acid 455, wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0154] In some embodiments, the AAV capsid variant further comprises one, two, or all of an amino acid other than T at amino acid 450 (e.g., S, Y, or G), an amino acid other than I at amino acid 451 (e.g., M or L), and/or an amino acid other than N at amino acid 452 (e.g., S), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an S at amino acid 450 and an M at amino acid 451, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a Y at amino acid 450, an L at amino acid 451, and an S at amino acid 452, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a G at amino acid 450, an L at amino acid 451, and an S at amino acid 452, relative to a reference sequence of SEQ ID NO: 138.

[0155] In some embodiments, the AAV capsid variant further comprises one, two, three, four, or all of an amino acid other than Q at amino acid 456 (e.g., R or L), N at amino acid 457 (e.g., H, K, or R), Q at amino acid 458 (e.g., R or T), Q at amino acid 459 (H), and/or T at amino acid 460 (N or S), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an R at amino acid 456, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an L at amino acid 456, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an H at amino acid 457 and an R at amino acid 458, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a K at amino acid 457 and an N at amino acid 460, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a T at amino acid 458, an H at amino acid 459, and an S at amino acid 460, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an R at amino acid 456, an R at amino acid 457, and an R at amino acid 458, relative to a reference sequence of SEQ ID NO: 138.

[0156] In some embodiments, an AAV capsid variant comprises an amino acid other than I at amino acid 451, an amino acid other than N at amino acid 452, and an amino acid other than G at amino acid 453, numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises E at amino acid 451, R at amino acid 452, and V at amino acid 453, numbered according to SEQ ID NO: 138 or 981.

[0157] In some embodiments, the AAV capsid variant comprises the substitutions I451E, N452R, and G453V, numbered according to SEQ ID NO: 138 or 981.

[0158] In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to amino acid 455 and wherein the AAV capsid variant comprises the E at amino acid 451, R at amino acid 452, and V at amino acid 453, numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises the substitutions I451E, N452R, and G453V, and

further comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to amino acid 455, numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises the amino acid sequence of ERVSGSPHSKA (SEQ ID NO: 6399), wherein the amino acid sequence is present immediately subsequent to amino acid 449 and replaces amino acids 450-455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589), wherein the amino acid sequence is present immediately subsequent to amino acid 448 and replaces amino acids 449-460, numbered according to SEQ ID NO: 138.

[0159] In some embodiments, an AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981, or 4; and (ii) one or both of E at position 451 and/or V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981. In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981, or 4; and (ii) one or both of E at position 451 and/or V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981, wherein the AAV capsid variant is an AAV9 variant.

[0160] In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981, or 4; and (ii) E at position 451 and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981. In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981, or 4; and (ii) E at position 451 and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981, wherein the AAV capsid variant is an AAV9 variant.

[0161] In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 4, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 4, 138, or 981); and (ii) E at position 451 and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 4, 138, or 981). In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 4, 138, or 981, and (ii) E at position 451 and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 4, 138, or 981, wherein the AAV capsid variant is an AAV9 variant.

[0162] In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 36, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 36, 138, or 981), and (ii) one, two, or all of E at position 451, R at position 452, and/or V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 36, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 36, 138, or 981). In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 36, 138, or 981 and (ii) one, two, or all of E at position 451, R at position 452, and/or V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 36, 138, or 981, wherein the AAV capsid variant is an AAV9 variant.

[0163] In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 36, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 36, 138, or 981); and (ii) E at position 451, R at position 452, and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 36, 138, or 981 (i.e., at a sequence position corresponding to that in SEQ ID NO: 36, 138, or 981). In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present at amino acids 456-461, numbered according to SEQ ID NO: 36, 138, or 981 and (ii) E at position 451, R at position 452, and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 36, 138, or 981, wherein the AAV capsid variant is an AAV9 variant.

[0164] In some embodiments, the AAV capsid variant comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), which is present immediately subsequent to amino acids 453, and further comprises A at amino acid 450, E at amino acid 451, and I at amino acid 452, all numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises the substitutions T450A, I451E, and N452I, and further comprises the amino acid sequence HDSPHK (SEQ ID NO: 2) present immediately subsequent to amino acid 453, all numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises the amino acid sequence of AEIGHDSPHKSG (SEQ ID NO: 6400), wherein the amino acid sequence is present immediately subsequent to amino acid 449 and replaces amino acids 450-455, numbered according to SEQ ID NO: 138.

[0165] In some embodiments, the AAV capsid variant comprises the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754), wherein the amino acid sequence is present immediately subsequent to amino acid 448 and replaces amino acids 449-460, numbered according to SEQ ID NO: 138.

[0166] In some embodiments, the AAV capsid variant, further comprises a substitution at amino acid K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant, further comprises an amino acid other than K at amino acid 449 (e.g., R), relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises an R at amino acid 449, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a modification, e.g., an insertion, substitution, and/or deletion in loop I, II, VI, and/or VIII.

[0167] In some embodiments, the AAV capsid variant, further comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, of the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 amino acids that differ from the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 70% (e.g., at least 80%, at least 85%, at least 90, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0168] In some embodiments, the AAV capsid variant further comprises (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982, 36, or 4; (b) a VP2 protein comprising amino acids 138-742 of SEQ ID NO: 982, 36, or 4; (c) a VP3 protein comprising amino acids 203-742 of SEQ ID NO: 982, 36, or 4; or (d) an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to any of the amino acid sequences in (a)-(c), an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids relative to any of the amino acid sequences in (a)-(c), or an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to any of the amino acid sequences in (a)-(c).

[0169] In some embodiments, the AAV capsid variant further comprises an amino acid sequence encoded by the nucleotide sequence that is at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical to SEQ ID NO: 137. In some embodiments, the AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of SEQ ID NO: 137. In some embodiments, the AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 137.

[0170] In some embodiments, the nucleotide sequence encoding the AAV capsid variant further comprises the nucleotide sequence that is at least 70% (e.g., at least about 70%, at least about 75%, at least 80%, at least 85%, at least 90, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%%) identical to SEQ ID NO: 137. In some embodiments, the nucleotide sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of SEQ ID NO: 137. In some embodiments, the nucleotide sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 137.

[0171] In some embodiments, an AAV capsid variant of the present disclosure comprises an amino acid sequence as described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 4. In some embodiments, an AAV capsid variant of the present disclosure comprises an amino acid sequence as described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, TTM-026, or TTM-027, e.g., as described in Table 4. In some embodiments, the AAV capsid variant comprises an amino acid sequence of SEQ ID NO: 36 (TTM-003; comprising a peptide of SEQ ID NO: 3589), SEQ ID NO: 39 (TTM-006; comprising a peptide of SEQ ID NO: 3241), or SEQ ID NO: 4 (TTM-027; comprising a peptide of SEQ ID NO: 3272).

[0172] In some embodiments, an AAV capsid variant comprises a VP1, VP2, and/or VP3 protein comprising an amino acid sequence described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 4. In some embodiments, an AAV capsid variant comprises a VP1, VP2, and/or VP3 protein comprising an amino acid sequence described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, TTM-026 or TTM-027 e.g., as described in Table 4.

[0173] In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence as described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 5. In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence as described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, TTM-026, or TTM-027 e.g., as described in Table 5.

[0174] In some embodiments, a polynucleotide or nucleic acid encoding an AAV capsid variant, of the present disclosure comprises a nucleotide sequence described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 5. In some embodiments, a polynucleotide or nucleic acid encoding an AAV capsid variant, of the present disclosure comprises a nucleotide sequence described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, TTM-026, or TTM-027 e.g., as described in Table 5.

Table 3. Exemplary full length capsid sequences

Name	VP1 DNA SEQ ID NO:	VP1 (amino acid) SEQ ID NO:	Peptide (amino acid) SEQ ID NO:	Peptide DNA SEQ ID NO:
TTM-001	983	981	941	942
TTM-002	984	982	2	3

Table 4. Exemplary full length capsid amino acid sequences

Name and Annotation	SEQ ID NO:	Amino Acid Sequence
TTM-001 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); 742 aa	981	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTINGSG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-002 6mer peptide underlined, starts at amino acid 454 (immediately subsequent to amino acid 453); 742 aa	982	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHK**SGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL

TTM-003 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 452, and 453 underlined; 742 aa	36	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**ERV**SG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-004 6mer peptide underlined, starts at amino acid 454 (immediately subsequent to amino acid 453); modifications at amino acids 450, 451, and 452 underlined; 742 aa	37	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS K**AEI**G**HDSPHK**SGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSLITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-005 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 452, 464, and 465 underlined; 742 aa	38	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTI**I**GSG**SPHSKA**QN**RH**TLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-006 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 452, and 453 underlined; 742 aa	39	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**EKM**SG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-007 6mer peptide underlined, starts at amino	40	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS

acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 450 and 454 underlined; 742 aa		SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS K**E**ING**R**G**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-008 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 462, and 464 underlined; 742 aa	41	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**F**NGSG**SPHSKAP**N**L**QTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-009 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 452, and 453 underlined; 742 aa	42	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**EKT**SG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-010 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 454, and 455 underlined; 742 aa	43	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**M**NG**HDSPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-011 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid	44	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS	

455); modifications at amino acids 452, 454, and 455 underlined; 742 aa		KTI**D**G**HDSPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-012 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 452, 454, and 455 underlined; 742 aa	45	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTN**N**G**HDSPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-013 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 452, and 453 underlined; 742 aa	46	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**QRK**SG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-014 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 463, 464, and 465 underlined; 742 aa	47	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTINGSG**SPHSKA**Q**ARK**TLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-015 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to 455); modifications at amino acids 450 and 452 underlined;	48	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS K**Y**I**V**GSG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK

742 aa		LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-016 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 452, 453, and 454 underlined; 742 aa	49	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTI**SKR**G**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-017 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 450, 451, and 452 underlined; 742 aa	50	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS K**GLG**GSG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-018 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 454, 455, and 464 underlined; 742 aa	51	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHSKA**QN**L**QTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-019 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids451, 454, and 455 underlined; 742 aa	52	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**V**NG**HDSPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL

TTM-020 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 454, 455, and 462 underlined; 742 aa	53	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHSKAL**NQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-021 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 454, 455, and 466 underlined; 742 aa	54	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHSKA**QNQQ**S**LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-022 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 454, 455, and 466 underlined; 742 aa	55	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHSKA**QNQQ**I**LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-023 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); 742 aa	56	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTINGSG**SPHFTR**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-024 6mer peptide underlined, starts at amino	57	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS

acid 456 (immediately subsequent to amino acid 455); modifications at amino acids 451, 454, and 455 underlined; 742 aa		SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**S**NG**HDSPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-025 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modification at amino acid 462 underlined; 742 aa	58	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTINGSG**SPHSLPW**NQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-026 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modification at amino acids 454, 455, and 464 underlined; 742 aa	59	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING**HDSPHSKA**QN**H**QTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	
TTM-027 6mer peptide underlined, starts at amino acid 456 (immediately subsequent to amino acid 455); modification at amino acids 451 and 453 underlined; 742 aa	4	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPG NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLS KT**E**N**V**SG**SPHSKA**QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYS EPRPIGTRYLTRNL	

Table 5. Exemplary full length capsid nucleic acid sequences

Name and Annotation	SEQ ID NO:	NT Sequence
TTM-001	983	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC

9mer peptide underlined		ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTATtTActTgagt AAaACaATTAACGGAAGCGGA**AGCCCACACAGCAAAGCA**CAAAACCAACAGACCtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTaTAA
TTM-002 7mer peptide underlined	984	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC

		AAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTAtTActTgagt AAaACaATTAACGGA**CACGACAGCCCACACAAA**AGCGGACAAAACCAACAGACCtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTaTAA
TTM-003	12	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGGAGCGTGTGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGcAAcATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-004	13	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA

		CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGGCGGAGATTGGTCATGATTCTCCGCATAAGTCTGGTCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGcAAcATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTAATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-005	14	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTATTGGTTCTGGTTCTCCGCATTCTAAGGCGCAGAATCGTCATACGtT

		gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-006	15	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGGAGAAGATGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-007	16	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC

		AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGGAGATTAATGGTCGTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-008	17	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGTTTAATGGTTCTGGTTCTCCGCATTCTAAGGCGCCGAATCTGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC

		AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-009	18	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGGAGAAGACGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-010	19	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC

		CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATGAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-011	20	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTGATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC

		CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-012	21	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGAATAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-013	22	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC

		AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGCAGCGTAAGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-014	23	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTTCTGGTTCTCCGCATTCTAAGGCGCAGGCGCGTAAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC

		AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-015	24	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGTATATTGTGGGTTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-016	25	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC

		TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTTCTAAGCGTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-017	26	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGGGTCTGGGTGGTTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA

		GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-018	27	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCTGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-019	28	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA

		ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGGTGAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-020	29	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCTGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC

		TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-021	30	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGTCTtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-022	31	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA

		GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGATTtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-023	32	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTTCTGGTTCTCCGCATTTTACGCGTCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG

		GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-024	33	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGTCTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-025	34	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT

		AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTTCTGGTTCTCCGCATTCTCTGCCGTGGAATCAGCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-026	35	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCATCAGACGtT gAAgTTttcgGTaGCtGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA

		ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-027	5	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCT AAGACTGAGAATGTGAGCGGGAGCCCTCATAGCAAGGCTCAGAATCAGCAGACTCT AAAATTCAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGTGGCCACAAACCACCAGAGTGCCCAAGCACAGGCGC AGACCGGCTGGGTTCAAAACCAAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTG

[0175] In some embodiments, the polynucleotide encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0176] In some embodiments, the polynucleotide encoding an AAV capsid variant, comprises the nucleotide sequence of any one of SEQ ID NOs: 5, 12-35, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0177] In some embodiments, the polynucleotide encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 12 or a nucleotide sequence with at least 70% (e.g., at least 70%,

at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0178] In some embodiments, the polynucleotide encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 5 or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0179] In some embodiments, the polynucleotide encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, at least two, or at least three modifications but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of SEQ ID NO: 983. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, at least two, or at least three substitutions, but not more than 30, not more than 20, or not more than 10 substitutions relative to the amino acid sequence of SEQ ID NO: 983. In some embodiments, the nucleic acid sequence encoding an AAV capsid variant is codon optimized. In some embodiments, the polynucleotide encoding an AAV capsid variant comprises SEQ ID NO: 983. In some embodiments, the polynucleotide encoding an AAV capsid variant comprises SEQ ID NO: 983. In some embodiments, the polynucleotide encoding an AAV capsid variant consists of SEQ ID NO: 983.

[0180] In some embodiments, the polynucleotide encoding an AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of SEQ ID NO: 984. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different nucleotides, relative to the sequence of SEQ ID NO: 984. In some embodiments, the nucleic acid sequence encoding an AAV capsid variant is codon optimized. In some embodiments, the polynucleotide encoding an AAV capsid variant comprises SEQ ID NO: 984. In some embodiments, the polynucleotide encoding an AAV capsid variant consists of SEQ ID NO: 984.

[0181] In some embodiments, an AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 4, 36-59, 981, or 982, or an amino acid sequence with at least 70% (e.g., at least

70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 4, 36-59, 981, or 982. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 4, 36-59, 981, or 982.

[0182] In some embodiments, the AAV capsid variant comprises one or more substitutions in loop IV and comprises the amino acid sequence of SEQ ID NO: 981, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 981. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three substitutions, but not more than 30, not more than 20, or not more than 10 substitutions, relative to the amino acid sequence of SEQ ID NO: 981.

[0183] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 982. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 982. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 982. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 982. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 982. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 982. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 982. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 982.

[0184] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 36, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 36. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 36. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 36. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 36. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 36. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 36. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 36. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 36. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 36.

[0185] SEQ ID NO: 4, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity theretoan amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 4. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 4. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 4. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 4. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 4. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 4. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 4. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 4. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 4.

[0186] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 39, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%)

sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 39. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 39. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 39. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 39. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 39. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 39. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 39. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 39. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 39.

[0187] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 51, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 51. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 51. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 51. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 51. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 51. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 51. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 51. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 51. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 51.

[0188] In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 52, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid

sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the amino acid sequence of SEQ ID NO: 52. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 52. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 52. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 98% identical to SEQ ID NO: 52. In some embodiments, an AAV capsid variant comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 52. In some embodiments, an AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 52. In some embodiments, an AAV capsid variant consists of the amino acid sequence of SEQ ID NO: 52. In some embodiments, an AAV capsid variant comprises amino acid residues 2-742 of SEQ ID NO: 52. In some embodiments, an AAV capsid variant consists of amino acid residues of 2-742 of SEQ ID NO: 52.

[0189] In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three substitutions, but not more than 30, not more than 20, or not more than 10 substitutions, relative to the amino acid sequence of SEQ ID NO: 983. In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of SEQ ID NO: 983.

[0190] In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 5, 12-35, or a nucleotide sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three, but not more than 30, not more than 20, or not more than 10 different nucleotides, relative to the amino acid sequence of any one of SEQ ID NOs: 5, 12-35. In some embodiments, an AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, at least two, or at least three modifications, but not more than 30, not more than 20, or not more than 10 modifications, relative to the nucleotide sequence of any one of SEQ ID NOs: 5, 12-35.

[0191] In some embodiments, an AAV capsid variant comprises a VP1, VP2, VP3 protein, the VP1, VP2, and VP3 comprise one or more insertions in loop IV. In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to amino acids 138-742, e.g., a VP2, of SEQ ID NO: 981 or 982, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to amino acids 203-742, e.g., a VP3, of SEQ ID NO: 981 or 982, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to amino acids 1-742, e.g., a VP1, of SEQ ID NO: 981 or 982, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0192] In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to amino acids 138-742, e.g., a VP2, of SEQ ID NO: 982, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, e.g., 100%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to amino acids 203-742, e.g., a VP3, of SEQ ID NO: 982, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, e.g., 100%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to amino acids 1-742, e.g., a VP1, of SEQ ID NO: 982, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, e.g., 100%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises or consists of the amino acid sequence of SEQ ID NO: 982. In some embodiments, the AAV capsid variant comprises or consists of amino acid residues 2-742 of SEQ ID NO: 982.

[0193] In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to amino acids 138-74236, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to amino acids 203-74236, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to amino acids 1-742, e.g., a VP1, of SEQ ID NO: 36, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%)

sequence identity thereto. In some embodiments, the AAV capsid variant comprises or consists of the amino acid sequence of SEQ ID NO: 36. In some embodiments, the AAV capsid variant comprises or consists of amino acid residues 2-742 of SEQ ID NO: 36.

[0194] In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to amino acids 138-742, e.g., a VP2, of SEQ ID NO: 4, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to amino acids 203-742, e.g., a VP3, of SEQ ID NO: 4, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to amino acids 1-742, e.g., a VP1, of SEQ ID NO: 4, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises or consists of the amino acid sequence of SEQ ID NO: 4. In some embodiments, the AAV capsid variant comprises or consists of amino acid residues 2-742 of SEQ ID NO: 4.

[0195] In some embodiments, an AAV capsid variant comprises a VP1, VP2, VP3 protein, or a combination thereof. In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to amino acids 138-742, e.g., a VP2, of any one of SEQ ID NOs: 4, 36-59, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to amino acids 203-742, e.g., a VP3, of any one of SEQ ID NOs: 4, 36-59, or a sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to amino acids 1-742, e.g., a VP1, of any one of SEQ ID NOs: 4, 36-59, or an amino acid sequence with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity thereto.

[0196] In some embodiments, an AAV capsid variant has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of an AAV capsid comprising SEQ ID NO: 138.

[0197] In some embodiments, an AAV capsid variant transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem. In some embodiments, the level of transduction is at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or at least 65-fold greater as compared to a reference

sequence of SEQ ID NO: 138. In some embodiments, the level of transduction is at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or at least 65-fold greater as compared to an AAV capsid variant comprising SEQ ID NO: 138.

[0198] In some embodiments, an AAV capsid variant is enriched at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10-fold in the brain compared to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant is enriched at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80 or at least 85-fold in the brain compared to an AAV capsid variant comprising SEQ ID NO: 138.

[0199] In some embodiments, an AAV capsid variant is enriched in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse) species, compared to an AAV capsid variant comprising SEQ ID NO: 138. In some embodiments, an AAV capsid variant is enriched at least 2, at least 3, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, at least 100, at least 105, at least 115, at least 120, at least 125, at least 130, at least 135, at least 140, at least 145, at least 150, at least 155, at least 160, at least 165, at least 170, at least 175, at least 180, at least 190, at least 200, at least 205, or at least 210-fold in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse) species, compared to an AAV capsid variant comprising SEQ ID NO: 138. In some embodiments, the at least two to three species are *Macaca fascicularis*, *Chlorocebus sabaeus*, *Callithrix jacchus*, and/or mouse (e.g., outbred mice).

[0200] In some embodiments, an AAV capsid variant is enriched at least 2, at least 2.5, at least 3, at least 3.5, at least 4, at least 4.5, at least 5, at least 5.5, at least 6, at least 6.5, at least 7, at least 7.5, or at least 8-fold, in the brain compared to an AAV capsid variant comprising SEQ ID NO: 981. In some embodiments, an AAV capsid variant is enriched about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, or about 5.5-fold, in the brain compared to an AAV capsid variant comprising SEQ ID NO: 982.

[0201] In some embodiments, an AAV capsid variant delivers an increased level of viral genomes to a brain region. In some embodiments, the level of viral genomes is increased by at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50-fold, as compared to an AAV capsid variant comprising SEQ ID NO: 138. In some embodiments, the brain region comprises a midbrain region (e.g., the hippocampus or thalamus) and/or the brainstem.

[0202] In some embodiments, an AAV capsid variant delivers an increased level of a payload to a brain region. In some embodiments, the level of the payload is increased by at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, or at least 70-fold, as compared to an AAV capsid variant comprising SEQ ID NO: 138. In some embodiments, the brain region comprises a midbrain region (e.g., the hippocampus or thalamus) and/or the brainstem.

[0203] In some embodiments, an AAV capsid variant is enriched at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35-fold, in the spinal cord compared to an AAV capsid comprising SEQ ID NO: 138.

[0204] In some embodiments, an AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG). In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the liver. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the liver and the DRG. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart and DRG. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart, DRG, and liver. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region and/or a heart region relative to the transduction in the liver and DRG.

[0205] In some embodiments, an AAV capsid variant is capable of transducing non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes). In some embodiments, the AAV capsid variant is capable of transducing neuronal cells and non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes). In some embodiments, the non-neuronal cells are glial cells, oligodendrocytes (e.g., Olig2 positive oligodendrocytes), or astrocytes (e.g., Olig2 positive astrocytes). In some embodiments, the AAV capsid variant is capable of transducing Olig2 positive cells, e.g., Olig2 positive astrocytes or Olig2 positive oligodendrocytes.

[0206] In some embodiments, an AAV capsid variant of the present disclosure has decreased tropism for the liver. In some embodiments, an AAV capsid variant comprises a modification that results in reduced tropism (e.g., de-targeting) and/or activity in the liver. In some embodiments, the reduced tropism in the liver is compared to an otherwise similar capsid that does not comprise the modification, e.g., a wild-type capsid polypeptide. In some embodiments, an AAV capsid variant comprises a modification that results in one or more of the following properties: (1) reduced tropism in the liver; (2) reduced, e.g., de-targeted expression in the liver; (3) reduced activity in the liver; and/or (4) reduced binding to galactose. In some embodiments, the reduction in any one or all of properties (1)-(3) is compared to an otherwise similar AAV capsid variant that does not comprise the modification.

[0207] Exemplary modifications are provided in WO 2018/119330; Pulicherla et al. (2011) *Mol. Ther.* 19(6): 1070-1078; Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075; and Bell et al. (2012) *J. Virol.* 86(13): 7326-33; the contents of which are hereby incorporated by reference in their entirety. In some embodiments, the AAV capsid variant comprises a modification at amino acid N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N272A), Y446 (e.g., Y446A), N498 (e.g., N498Y or N498I), W503 (e.g., W503R or W503A), L620

(e.g., L620F), or a combination thereof, as numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises one, two, three, four, five, or all of an amino acid other than N at amino acid 470 (e.g., A), an amino acid other than D at amino acid 271 (e.g., A), an amino acid other than N at amino acid 272 (e.g., A), an amino acid other than Y at amino acid 446 (e.g., A), and amino acid other than N at amino acid 498/ (e.g., Y or I), and amino acid other than W at amino acid 503 (e.g., R or A), and amino acid other than L at amino acid 620 (e.g., F), as numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification at amino acid N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N272A), Y446 (e.g., Y446A), and W503 (e.g., W503R or W503A), numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification at N498 (e.g., N498Y) and L620 (e.g., L620F).

[0208] In some embodiments, the AAV capsid variant comprises a modification as described in Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075, the contents of which are hereby incorporated by reference in its entirety. Exemplary modifications that alter or do not alter tissue transduction in at least the brain, liver, heart, lung, and/or kidney can be found in Supplementary Data 2 showing the AAV Barcode-Seq data obtained with AAV9-AA-VBCLib of Adachi et al. (*supra*), the contents of which are hereby incorporated by reference in their entirety.

[0209] In some embodiments, the AAV capsid variant is an isolated capsid variant. In some embodiments, the AAV capsid variant is a recombinant capsid variant. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant is an isolated and/or a recombinant AAV capsid polypeptide.

[0210] Also provided herein are polynucleotide sequences encoding any of the AAV capsid variants described above and AAV particles, vectors, and cells comprising the same.

Certain Properties of AAV Capsids

[0211] In some embodiments, an AAV particle of the present disclosure may comprise a capsid protein or variant thereof any natural or recombinant AAV serotype. AAV serotypes may differ in characteristics such as, but not limited to, packaging, tropism, transduction, and immunogenic profiles.

[0212] In some embodiments, an AAV capsid variant described herein allows for blood brain barrier penetration following intravenous administration. In some embodiments, the AAV capsid variant allows for blood brain barrier penetration following intravenous administration, focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration. In some embodiments the AAV capsid variant allows for increased distribution to a brain region. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, or a combination thereof. In some

embodiments, the AAV capsid variant allows for preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG). In some embodiments, the AAV capsid variant allows for preferential transduction in a brain region relative to the transduction in the liver. In some embodiments, the AAV capsid variant allows for transduction in a non-neuronal cell, e.g., a glial cell (e.g., an astrocyte, an oligodendrocyte, or a combination thereof).

[0213] In some embodiments, an AAV capsid variant allows for increased distribution to a spinal cord region. In some embodiments, the spinal region comprises a cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0214] In some embodiments, the initiation codon for translation of the AAV VP1 capsid protein, e.g., a capsid variant, described herein may be CTG, TTG, or GTG as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in its entirety.

[0215] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell (e.g., capsid) of a viral vector such as AAV. VP capsid proteins synthesized from Cap polynucleotides generally include a methionine as the first amino acid in the peptide sequence (Met1), which is associated with the start codon (AUG or ATG) in the corresponding Cap nucleotide sequence. However, it is common for a first-methionine (Met1) residue or generally any first amino acid (AA1) to be cleaved off after or during polypeptide synthesis by protein processing enzymes such as Met-aminopeptidases. This "Met/AA-clipping" process often correlates with a corresponding acetylation of the second amino acid in the polypeptide sequence (e.g., alanine, valine, serine, threonine, etc.). Met-clipping commonly occurs with VP1 and VP3 capsid proteins but can also occur with VP2 capsid proteins.

[0216] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, et al. Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid Proteins. *Hum Gene Ther Methods.* 2017 Oct. 28(5):255-267; Hwang, et al. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science.* 2010 February 19. 327(5968): 973–977; the contents of which are each incorporated herein by reference in its entirety.

[0217] According to the present disclosure, references to capsid proteins, e.g., AAV capsid variants, is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce, or result in capsid proteins of the present disclosure. A direct reference to a capsid protein or capsid polypeptide (such as VP1, VP2 or VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid

(Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0218] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes one or more capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0219] As a non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length, and which includes a "Met1" amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length, and which does not include the "Met1" amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length, and which includes an "AA1" amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length, and which does not include the "AA1" amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0220] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0221] As a non-limiting example, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3 (Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

Additional AAV Sequences

[0222] In some embodiments, an AAV capsid polypeptide or AAV capsid variant described herein may comprise a VOY101 capsid polypeptide, an AAVPHP.B (PHP.B) capsid polypeptide, a AAVPHP.N (PHP.N) capsid polypeptide, an AAV1 capsid polypeptide, an AAV2 capsid polypeptide, an AAV5 capsid polypeptide, an AAV9 capsid polypeptide, an AAV9 K449R capsid polypeptide, an AAVrh10 capsid polypeptide, or a functional variant thereof. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, comprises an amino acid sequence of any of the AAV capsid polypeptides in Table 6, or an amino acid sequence substantially identical (e.g., having at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide comprises any one of the nucleotide sequences in Table 6, or a nucleotide sequence substantially identical (e.g., having at

least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto.

[0223] In some embodiments, an AAV capsid polypeptide or an AAV capsid variant described herein comprises an amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO: 138. In some embodiments the AAV capsid polypeptide or the AAV capsid variant comprises an amino acid sequence comprising at least one, at least two, or at least three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, no more than 20, or no more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence having at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 137. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide or the AAV capsid variant comprises a nucleotide sequence having at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 137. In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises substitution at position K449, e.g., a K449R substitution, numbered relative to SEQ ID NO: 138.

[0224] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680). In some embodiments, the peptide is present immediately subsequent to position 588, numbered according to SEQ ID NO: 138. In some embodiments, the capsid polypeptide comprises the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0225] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; and a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the peptide is present immediately subsequent to position 588, numbered according to SEQ ID NO: 138.

[0226] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the peptide is present immediately subsequent to position 588, numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0227] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the insert is present immediately subsequent to position 588, numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0228] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g.,

having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, no more than 20, or no more than 10 modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 11, optionally wherein position 449 is not R.

[0229] In some embodiments, the AAV capsid polypeptide or AAV capsid variant, comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98%, or at least 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, no more than 20, or no more than 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 1.

Table 6. AAV Sequences

Serotype	SEQ ID NO:	Sequence
VOY101	1	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDWQR LINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAH EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSDGTLAVPFKAQAQT GWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTP VPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEF AVNTEGVYSEPRPIGTRYLTRNL
AAV9/hu.14 K449R	11	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDWQR LINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAH EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLSRTINGSGQNQQTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQG ILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPT AFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGV YSEPRPIGTRYLTRNL
AAV9/hu.14 WT (amino acid)	138	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDWQR LINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAH

		EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQG ILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPT AFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGV YSEPRPIGTRYLTRNL
AAV9/hu.14 WT (DNA)	137	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGC GAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAACATCAAGAC AACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTCGAC AAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACGACAAGGCCTACGAC CAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCGAGTTC CAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAG GCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCT GGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGGGTATTGGC AAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTTCGGTCAGACTGGCGACACAGAG TCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCT CTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGA GTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATC ACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATC TCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGA CTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATT CAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGC ACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGTGCTCGGGTCGGCTCAC GAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGATTCCTCAGTACGGGTATCTG ACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCTTTTACTGCCTGGAATATTTC CCGTCGCAAATGCTAAGAACGGGTAACAACTTCCAGTTCAGCTACGAGTTTGAGAACGTA CCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATC GACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAACG CTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAAACTACATACCT GGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAA TTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCT GGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTCCTTTGTCTGGATCT TTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGATGCGGACAAAGTCATGATA ACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGCAACGGAGTCCTATGGACAAGTG GCCACAAACCACCAGAGTGCCCAAGCACAGGCGCAGACCGGCTGGGTTCAAAACCAAGGA ATACTTCCGGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCC AAAATTCCTCACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTTGGAATG AAGCACCCGCCTCCTCAGATCCTCATCAAAAACACACCTGTACCTGCGGATCCTCCAACG GCCTTCAACAAGGACAAGCTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGC GTGGAGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAG TACACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTA TATAGTGAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTGTAA

AAV Viral Genome

[0230] In some embodiments, the AAV particle of the present disclosure serves as an expression vector comprising a viral genome that encodes a FXN protein (e.g., a human FXN protein).

[0231] In some embodiments, an AAV particle, e.g., an AAV particle for the vectorized delivery of a FXN protein described herein, comprises a viral genome, e.g., an AAV viral genome (e.g., an AAV genome, vector genome, or AAV vector genome). In some embodiments, the viral genome, e.g., the AAV viral genome, further comprises an inverted terminal repeat (ITR) region, an enhancer, a promoter, an intron region, an exon region, a nucleic acid encoding a transgene encoding a payload (e.g., a FXN protein sequence known in the art, e.g., any one of the sequences in Table 7), a

nucleotide sequence encoding at least one miR binding site (e.g., at least one miR122 binding site), a polyA region, or a combination thereof.

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0232] In some embodiments, the viral genome may comprise at least one inverted terminal repeat (ITR) region. The AAV particles of the present disclosure comprise a viral genome with at least one ITR region and a FXN-encoding region. In some embodiments, the viral genome has two ITRs. These two ITRs flank the FXN-encoding region at the 5' and 3' ends. In some embodiments, the ITR functions as an origin of replication comprising a recognition site for replication. In some embodiments, the ITR comprises a sequence region which can be complementary and symmetrically arranged. In some embodiments, the ITR incorporated into a viral genome described herein may be comprised of a naturally occurring polynucleotide sequence or a recombinantly derived polynucleotide sequence.

[0233] In some embodiments, the AAV viral genome may comprise at least one inverted terminal repeat (ITR) region having a length of 50-250 nucleotides. In some embodiments, the AAV viral genome comprises a 5' ITR region that is 50-250 nucleotides in length and a 3' ITR region that is 50-250 nucleotides in length. In some embodiments, the 5' ITR region and the 3' ITR region may comprise the same length and/or the same sequence. In some embodiments, the 5' ITR region and the 3' ITR region are different in length and/or in sequence. In some embodiments, the viral genome comprises a 5' ITR region that is 141 nucleotides in length. In some embodiments, the viral genome comprises a 3' ITR region that is 141 nucleotides in length. In some embodiments, the viral genome comprises a 5' ITR region that is 141 nucleotides in length and a 3' ITR region that is 141 nucleotides in length.

[0234] Non-limiting examples of ITR sequence regions are described in Table 7A. In some embodiments, the viral genome comprises a an ITR comprising the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the viral genome comprises an ITR comprising the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the viral genome comprises a 5' ITR region comprising the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or the viral genome comprises a 3' ITR region comprising the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at

least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

Table 7A. Exemplary Inverted Terminal Repeat (ITR) Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO	Sequence
ITR1	141	1811	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGG CCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTG GTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAG AGGGAGTGGCCAACTCCATCACTAGGGGTTCCT
ITR2	141	1812	AGGAACCCCTAGTGATGGAGTTGGCCACTCCC TCTCTGCGCGCTCGCTCGCTCACTGAGGCCGG GCGACCAAAGGTCGCCCGACGCCCGGGCTTTG CCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGC AGCTGCCTGCAGG

Viral Genome Component: Promoters and Enhancers

[0235] In some embodiments, the payload region of the viral genome comprises at least one element to enhance the transgene target specificity and expression. See, *e.g.*, Powell *et al.* Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy, 2015; the contents of which are herein incorporated by reference in their entirety. Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) sequences, upstream enhancers (USEs), CMV enhancers, and introns.

[0236] In some embodiments, expression of the polypeptides in a target cell may be driven by a specific promoter, including but not limited to, a promoter that is species specific, inducible, tissue-specific, or cell cycle-specific (Parr *et al.*, *Nat. Med.*3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[0237] In some embodiments, the viral genome comprises a promoter that is sufficient for expression, e.g., in a target cell, of a FXN protein, e.g., a human FXN protein, encoded by a transgene. In some embodiments, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded in the FXN-encoding region of the viral genome of the AAV particle.

[0238] In some embodiments, the promoter is a promoter deemed to be efficient when it drives expression in the cell or tissue being targeted.

[0239] Promoters may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include viral promoters, plant promoters and mammalian promoters. In some embodiments, the promoters may be human promoters. In some embodiments, the promoter may be truncated.

[0240] Promoters that promote expression in most mammalian tissues includes, but is not limited to, a human elongation factor 1α-subunit (EF1α) promoter, a cytomegalovirus (CMV) immediate-early enhancer and/or promoter, a chicken β-actin (CBA) promoter, a CAG promoter, a CAG

derivative promoter, a β glucuronidase (GUSB) promoter, and a ubiquitin C (UBC) promoter. A CAG promoter typically comprises: (C) the cytomegalovirus early enhancer element; (A) the promoter, the first exon, and the first intron of the chicken beta-actin gene, and (G) the splice acceptor of the rabbit beta-globin gene. In some embodiments, a derivative of a CAG promoter may comprise (i) a CMVie enhancer and a beta-actin promoter or (ii) a beta-actin promoter and an intron sequence.

[0241] Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes. Non-limiting examples of tissue-specific expression elements for neurons include neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), CaMKII, mGluR2, NFL, NFH, nβ2, PPE, Enk, and EAAT2 promoters. Non-limiting examples of tissue-specific expression elements for astrocytes include the glial fibrillary acidic protein (GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes include the myelin basic protein (MBP) promoter.

[0242] In some embodiments, the viral genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include H1, U6, CMV, CBA (including derivatives CAG, CBh, etc.), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX$_3$).

[0243] In some embodiments, the viral genome comprises a CBA promoter. In some embodiments, the viral genome comprises a truncated CBA promoter, e.g., a CBA promoter that is 50-400 nucleotides in length, e.g., 100-332 nucleotides in length. In some embodiments, the viral genome comprises a CMV promoter. In some embodiments, the viral genome comprises a truncated CMV promoter, e.g., a CMV promoter that is 50-300 nucleotides in length, e.g., a CMV promoter that is 109 nucleotides in length.

[0244] In some embodiments, the AAV vector comprises an enhancer element, a promoter, and/or a 5'UTR intron. The enhancer may be, but is not limited to, a CMV enhancer; the promoter may be, but is not limited to, a CMV, CBA, FXN, UBC, GUSB, NSE, Synapsin, MeCP2, or GFAP promoter; and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. In some embodiments, the enhancer, promoter, and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter; (9) GFAP promoter; (10) H1 promoter; and/or (11) U6 promoter.

[0245] In some embodiments, the viral genome comprises an engineered promoter.

[0246] In some embodiments, the viral genome comprises an enhancer. In some embodiments, an enhancer may be a separate component of the viral genome than the promoter. In some embodiments, an enhancer may be 5' to a promoter sequence in a viral genome. In some embodiments, an enhancer may be 3' to a promoter sequence in a viral genome.

[0247] In some embodiments, the viral genome comprises an enhancer, for example an immediate-early "ie" enhancer or a CMV/globin enhancer. In some embodiments, the enhancer comprises ie1 exon 1 and ie1 intron 1 or a fragment thereof. In some embodiments, the enhancer comprises an ie1 exon 1, an ie1 intron 1 or fragment thereof, a human beta-globin intron 2, and a human beta-globin exon 3.

[0248] In some embodiments, an enhancer may comprise at least one intron sequence. In some embodiments, an enhancer may comprise at least one exon sequence. In some embodiments, an enhancer comprises one intron sequence and one exon sequence. In some embodiments, an enhancer sequence comprises two intron sequences. In some embodiments, an enhancer sequence comprises two exon sequences. In some embodiments, an enhancer sequence comprises two intron sequences and two exon sequences.

[0249] Exemplary promoters are provided in Table 7B. In some embodiments, the promoter comprises or consists of any one of the nucleotide sequences provided in Table 7B, or a nucleotide sequence at least 90% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) identical thereto. In some embodiments, the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1738. In some embodiments, the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1740. In some embodiments, the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1742. In some embodiments, the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1745.

Table 7B. Exemplary Promoters

Promoter	SEQ ID NO:	Sequence
CBA-D4	1738	TACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTC ATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCCC CCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTG CAGCGATGGGGGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGG CGAGGGGCGGGGCGGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAG CGGCGCGCTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGGCC CTATAAAAAGCGAAGCGCGCGGCGGG
CBA-D6	1740	CCACGTTCTGCTTCACTCTCCCCATCTCCCCCCCCTCCCCACCCCCAATTT TGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGGGGCGGGGGGGG GGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCC TTTTATGGCGAGGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCG GCGGG
CBA-D8	1742	GGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATG GCGAGGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGG
CMV-D7	1750	TTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCC CCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGC AGAGCTC

Viral Genome Component: Introns and Exon Sequences

[0250] In some embodiments, the AAV viral genome comprises at least one intron and/or exon sequence region.

[0251] In some embodiments, the AAV viral genome may comprise at least one intron sequence region. The intron sequence region(s) may be 10-1200 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 32 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 53 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 134 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 347 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 379 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 566 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is about 1016 nucleotides in length. As a non-limiting example, the viral genome comprises an intron sequence region that is more than about 1016 nucleotides in length.

[0252] In some embodiments, the AAV viral genome comprises two intron sequence regions. In some embodiments, the AAV viral genome comprises three intron sequence regions. In some embodiments, the AAV viral genome comprises more than three intron sequence regions.

[0253] In some embodiments, the AAV viral genome may comprise at least one exon sequence region. In some embodiments, the exon sequence may be 10-1200 nucleotides in length. As a non-limiting example, the viral genome comprises an exon region that is about 32 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 53 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 134 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 347 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 379 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 566 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is about 1016 nucleotides in length. As a non-limiting example, the viral genome comprises an exon sequence region that is more than about 1016 nucleotides in length.

[0254] In some embodiments, the AAV particle viral genome comprises two exon sequence regions. In some embodiments, the AAV particle viral genome comprises three exon sequence regions. In some embodiments, the AAV particle viral genome comprises more than three exon sequence regions.

[0255] In some embodiments, the AAV particle viral genome comprises a hybrid intron/exon sequence region comprising at least one intron and at least one exon. In some embodiments, the hybrid intron/exon sequence region comprises one intron and one exon. In some embodiments, the

hybrid intron/exon sequence region comprises two introns and two exons. In some embodiments, an intron or exon sequence may comprise a full-length intron or exon. In some embodiments, an intron or exon sequence may comprise a fragment or variant of an intron or exon sequence.

[0256] The hybrid intron/exon sequence region(s) may, independently, have a length such as, but not limited to, 15-100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, and more than 1200 nucleotides. As a non-limiting example, the viral genome comprises a hybrid intron/exon sequence region that is about 379 nucleotides in length. As a non-limiting example, the viral genome comprises a hybrid intron/exon sequence region that is about 566 nucleotides in length. As a non-limiting example, the viral genome comprises a hybrid intron/exon region that is about 379 nucleotides in length.

[0257] In some embodiments, the intron/exon sequence region is an enhancer sequence. In some embodiments, the intron/exon sequence region is not an enhancer sequence.

[0258] In some embodiments, the intron/exon sequence region is a component of a promoter sequence. In some embodiments, the intron/exon sequence region is not a component of a promoter sequence.

[0259] In some embodiments, the AAV particle viral genome comprises at least one intron and/or exon sequence region. Non-limiting examples of intron and exon sequence regions are described in Table 7C. In some embodiments, the exon sequence region comprises the nucleotide sequence of SEQ ID NO: 1816, or a nucleotide sequence with at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto. In some embodiments, the exon sequence region comprises the nucleotide sequence of SEQ ID NO: 1817, or a nucleotide sequence with at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto. In some embodiments, the exon sequence region comprises the nucleotide sequence of SEQ ID NO: 1819, or a nucleotide sequence with at least at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto. In some embodiments, the exon sequence region comprises the nucleotide sequence of SEQ ID NO: 1820, or a nucleotide sequence with at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto. In some embodiments, the exon sequence region comprises the nucleotide sequence of SEQ ID NO: 1821, or a nucleotide sequence with at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto.

Table 7C. Exemplary Intron and Exon Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO	Sequence
hBglobin intron/exon	566	1816	TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGA AGACACCGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGG GAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAA GTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCTTTCTTCTT

			TTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATC TCTTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTGC ACCATTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAG CAATATTTCTGCATATAAATATTTCTGCATATAAATTGTAACTGAT GTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCAT TCTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTC CAAGCTAGGCCCTTTTGCTAATCATGTTCATACCTCTTATCTTCCT CCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCAC TTTGGCAAAGAATT
ie1 exon 1	134	1817	TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGA AGACACCGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGG GAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGAC
ie1 intron 1 (partial)	32	1819	GTAAGTACCGCCTATAGAGTCTATAGGCCCAC
hBglobin intron 2	347	1820	AAAAAATGCTTTCTTCTTTTAATATACTTTTTTGTTTATCTTATTT CTAATACTTTCCCTAATCTCTTTCTTTCAGGGCAATAATGATACAA TGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGATAATT TCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGC ATATAAATTGTAACTGATGTAAGAGGTTTCATATTGCTAATAGCAG CTACAATCCAGCTACCATTCTGCTTTTATTTTATGGTTGGGATAAG GCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTT CATACCTCTTATCTTCCTCCCACAG
hBglobin exon 3	53	1821	CTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCA AAGAATT

Viral Genome Component: miR Binding Site

[0260] Tissue- or cell-specific expression of the AAV viral particles of the disclosure can be enhanced by introducing tissue- or cell-specific regulatory sequences, *e.g.*, promoters, enhancers, microRNA binding sites, *e.g.*, a detargeting site. Without wishing to be bound by theory, it is believed that an encoded miR binding site can modulate, *e.g.*, prevent, suppress, or otherwise inhibit, the expression of a gene of interest in the viral genome of the disclosure, based on the expression of the corresponding endogenous microRNA (miRNA) or a corresponding controlled exogenous miRNA in a tissue or cell, *e.g.*, a non-targeting cell or tissue. In some embodiments, a miR binding site modulates, *e.g.*, reduces, expression of the payload encoded by a viral genome of an AAV particle described herein in a cell or tissue where the corresponding mRNA is expressed. In some embodiments, the miR binding site modulates, e.g., reduces, expression of the encoded FXN protein in a cell or tissue of the DRG or liver.

[0261] In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a microRNA binding site, *e.g.*, a detargeting site. In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a miR binding site, a microRNA binding site series (miR BSs), or a reverse complement thereof. In some embodiments, the 3' UTR of the viral genome may be engineered to include at least one miRNA binding site.

[0262] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, *e.g.*, 1-3, 2-4, or 3-5 copies, or at least 1, at least 2, at least 3, at least 4, at least 5 or more copies of a

miR binding site (miR BS). In some embodiments, the encoded miR binding site series comprises 4 copies of a miR binding site. In some embodiments, all copies are identical, *e.g.*, comprise the same miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, *e.g.*, a non-coding sequence.

[0263] In some embodiments, the nucleotide genome comprises at least one sequence encoding a miRNA binding site to reduce the expression of the transgene in a specific tissue. In some embodiments, the viral genome may comprise a miR-122 miRNA binding site (miR-122BS) or tandem copies of the miR-122BS to reduce the expression of the viral genome in the liver. In some embodiments, the viral genome may comprise a miR-183 miRNA binding site (miR-183BS) or tandem copies of the miR-183BS to reduce expression of the viral genome in the DRG.

[0264] In some embodiments, the miR binding site may be 20-75 nucleotides in length. In some embodiments, the miR binding site is 23 nucleotides in length. In some embodiments, the miR binding site is 71 nucleotides in length.

[0265] Non-limiting examples of miR-binding site sequence regions are shown in Table 7D.

[0266] In some embodiments, the encoded miR binding site is fully complementary to an miR. In some embodiments, the encoded miR binding site is partially complementary to an miR. In some embodiments, the miR is expressed in the liver or in hepatocytes. In some embodiments, the miR is miR122. In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR122 binding site sequence. In some embodiments, the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1827, or a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity, or comprising at least one, at least two, at least three, at least four, at least five, or six modifications, but no more than six modifications, relative to the nucleotide sequence of SEQ ID NO: 1827, wherein the modification(s) can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises an encoded miR122 binding site series comprising at least 2, at least 3, at least 4, or at least 5 copies of the encoded miR122 binding site, optionally wherein the encoded miR122 binding site series comprises the nucleotide sequence of SEQ ID NO: 1826, or a nucleotide sequence having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity, or comprising at least one, at least two, at least three, at least four, at least five, at least six, or at least seven modifications, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 1826, wherein the modification(s) can result in a mismatch between the encoded miR binding site and the corresponding miRNA.

Table 7D. Exemplary miR Binding Site Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO	Sequence

miR122 binding site series	71	1826	ACAAACACCATTGTCACACTCCACACAAACACC ATTGTCACACTCCACACAAACACCATTGTCACA CTCCA
Single miR122 binding site	23	1827	ACAAACACCATTGTCACACTCCA

Viral Genome Component: Polyadenylation Region

[0267] In some embodiments, the viral genome of an AAV particle of the present disclosure comprises at least one polyadenylation (polyA) region. In some embodiments, the polyA region is positioned 3' relative to the nucleic acid encoding a FXN protein described herein.

[0268] In some embodiments, the polyA region comprises a length of about 100 to 500 nucleotides, e.g., about 477 nucleotides. In some embodiments, the polyA region comprises a length of 477 nucleotides.

[0269] A non-limiting example of a polyA region is described in Table 7E. In some embodiments, the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828, or a nucleotide sequence at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto.

Table 7E. Exemplary PolyA Region

Sequence Region Name	Sequence Length	SEQ ID NO	Sequence
hGHpA	477	1828	GGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCT GGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAAT TAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATT ATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAA GACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGA GTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGG GTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATT CCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGT AGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTCC TAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGG ATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTT

Viral Genome Component: Filler (Stuffer) Sequence

[0270] As used herein, the terms "stuffer sequence" and "filler sequence" are used interchangeably. In some embodiments, the AAV particle viral genome comprises at least one filler sequence. In some embodiments, the AAV particle viral genome comprises a filler sequence comprising a human albumin sequence. In some embodiments, the AAV particle viral genome comprises the filler sequence of Alb2034. In some embodiments, the AAV particle viral genome comprises the filler sequence of Alb2106. In some embodiments, the AAV particle viral genome comprises the filler sequence of Alb2264. In some embodiments, the AAV particle viral genome comprises the filler sequence of Alb2266

[0271] Non-limiting examples of filler sequences are described in Table 7F. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1838, or a nucleotide sequence at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1839, or a nucleotide sequence at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1840, or a nucleotide sequence at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1841, or a nucleotide sequence at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical thereto.

Table 7F. Exemplary Filler Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO	Sequence
Alb2034	2034	1838	TCTCCTGAACAACTAGTTAAACTTGGCTTTGAGTTCCAC CTGTACCACTTGCATAATCTTGGGAAAGTGAGTTGCCT AATTCAGTGACATTAATAAATTTATTAATTTCTTCTTTC AATAAAACCTGGAGAGAGCTTCATATGTATCAGCATAT GCTAAACTTGAAAGATACAAGTAGAAAATGGAAGGAA ATATATCTGACTCAATAGGGATAGTTCAAGGGTTAAAT TAAAAGTAGTAAAGTATTATAATTAATCTGACATGGTA CCTAATATATAATAATCATGTATTAAGAATGCCAGTCA CCATTAAAAGTCAATGTATGACTTTAATCTACTCGAGG AAAGAAACTATGTCTTGTTCACTGTTATTATCTCTAAAA TCCATAATCAGAAGAGCACCATGTGTATGAGCCACACA ATAAATATCTACTGTATAATATGTCTCTTCTTGTTTTTA ACCTTCATAGATAAGACTCTATTGAATTGGGACATTAG TCCAGCAAGCCATTCTGTCTCTGTCTCTTCTATGGAGGG AAAGGTTTAACCATCAAAGACTAGGTGCATCTCCCAAA CAACCTGAATTTAATATTCAAATATGTATCTAAATTCAT TTGTTACATTTTTGTGTTCAGCTTACATATTACTTTTTGA GCGACATCTATTCAAGGCCTACTACTTGCTGCTCTACAA AATATTGCCATGCTCTATTTGCCCATTAACTATTTCTTA ACCTTCAAGGGACATGCTCAGTTCTGATATACCAAGAT TTGGTATTTACCCTCCCAGCCTACATACTTCCAATCTTA AGAGAACAATTTTTAGACTACATTCAAATATAGACCTC TCCACCCCATCAACTATTTTATCTCTCCTCTCCTATCTTT CTTGACAAAGAGTGATTAGAAATATGCAATGTATTTTC ATTCTTAAAAGTTCTATGCTAGGTGGCTCATATATTAAG TCTTAAATAATTACAAATTGATAAAAAAAATCAGTCAA TAAAAATTACTTACGCATTCTGGAATTTGTACTCTCCAA GCTGCTCAAAAAGCTCACAATTTTGTTTGATTAAATTCT GAGGCTCTTCCACAAGAGGTTTAAATTCATCGAACTGA

			AACATAAAAGAATTGTGTTAATAGTATTATGCCTCAGG ATCAGATGCAGGTTGTTTTTCACCCCTCTGGTCAGAATG ATATCCTTTCTTCTTCCTACTCAAAGCCACATGAATAGA TGAATATCAATGCCGCTCTGTCACAATACATTCGAACT ATTTATTTGGTGAGCTTGCATCATGTAAGTGGTTAAGA ATATTCAGGCTCTGGAGTTCAATGACCAGTATTTGAGC CAAGTCATGTAACTCATTCTTCAGTTGTGCAATTTTACT TACCATCTCCACATTTCAGAATCCTTATCCCTAAAATAG GGGCAAAGATGGCACTCATCTCATAGAGCTGCTCTGTA AACCAGGTAAGCTAATGAAATTAAACAGTGCCTTGCAT ATAATAAAAGTTTAATAAATGATGGCTATGATTGTACA TATTATTATTATTAGTTCACCTTTCCAGTTAGATTCCAG GCTCTCCAAAATGAGAGATTTTACGTTGGTCATTGTTTG TGCATGGTGCCTGGCATACAGTAGCTTCTTGAAAGCAG GAAAAATGAGTTTTCTCTGATTCTGAATAGTTCAGAAA CCATTACATATGCTAGTGGGAACCCTAAAAATCCTCCA GAACAGATTTCCTCTCCTAACTTAATTTCTTGTAAAACT ATTCCTAAACATCCTCAAAAAGATTTGAAAATATTCTA AAGGGATAGGTTCTATAATTTGCCATAAGATACTAATT CTAGTACTTGATTAATCCTGGAATCAGGTTAACTCACTT TACATCTAAGTTAAATATCTTCTAATTAACATTTAAATT TAATTTTTTTTTGTTCTCAGGATTGTGAAAAAGAGAAAA AAAGATCAAAATTTTTTAGAGATTGCTCTATTCAGATCT TTCTATTCTAACTAGTCTAAATTTTGTCCTAG
Alb2106	2106	1839	GATGTTGCTATGTTCCATTCATCATATTATCTCCATCTG CAGAGTAGTGGGTTAGTGGAGGGTAGAAAACATTCTCC TGAACAACTAGTTAAACTTGGCTTTGAGTTCCACCTGTA CCACTTGCATAATCTTGGGAAAGTGAGTTGCCTAATTC AGTGACATTAATAAATTTATTAATTTCTTCTTTCAATAA AACCTGGAGAGAGCTTCATATGTATCAGCATATGCTAA ACTTGAAAGATACAAGTAGAAAATGGAAGGAAATATA TCTGACTCAATAGGGATAGTTCAAGGGTTAAATTAAAA GTAGTAAAGTATTATAATTAATCTGACATGGTACCTAA TATATAATAATCATGTATTAAGAATGCCAGTCACCATT AAAAGTCAATGTATGACTTTAATCTACTCGAGGAAAGA AACTATGTCTTGTTCACTGTTATTATCTCTAAAATCCAT AATCAGAAGAGCACCATGTGTATGAGCCACACAATAA ATATCTACTGTATAATATGTCTCTTCTTGTTTTTAACCTT CATAGATAAGACTCTATTGAATTGGGACATTAGTCCAG CAAGCCATTCTGTCTCTGTCTCTTCTATGGAGGGAAAG GTTTAACCATCAAAGACTAGGTGCATCTCCCAAACAAC CTGAATTTAATATTCAAATATGTATCTAAATTCATTTGT TACATTTTTGTGTTCAGCTTACATATTACTTTTTGAGCG ACATCTATTCAAGGCCTACTACTTGCTGCTCTACAAAAT ATTGCCATGCTCTATTTGCCCATTAACTATTTCTTAACC TTCAAGGGACATGCTCAGTTCTGATATACCAAGATTTG GTATTTACCCTCCCAGCCTACATACTTCCAATCTTAAGA GAACAATTTTTAGACTACATTCAAATATAGACCTCTCC ACCCCATCAACTATTTTATCTCTCCTCTCCTATCTTTCTT GACAAAGAGTGATTAGAAATATGCAATGTATTTTCATT CTTAAAAGTTCTATGCTAGGTGGCTCATATATTAAGTCT TAAATAATTACAAATTGATAAAAAAAATCAGTCAATAA AAATTACTTACGCATTCTGGAATTTGTACTCTCCAAGCT GCTCAAAAAGCTCACAATTTTGTTTGATTAAATTCTGAG

			GCTCTTCCACAAGAGGTTTAAATTCATCGAACTGAAAC ATAAAAGAATTGTGTTAATAGTATTATGCCTCAGGATC AGATGCAGGTTGTTTTTCACCCCTCTGGTCAGAATGATA TCCTTTCTTCTTCCTACTCAAAGCCACATGAATAGATGA ATATCAATGCCGCTCTGTCACAATACATTCGAACTATTT ATTTGGTGAGCTTGCATCATGTAAGTGGTTAAGAATAT TCAGGCTCTGGAGTTCAATGACCAGTATTTGAGCCAAG TCATGTAACTCATTCTTCAGTTGTGCAATTTTACTTACC ATCTCCACATTTCAGAATCCTTATCCCTAAAATAGGGG CAAAGATGGCACTCATCTCATAGAGCTGCTCTGTAAAC CAGGTAAGCTAATGAAATTAAACAGTGCCTTGCATATA ATAAAAGTTTAATAAATGATGGCTATGATTGTACATAT TATTATTATTAGTTCACCTTTCCAGTTAGATTCCAGGCT CTCCAAAATGAGAGATTTTACGTTGGTCATTGTTTGTGC ATGGTGCCTGGCATACAGTAGCTTCTTGAAAGCAGGAA AAATGAGTTTTCTCTGATTCTGAATAGTTCAGAAACCAT TACATATGCTAGTGGGAACCCTAAAAATCCTCCAGAAC AGATTTCCTCTCCTAACTTAATTTCTTGTAAAACTATTC CTAAACATCCTCAAAAAGATTTGAAAATATTCTAAAGG GATAGGTTCTATAATTTGCCATAAGATACTAATTCTAGT ACTTGATTAATCCTGGAATCAGGTTAACTCACTTTACAT CTAAGTTAAATATCTTCTAATTAACATTTAAATTTAATT TTTTTTTGTTCTCAGGATTGTGAAAAAGAGAAAAAAAG ATCAAAATTTTTTAGAGATTGCTCTATTCAGATCTTTCT ATTCTAACTAGTCTAAATTTTGTCCTAG
Alb2264	2264	1840	CTAGGTTTCTTGAGACCTCTACAAGAGTTGGAGTTGAC ACTTGGGGTACTTTCTTGGTGTAACGAACTAATAGCCT GAAAAAAAGAAGTCATGTGTTTTCAGCAAGGCAAGAA ACTGTCTAACATAGTAGATAAAACAGAGAACACTTGGC CGGAATCAACTAAGATGTTGCTATGTTCCATTCATCATA TTATCTCCATCTGCAGAGTAGTGGGTTAGTGGAGGGTA GAAAACATTCTCCTGAACAACTAGTTAAACTTGGCTTT GAGTTCCACCTGTACCACTTGCATAATCTTGGGAAAGT GAGTTGCCTAATTCAGTGACATTAATAAATTTATTAATT TCTTCTTTCAATAAAACCTGGAGAGAGCTTCATATGTAT CAGCATATGCTAAACTTGAAAGATACAAGTAGAAAATG GAAGGAAATATATCTGACTCAATAGGGATAGTTCAAGG GTTAAATTAAAAGTAGTAAAGTATTATAATTAATCTGA CATGGTACCTAATATATAATAATCATGTATTAAGAATG CCAGTCACCATTAAAAGTCAATGTATGACTTTAATCTA CTCGAGGAAAGAAACTATGTCTTGTTCACTGTTATTATC TCTAAAATCCATAATCAGAAGAGCACCATGTGTATGAG CCACACAATAAATATCTACTGTATAATATGTCTCTTCTT GTTTTTAACCTTCATAGATAAGACTCTATTGAATTGGGA CATTAGTCCAGCAAGCCATTCTGTCTCTGTCTCTTCTAT GGAGGGAAAGGTTTAACCATCAAAGACTAGGTGCATCT CCCAAACAACCTGAATTTAATATTCAAATATGTATCTA AATTCATTTGTTACATTTTTGTGTTCAGCTTACATATTA CTTTTTGAGCGACATCTATTCAAGGCCTACTACTTGCTG CTCTACAAAATATTGCCATGCTCTATTTGCCCATTAACT ATTTCTTAACCTTCAAGGGACATGCTCAGTTCTGATATA CCAAGATTTGGTATTTACCCTCCCAGCCTACATACTTCC AATCTTAAGAGAACAATTTTTAGACTACATTCAAATAT AGACCTCTCCACCCCATCAACTATTTTATCTCTCCTCTC CTATCTTTCTTGACAAAGAGTGATTAGAAATATGCAAT

			GTATTTTCATTCTTAAAAGTTCTATGCTAGGTGGCTCAT ATATTAAGTCTTAAATAATTACAAATTGATAAAAAAAA TCAGTCAATAAAAATTACTTACGCATTCTGGAATTTGTA CTCTCCAAGCTGCTCAAAAAGCTCACAATTTTGTTTGAT TAAATTCTGAGGCTCTTCCACAAGAGGTTTAAATTCATC GAACTGAAACATAAAAGAATTGTGTTAATAGTATTATG CCTCAGGATCAGATGCAGGTTGTTTTTCACCCCTCTGGT CAGAATGATATCCTTTCTTCTTCCTACTCAAAGCCACAT GAATAGATGAATATCAATGCCGCTCTGTCACAATACAT TCGAACTATTTATTTGGTGAGCTTGCATCATGTAAGTGG TTAAGAATATTCAGGCTCTGGAGTTCAATGACCAGTAT TTGAGCCAAGTCATGTAACTCATTCTTCAGTTGTGCAAT TTTACTTACCATCTCCACATTTCAGAATCCTTATCCCTA AAATAGGGGCAAAGATGGCACTCATCTCATAGAGCTGC TCTGTAAACCAGGTAAGCTAATGAAATTAAACAGTGCC TTGCATATAATAAAAGTTTAATAAATGATGGCTATGAT TGTACATATTATTATTATTAGTTCACCTTTCCAGTTAGA TTCCAGGCTCTCCAAAATGAGAGATTTTACGTTGGTCAT TGTTTGTGCATGGTGCCTGGCATACAGTAGCTTCTTGAA AGCAGGAAAAATGAGTTTTCTCTGATTCTGAATAGTTC AGAAACCATTACATATGCTAGTGGGAACCCTAAAAATC CTCCAGAACAGATTTCCTCTCCTAACTTAATTTCTTGTA AAACTATTCCTAAACATCCTCAAAAAGATTTGAAAATA TTCTAAAGGGATAGGTTCTATAATTTGCCATAAGATAC TAATTCTAGTACTTGATTAATCCTGGAATCAGGTTAACT CACTTTACATCTAAGTTAAATATCTTCTAATTAACATTT AAATTTAATTTTTTTTTGTTCTCAGGATTGTGAAAAAGA GAAAAAAAGATCAAAATTTTTTAGAGATTGCTCTATTC AGATCTTTCTATTCTAACTAGTCTAAATTTTC
Alb2266	2266	1841	GTTTCTTGAGACCTCTACAAGAGTTGGAGTTGACACTT GGGGTACTTTCTTGGTGTAACGAACTAATAGCCTGAAA AAAAGAAGTCATGTGTTTTCAGCAAGGCAAGAAACTGT CTAACATAGTAGATAAAACAGAGAACACTTGGCCGGA ATCAACTAAGATGTTGCTATGTTCCATTCATCATATTAT CTCCATCTGCAGAGTAGTGGGTTAGTGGAGGGTAGAAA ACATTCTCCTGAACAACTAGTTAAACTTGGCTTTGAGTT CCACCTGTACCACTTGCATAATCTTGGGAAAGTGAGTT GCCTAATTCAGTGACATTAATAAATTTATTAATTTCTTC TTTCAATAAAACCTGGAGAGAGCTTCATATGTATCAGC ATATGCTAAACTTGAAAGATACAAGTAGAAAATGGAA GGAAATATATCTGACTCAATAGGGATAGTTCAAGGGTT AAATTAAAAGTAGTAAAGTATTATAATTAATCTGACAT GGTACCTAATATATAATAATCATGTATTAAGAATGCCA GTCACCATTAAAAGTCAATGTATGACTTTAATCTACTCG AGGAAAGAAACTATGTCTTGTTCACTGTTATTATCTCTA AAATCCATAATCAGAAGAGCACCATGTGTATGAGCCAC ACAATAAATATCTACTGTATAATATGTCTCTTCTTGTTT TTAACCTTCATAGATAAGACTCTATTGAATTGGGACATT AGTCCAGCAAGCCATTCTGTCTCTGTCTCTTCTATGGAG GGAAAGGTTTAACCATCAAAGACTAGGTGCATCTCCCA AACAACCTGAATTTAATATTCAAATATGTATCTAAATTC ATTTGTTACATTTTTGTGTTCAGCTTACATATTACTTTTT GAGCGACATCTATTCAAGGCCTACTACTTGCTGCTCTAC AAAATATTGCCATGCTCTATTTGCCCATTAACTATTTCT TAACCTTCAAGGGACATGCTCAGTTCTGATATACCAAG

			ATTTGGTATTTACCCTCCCAGCCTACATACTTCCAATCT TAAGAGAACAATTTTTAGACTACATTCAAATATAGACC TCTCCACCCCATCAACTATTTTATCTCTCCTCTCCTATCT TTCTTGACAAAGAGTGATTAGAAATATGCAATGTATTT TCATTCTTAAAAGTTCTATGCTAGGTGGCTCATATATTA AGTCTTAAATAATTACAAATTGATAAAAAAAAATCAGTC AATAAAAATTACTTACGCATTCTGGAATTTGTACTCTCC AAGCTGCTCAAAAAGCTCACAATTTTGTTTGATTAAATT CTGAGGCTCTTCCACAAGAGGTTTAAATTCATCGAACT GAAACATAAAAGAATTGTGTTAATAGTATTATGCCTCA GGATCAGATGCAGGTTGTTTTTCACCCCTCTGGTCAGA ATGATATCCTTTCTTCTTCCTACTCAAAGCCACATGAAT AGATGAATATCAATGCCGCTCTGTCACAATACATTCGA ACTATTTATTTGGTGAGCTTGCATCATGTAAGTGGTTAA GAATATTCAGGCTCTGGAGTTCAATGACCAGTATTTGA GCCAAGTCATGTAACTCATTCTTCAGTTGTGCAATTTTA CTTACCATCTCCACATTTCAGAATCCTTATCCCTAAAAT AGGGGCAAAGATGGCACTCATCTCATAGAGCTGCTCTG TAAACCAGGTAAGCTAATGAAATTAAACAGTGCCTTGC ATATAATAAAAGTTTAATAAATGATGGCTATGATTGTA CATATTATTATTATTAGTTCACCTTTCCAGTTAGATTCC AGGCTCTCCAAAATGAGAGATTTTACGTTGGTCATTGTT TGTGCATGGTGCCTGGCATACAGTAGCTTCTTGAAAGC AGGAAAAATGAGTTTTCTCTGATTCTGAATAGTTCAGA AACCATTACATATGCTAGTGGGAACCCTAAAAATCCTC CAGAACAGATTTCCTCTCCTAACTTAATTTCTTGTAAAA CTATTCCTAAACATCCTCAAAAAGATTTGAAAATATTCT AAAGGGATAGGTTCTATAATTTGCCATAAGATACTAAT TCTAGTACTTGATTAATCCTGGAATCAGGTTAACTCACT TTACATCTAAGTTAAATATCTTCTAATTAACATTTAAAT TTAATTTTTTTTTGTTCTCAGGATTGTGAAAAAGAGAAA AAAAGATCAAAATTTTTTAGAGATTGCTCTATTCAGAT CTTTCTATTCTAACTAGTCTAAATTTTGTCCTAG

Viral Genome Component: Frataxin-Encoding Sequence

[0272] In some embodiments, the disclosure provides an AAV particle comprising a viral genome encoding a FXN protein, e.g., a human frataxin protein, wherein the viral genome comprises a wild-type FXN-encoding sequence such as the nucleotide sequence of SEQ ID NO: 1824. In some embodiments, the AAV particle comprises a viral genome comprising any one of SEQ ID NOs: 1797, 1801, 1808, or 1809. In some embodiments, the viral genome comprises the nucleotide sequence of SEQ ID NO: 1797. In some embodiments, the viral genome comprises a promoter operably linked to a polynucleotide sequence encoding a FXN protein (i.e., operably linked to the FXN-encoding sequence).

[0273] In some embodiments, the disclosure herein provides constructs that allow for improved expression of FXN protein (e.g., a human frataxin protein) delivered by gene therapy vectors.

[0274] In some embodiments, the disclosure provides constructs that allow for improved biodistribution of FXN protein (e.g., a human frataxin protein) delivered by gene therapy vectors.

[0275] In some embodiments, the present disclosure relates to a composition containing or comprising a nucleic acid sequence encoding a FXN protein (e.g., a human frataxin protein) or a functional fragment or variant thereof and methods of administering the composition *in vitro* or *in vivo* in a subject, e.g., a human subject and/or an animal model of disease, e.g., Friedreich's Ataxia.

[0276] In some embodiments, the disclosure provides a nucleotide sequence encoding a FXN protein (e.g., a human frataxin protein) for use in an AAV viral genome, wherein the nucleotide sequence comprises any one of the sequences provided in Table 12, or a sequence that is at least 90% identical to any one of the sequences provided in Table 12. In some embodiments, the AAV viral genome further comprises one or more, e.g., all of, a 5' ITR sequence, a promoter, an intron sequence, a polyA sequence, at least one miR122 binding site, and a 3' ITR sequence. In some embodiments, the FXN protein encoded by the viral genome is a human FXN protein.

Table 12. Exemplary Frataxin Sequences

Type	Species	Description
PRT	*Homo sapiens*	NP_000135.2
PRT	*Homo sapiens*	NP_852090.1
PRT	*Homo sapiens*	NP_001155178.1
DNA	*Homo sapiens*	NM_000144.4 encodes NP_000135.2
DNA	*Homo sapiens*	NM_181425.2 encodes NP_852090.1
DNA	*Homo sapiens*	NM_001161706.1 encodes NP_001155178.1

[0277] In some embodiments, the FXN protein is encoded by the nucleotide sequence (i.e., the FXN-encoding sequence) of SEQ ID NO: 1824.

[0278] SEQ ID NO: 1824:

atgtggactc tcgggcgccg cgcagtagcc ggcctcctgg cgtcacccag cccagcccag 60

gcccagaccc tcacccgggt cccgcggccg gcagagttgg ccccactctg cggccgccgt 120

ggcctgcgca ccgacatcga tgcgacctgc acgccccgcc gcgcaagttc gaaccaacgt 180

ggcctcaacc agatttggaa tgtcaaaaag cagagtgtct atttgatgaa tttgaggaaa 240

tctggaactt tgggccaccc aggctctcta gatgagacca cctatgaaag actagcagag 300

gaaacgctgg actctttagc agagtttttt gaagaccttg cagacaagcc atacacgttt 360

gaggactatg atgtctcctt tgggagtggt gtcttaactg tcaaactggg tggagatcta 420

ggaacctatg tgatcaacaa gcagacgcca aacaagcaaa tctggctatc ttctccatcc 480

agtggaccta agcgttatga ctggactggg aaaaactggg tgtactccca cgacggcgtg 540

tccctccatg agctgctggc cgcagagctc actaaagcct taaaaaccaa actggacttg 600

tcttccttgg cctattccgg aaaagatgct tga 633

[0279] In some embodiments, the AAV genome encodes a payload construct that comprises a combination of coding and non-coding nucleic acid sequences.

[0280] In some embodiments, the payload comprises a gene therapy product including, but not limited to, a polypeptide, RNA molecule, or other gene product that, when expressed in a target cell, provides a desired therapeutic effect. In some embodiments, a gene therapy product may comprise a substitute for a non-functional gene or a gene that is absent, expressed in insufficient amounts, or mutated. In some embodiments, a gene therapy product may comprise a substitute for a non-functional protein or polypeptide or a protein or polypeptide that is absent, expressed in insufficient amounts, misfolded, degraded too rapidly, or mutated. For example, a gene therapy product may comprise a polynucleotide encoding a FXN protein to treat FA. In some embodiments, the gene therapy product is encoded by the polynucleotide sequence of SEQ ID NO: 1797. In some embodiments, the gene therapy product comprises is encoded by the polynucleotide sequence of SEQ ID NO: 1801. In some embodiments, the gene therapy product comprises is encoded by the polynucleotide sequence of SEQ ID NO: 1808. In some embodiments, the gene therapy product comprises is encoded by the polynucleotide sequence of SEQ ID NO: 1809.

[0281] In some embodiments, the payload encodes a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide that encodes a polypeptide of interest and that is capable of being translated to produce the encoded polypeptide of interest *in vitro*, *in vivo*, *in situ*, or *ex vivo*. Certain embodiments provide the mRNA as encoding FXN (e.g., human FXN) or a variant thereof.

[0282] A payload construct encoding a payload may comprise or encode a selectable marker. A selectable marker may comprise a gene sequence or a protein or polypeptide encoded by a gene sequence expressed in a host cell that allows for the identification, selection, and/or purification of the host cell from a population of cells that may or may not express the selectable marker. In some embodiments, the selectable marker provides resistance to survive a selection process that would otherwise kill the host cell, such as treatment with an antibiotic. In some embodiments, an antibiotic selectable marker may comprise one or more antibiotic resistance factors, including but not limited to neomycin resistance (*e.g.*, neo), hygromycin resistance, kanamycin resistance, and/or puromycin resistance. In some embodiments, a payload construct encoding a payload may comprise a selectable marker including, but not limited to, β-lactamase, luciferase, β-galactosidase, or any other reporter gene as that term is understood in the art.

[0283] In some embodiments, a payload construct encoding a selectable marker may comprise a fluorescent protein. A fluorescent protein as herein described may comprise any fluorescent marker including but not limited to green, yellow, and/or red fluorescent protein (GFP, YFP, and/or RFP). In

some embodiments, a payload construct encoding a selectable marker may comprise a human influenza hemagglutinin (HA) tag.

[0284] In certain embodiments, a nucleic acid for expression of a payload in a target cell will be incorporated into the viral genome and located between two ITR sequences.

Exemplary FXN AAV Viral Genome Sequence Regions and ITR to ITR Sequences

[0285] In some embodiments, a viral genome, e.g., an AAV viral genome or vector genome, described herein, comprises a promoter operably linked to a transgene encoding a FXN protein (e.g., a human FXN protein). In some embodiments, the viral genome further comprises an inverted terminal repeat (ITR) region, a promoter, an intron/exon region, a miR binding site region, a polyA region, or a combination thereof (e.g., all of these elements).

[0286] Exemplary sequence regions within ITR-to-ITR sequences for viral genomes according to the description are provided in Table 13 and disclosures below.

Table 13. Representative ITR-to-ITR Sequences

	hFXN2	hFXN6	hFXN13	hFXN14
ITR to ITR	1797	1801	1808	1809
5'ITR	1811	1811	1811	1811
Promoter	1742	1750	1738	1740
Intron/Exon	1816	1816	1816	1816
Intron/Exon components	1817, 1819, 1820, 1821	1817, 1819, 1820, 1821	1817, 1819, 1820, 1821	1817, 1819, 1820, 1821
FXN Payload	1824	1824	1824	1824
miR122 BS (3x)	1826	1826	1826	1826
miR122 BS	1827 (3x)	1827 (3x)	1827 (3x)	1827 (3x)
Poly(A)	1828	1828	1828	1828
Filler	1841	1840	1838	1839
3'ITR	1812	1812	1812	1812

[0287] SEQ ID NO: 1797:

cctgcaggca gctgcgcgct cgctcgctca ctgaggccgc ccgggcaaag cccgggcgtc 60

gggcgacctt tggtcgcccg gcctcagtga gcgagcgagc gcgcagagag ggagtggcca 120

actccatcac taggggttcc ttgtagttaa tgattaaccc gccatgctac ttatctacgt 180

agccatgcgt cgacataacg cgtggtgcgg cggcagccaa tcagagcggc gcgctccgaa 240

agtttccttt tatggcgagg cggcggcggc ggcggcccta taaaaagcga agcgcgcggc 300

gggcgggagc aagcttcgtt tagtgaaccg tcagatcgcc tggagacgcc atccacgctg 360

ttttgacctc catagaagac accgggaccg atccagcctc cgcggattcg aatcccggcc 420

gggaacggtg cattggaacg cggattcccc gtgccaagag tgacgtaagt accgcctata 480

gagtctatag gcccacaaaa aatgctttct tcttttaata tacttttttg tttatcttat 540

ttctaatact ttccctaatc tctttctttc agggcaataa tgatacaatg tatcatgcct 600

ctttgcacca ttctaaagaa taacagtgat aatttctggg ttaaggcaat agcaatattt 660

ctgcatataa atatttctgc atataaattg taactgatgt aagaggtttc atattgctaa 720

tagcagctac aatccagcta ccattctgct tttattttat ggttgggata aggctggatt 780

attctgagtc caagctaggc ccttttgcta atcatgttca tacctcttat cttcctccca 840

cagctcctgg gcaacgtgct ggtctgtgtg ctggcccatc actttggcaa agaattggga 900

ttcgaaccgg tatgtggact ctcgggcgcc gcgcagtagc cggcctcctg gcgtcaccca 960

gcccagccca ggcccagacc ctcacccggg tcccgcggcc ggcagagttg gccccactct 1020

gcggccgccg tggcctgcgc accgacatcg atgcgacctg cacgccccgc cgcgcaagtt 1080

cgaaccaacg tggcctcaac cagatttgga atgtcaaaaa gcagagtgtc tatttgatga 1140

atttgaggaa atctggaact ttgggccacc caggctctct agatgagacc acctatgaaa 1200

gactagcaga ggaaacgctg gactctttag cagagttttt tgaagacctt gcagacaagc 1260

catacacgtt tgaggactat gatgtctcct ttgggagtgg tgtcttaact gtcaaactgg 1320

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gctcgctcgc tcactgaggc cgggcgacca aaggtcgccc gacgcccggg ctttgcccgg 4560

gcggcctcag tgagcgagcg agcgcgcagc tgcctgcagg 4600

[0291] In some embodiments, the AAV viral genome comprises a FXN protein-encoding sequence comprising SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824. In some embodiments, the AAV viral genome comprises a 5' ITR region comprising SEQ ID NO: 1811 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1811 and/or a 3' ITR region comprising SEQ ID NO: 1812 or a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1812.

[0292] In some embodiments, the AAV viral genome further comprises or consists of a truncated promoter region of 100-332 nucleotides in length and comprises any one of SEQ ID NOs: 1738, 1740, 1742, or 1750, or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to any one of SEQ ID NOs: 1738, 1740, 1742, or 1750.

[0293] In some embodiments, the AAV viral genome further comprises an intron/exon region comprising SEQ ID NO: 1816 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1816.

[0294] In some embodiments, the AAV viral genome comprises a miR-122 binding site comprising SEQ ID NO: 1827 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1827. In some embodiments, the AAV viral genome further comprises a miR-122 binding site series comprising SEQ ID NO: 1826 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1826.

[0295] In some embodiments, the AAV viral genome further comprises a polyA region comprising SEQ ID NO: 1828 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1828.

[0296] In some embodiments, the AAV viral genome further comprises a filler sequence comprising any one of SEQ ID NOs: 1838, 1839, 1840, or 1841, or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to any one of SEQ ID NOs: 1838, 1839, 1840, or 1841.

[0297] In some embodiments, the AAV viral genome does not comprise a filler sequence.

[0298] In some embodiments, the AAV particle comprises, from 5' to 3', a 5' ITR comprising the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; a promoter consisting of the nucleotide sequence of SEQ ID NO: 1742 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; an intron/exon region comprising the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; a FXN-encoding sequence comprising the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; a miR122 binding site series comprising the nucleotide sequence of SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; a polyA region comprising the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or a 3' ITR comprising the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto. In some embodiments, the AAV particle comprising the FXN-encoding sequence of SEQ ID NO: 1824 further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1841 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto, wherein the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR region.

[0299] In some embodiments, the viral genome comprises the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1809.

[0300] In some embodiments, the AAV used in the present disclosure is single-stranded.

[0301] In some embodiments, the AAV viral genome is capable of forming double-stranded DNA. In some embodiments, the viral genome is self-complementary.

[0302] In some embodiments, the AAV particle comprises a viral genome (e.g., comprising SEQ ID NO: 1797) that is packaged in an AAV capsid variant comprising an amino acid sequence selected from Table 3 or Table 4.

[0303] In some embodiments, the AAV capsid variant comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), which is present in loop IV, e.g., between amino acids 449-460 numbered according to SEQ ID NO: 982 (i.e., at a sequence position corresponding to that in SEQ ID NO: 982). In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence according to positions 138-742 of SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence according to positions 203-742 of SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0304] In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941), which is present in loop IV, e.g., between amino acids 449-460 numbered according to SEQ ID NO: 36 (i.e., at a sequence position corresponding to that in SEQ ID NO: 36). In some embodiments, the AAV capsid variant comprises the amino acid E at position 451, the amino acid R at position 452, and the amino acid V at position 453, numbered according to SEQ ID NO: 36. In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941) present immediately subsequent to position 455 (e.g., at positions 456-461), numbered according to SEQ ID NO: 36; and (ii) the amino acid E at position 451, the amino acid R at position 452, and the amino acid V at position 453, numbered according to SEQ ID NO: 36. In some embodiments, the AAV capsid variant comprises the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589) in loop IV, e.g., between amino acids 449-460 numbered according to SEQ ID NO: 36. In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence according to positions 138-742 of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence according to positions 203-742 of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0305] In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPSHKA (SEQ ID NO: 941), which is present in loop IV, e.g., between amino acids 449-460

numbered according to SEQ ID NO: 4 (i.e., at a sequence position corresponding to that in SEQ ID NO: 4). In some embodiments, the AAV capsid variant comprises the amino acid E at position 451, and the amino acid V at position 453, numbered according to SEQ ID NO: 4. In some embodiments, the AAV capsid variant comprises: (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941) present immediately subsequent to position 455 (e.g., at positions 456-461), numbered according to SEQ ID NO: 4; and (ii) the amino acid E at position 451 and the amino acid V at position 453, numbered according to SEQ ID NO: 4. In some embodiments, the AAV capsid variant comprises the amino acid sequence of KTENVSGSPHSKAQNQQT (SEQ ID NO: 3272) in loop IV, e.g., between amino acids 449-460 numbered according to SEQ ID NO: 4. In some embodiments, the AAV capsid variant comprises: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence according to positions 138-742 of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence according to positions 203-742 of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0306] In some embodiments, the AAV particle comprises the viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 or a sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) thereto, and further comprises an AAV capsid variant comprising: an amino acid sequence having the formula [N1]-[N2]-[N3], wherein: (i) [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G; (ii) [N2] comprises the amino acid sequence of SPH; and (iii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R; wherein [N1]-[N2]-[N3] is present in hypervariable loop IV; and wherein the AAV capsid variant comprises an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-736 of SEQ ID NO: 138.

[0307] In some embodiments, the AAV particle comprises the viral genome comprising the nucleotide sequence of SEQ ID NO: 1797, or a sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) thereto, and further comprises an AAV capsid variant comprising: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence of positions 203-742 of

SEQ ID NO: 982 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0308] In some embodiments, the AAV particle comprises the viral genome comprising the nucleotide sequence of SEQ ID NO: 1797, or a sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) thereto, and further comprises an AAV capsid variant comprising: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence of positions 138-742 of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence of positions 203-742 of SEQ ID NO: 36 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0309] In some embodiments, the AAV particle comprises the viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 or a sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) thereto, and further comprises an AAV capsid variant comprising: (i) a VP1 protein comprising or consisting of the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; (ii) a VP2 protein comprising or consisting of the amino acid sequence of positions 138-742 of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or (iii) a VP3 protein comprising or consisting of the amino acid sequence of positions 203-742 of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

[0310] The present disclosure provides, in some embodiments, vectors, cells, and/or AAV particles comprising the above-identified viral genomes and/or capsid variants.

[0311] Methods for producing and/or modifying AAV viral genome and particles are disclosed in the art such as pseudotyped AAV particles (International Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO 2005005610 and WO 2005072364, the content of each of which are incorporated herein by reference in their entirety).

Backbone

[0312] In certain embodiments, a cis-element such as a vector backbone is incorporated into the viral particle encoding, *e.g.*, a FXN protein, e.g., a human FXN protein described herein. Without

being by theory, it is believed, in some embodiments, the backbone sequence may contribute to the stability of FXN protein expression, and/or the level of expression of the FXN protein.

[0313] The present disclosure also provides in some embodiments, a nucleic acid encoding a viral genome disclosed herein (e.g., comprising SEQ ID NO: 1797), or a nucleotide sequence substantially identical (e.g., having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100%, sequence identity) thereto, and a backbone region suitable for replication of the viral genome in a cell, e.g., a bacterial cell (e.g., wherein the backbone region comprises one or both of a bacterial origin of replication and a selectable marker).

II. AAV Production

[0314] Viral production disclosed herein describes processes and methods for producing AAV particles (with enhanced, improved and/or increased tropism for a target tissue), e.g., an AAV particle comprising an AAV capsid variant that may be used to contact a target cell to deliver a payload.

[0315] In some embodiments, disclosed herein is a method of making AAV particle of the present disclosure, e.g., an AAV particle comprising an AAV capsid variant the method comprising: (i) providing a host cell comprising a viral genome described herein and (ii) incubating the host cell under conditions suitable to enclose the viral genome in an AAV capsid variant, e.g., an AAV capsid variant described herein (e.g., an AAV capsid variant listed in Tables 3, 4, or 5), thereby making the AAV particle. In some embodiments, the method comprises prior to step (i), introducing a first nucleic acid comprising the viral genome into a cell. In some embodiments, the host cell comprises a second nucleic acid encoding the AAV capsid variant. In some embodiments, the second nucleic acid is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule. In some embodiments, the AAV particle described herein is an isolated AAV particle. In some embodiments, the AAV particle described herein is a recombinant AAV particle.

[0316] Any method known in the art may be used for the preparation of AAV particles. In some embodiments, AAV particles are produced in mammalian cells (e.g., HEK293). In another embodiment, AAV particles are produced in insect cells (e.g., Sf9 cells).

[0317] Methods of making AAV particles are well known in the art and are described in e.g., U.S. Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597; Methods In Molecular Biology, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., Baculovirus Expression Vectors, A Laboratory Manual, Oxford Univ. Press (1994); Samulski et al., *J. Vir.*63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.,* 219:37-44 (1996); Zhao et al., *Vir.*272:382-93 (2000); the contents of each of

which are herein incorporated by reference in their entirety. In some embodiments, the AAV particles are made using the methods described in International Patent Publication WO2015191508, the contents of which are herein incorporated by reference in their entirety.

III. Pharmaceutical Compositions

[0318] The present disclosure additionally provides a method for treating Friedreich's Ataxia, e.g., in a human subject, comprising administering to the subject any of the AAV polynucleotides or AAV genomes described herein or administering to the subject a particle comprising said AAV polynucleotide or AAV genome, or administering to the subject any of the described compositions, including pharmaceutical compositions.

[0319] In some embodiments, a composition described herein comprises an AAV polynucleotide or AAV genome or AAV particle and at least one excipient.

[0320] Although pharmaceutical compositions provided herein, *e.g.*, comprising AAV particles comprising a payload encoding a FXN protein to be delivered, provided herein are principally directed to pharmaceutical compositions that are suitable for administration to humans, it will be understood by the skilled artisan that such compositions may be suitable for administration to any other animal, *e.g.*, non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various non-human animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[0321] In some embodiments, compositions are administered to humans, e.g., human patients or human subjects.

[0322] In some embodiments, the AAV particle formulations described herein may contain a nucleic acid encoding at least one payload. In some embodiments, the formulations may contain a nucleic acid encoding 1, 2, 3, 4, or 5 payloads. In some embodiments, the particle may contain a nucleic acid encoding a payload construct encoding proteins selected from categories such as, but not limited to, human proteins, veterinary proteins, bacterial proteins, biological proteins, antibodies, immunogenic proteins, therapeutic peptides and proteins, secreted proteins, plasma membrane proteins, cytoplasmic proteins, cytoskeletal proteins, intracellular membrane bound proteins, nuclear proteins, proteins associated with human disease, and/or proteins associated with non-human diseases. In some embodiments, the formulation contains at least three payload constructs encoding proteins. Certain embodiments provide that at least one of the payloads is FXN protein or a variant thereof.

[0323] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

IV. Formulations

[0324] Formulations of the AAV pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0325] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered.

[0326] For example, the composition may comprise about 0.1% to about 99% (w/w) of the active ingredient. By way of example, the composition may comprise about 0.1% to about 100%, e.g., about 0.5% to about 50%, about 1% to about30%, about 5% to about80%, or at least 80% (w/w) active ingredient.

[0327] The AAV particles of the disclosure can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed release; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein *in vivo*; (6) alter the release profile of encoded protein *in vivo* and/or (7) allow for regulatable expression of the payload.

[0328] Formulations of the present disclosure can include, without limitation, saline, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with viral vectors (e.g., for transplantation into a subject), nanoparticle mimics and combinations thereof. Further, the viral vectors of the present disclosure may be formulated using self-assembled nucleic acid nanoparticles.

[0329] In some embodiments, the viral vectors encoding FXN may be formulated to optimize baricity and/or osmolality. In some embodiments, the baricity and/or osmolality of the formulation may be optimized to ensure optimal drug distribution in the central nervous system or a region or component of the central nervous system.

Excipients

[0330] The formulations of the disclosure can include one or more excipients, each in an amount that together increases the stability of the AAV particle, increases cell transfection or transduction by the viral particle, increases the expression of viral particle encoded protein, and/or alters the release profile of AAV particle encoded proteins. In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0331] Excipients, which, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (*see* Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; the contents of which are herein incorporated by reference in their entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

Inactive Ingredients

[0332] In some embodiments, AAV formulations may comprise at least one excipient which is an inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more agents that do not contribute to the activity of the pharmaceutical composition included in formulations. In some embodiments, all, none, or some of the inactive ingredients which may be used in the formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0333] Formulations of AAV particles may include cations or anions. In some embodiments, the formulations include metal cations such as, but not limited to, Zn^{2+}, Ca^{2+}, Cu^{2+}, Mg^{+}, or combinations thereof. In one embodiment, formulations may include polymers or polynucleotides complexed with a metal cation (*See, e.g.*, U.S. Pat. Nos. 6,265,389 and 6,555,525, the contents of each of which are herein incorporated by reference in their entirety).

V. Uses and Applications

[0334] The compositions of the disclosure may be administered to a subject or used in the manufacture of a medicament for administration to a subject having a FXN protein deficiency, such as Friedreich's Ataxia (FA).

[0335] In some embodiments, the disclosure provides a method for treating a FXN protein deficiency, such as FA. In certain embodiments, the AAV particles comprising a FXN protein-encoding sequence may be administered to a subject to treat FA. In some embodiments, the delivery of the AAV particles may halt or slow progression of FA. In certain embodiments, the delivery of the AAV particles improves symptoms of FA.

[0336] In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, and/or modify their distribution within the body.

[0337] In some embodiments, the delivery of the AAV particles may stabilize, slow the progression of, or improve the subject's FA as determined by the modified Friedreich Ataxia Rating Scale (mFARS), the Scale for the Assessment and Rating of Ataxia (SARA), and/or the International Cooperative Ataxia Rating Scale (ICARS).

[0338] In some embodiments, the delivery of the AAV particles may halt or slow progression of Friedreich's ataxia as measured by mFARS, SARA, or ICARS by 50% relative to a comparator group. In certain embodiments, the delivery of the AAV particles increases the presence of functional FXN, improves and stabilizes gait, improves ataxia-associated heart conditions, decreases feelings of exhaustion, and treats metabolic disorders such as diabetes.

[0339] In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, and/or modify their distribution within the body.

[0340] In certain embodiments, the pharmaceutical compositions described herein are used as research tools, particularly in *in vitro* investigations using human cell lines such as HEK293T and *in vivo* testing in nonhuman primates which will occur prior to human clinical trials.

[0341] The present disclosure provides a method for treating a disease, disorder and/or condition in a mammalian subject, including a human subject, comprising administering to the subject any of the viral particles *e.g.*, AAV, AAV particle, or AAV genome that produces FXN protein described herein or administering to the subject a particle comprising said AAV particle or AAV genome, or administering to the subject any of the described compositions. including pharmaceutical compositions.

[0342] In some embodiments, AAV particles of the present disclosure, through delivery of a functional payload that is a therapeutic product comprising a FXN protein or variant thereof that can modulate the level or function of FXN in the CNS.

[0343] A functional payload may alleviate or reduce symptoms that result from abnormal level and/or function of a gene product (*e.g.*, an absence or defect in a protein) in a subject in need thereof or that otherwise confers a benefit to a CNS disorder in a subject in need thereof.

[0344] As non-limiting examples, companion or combination therapeutic products delivered by AAV particles of the present disclosure may include, but are not limited to, growth and trophic factors, cytokines, hormones, neurotransmitters, enzymes, anti-apoptotic factors, angiogenic factors, FXN polypeptides, and any protein known to be mutated in pathological disorders such as FA (e.g., brain specific Mir-128a, *See* Adlakha and Saini, Molecular cancer, 2014, 13:33, incorporated herein by reference in its entirety).

[0345] In some embodiments, the neurodegenerative disorder is Friedreich's ataxia, e.g., resulting from expansion of an intronic GAA triplet repeat in the FXN gene, which reduces expression of the mitochondrial protein frataxin causing progressive damage to the nervous system.

In some embodiments, the AAV particles of the present disclosure may be used to ameliorate at least one symptom of FA, including, but not limited to, impaired sensory functions, impaired motor function, e.g., ataxia and/or involuntary movements, fatigue, chronic pain, seizures, impaired speech, sleep disturbances, metabolic disorders, e.g., diabetes, and increased spasticity.

[0346] In some embodiments, the delivery of the AAV particles may halt or slow the disease progression of Friedreich's ataxia by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% using a known analysis method and comparator group for Friedreich's ataxia. As a non-limiting example, the delivery of the AAV particles may halt or slow progression of Friedreich's ataxia as measured by mFARS/SARA by 50% relative to a comparator group.

[0347] In some embodiments, the AAV particle encoding a payload may increase the amount of FXN in a tissue by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or more than 100%. In some embodiments, delivery of an AAV particle described herein encoding a payload may increase the amount of FXN in a tissue to be comparable to the amount of FXN in the corresponding tissue of a healthy individual. In some embodiments, delivery of the AAV particle encoding a payload may increase the amount of FXN in a tissue effective to reduce one or more symptoms of a disease associated with decreased FXN expression or a deficiency in the quantity and/or function of FXN, e.g., FA.

VI. Delivery of AAV Particles

Delivery to Cells

[0348] In some aspects, the present disclosure provides a method of delivering to a cell or tissue any of the above-described AAV particles, comprising contacting the cell or tissue with said AAV particle or contacting the cell or tissue with a formulation comprising said AAV particle, or contacting the cell or tissue with any of the described compositions, including pharmaceutical compositions. The method of delivering the AAV particle to a cell or tissue can be accomplished *in vitro, ex vivo*, or *in vivo*.

Delivery to Subjects

[0349] In some aspects, the present disclosure additionally provides a method of delivering to a subject, including a mammalian subject, any of the above-described AAV particles comprising administering to the subject said AAV particle, or administering to the subject a formulation comprising said AAV particle, or administering to the subject any of the described compositions, including pharmaceutical compositions.

[0350] In some embodiments, the AAV particles may be delivered to bypass anatomical blockages (e.g., the blood brain barrier).

[0351] In some embodiments, the AAV particles may be formulated and delivered to a subject by a route which increases the speed of drug effect as compared to oral delivery.

[0352] In some embodiments, the AAV particles may be delivered using intrathecal infusion.

[0353] In some embodiments, a subject may be administered the AAV particles described herein using a bolus infusion.

[0354] In some embodiments, the AAV particles encoding FXN may be delivered in a continuous and/or bolus infusion. Each site of delivery may use a different dosing regimen or the same dosing regimen may be used for each site of delivery. As a non-limiting example, the sites of delivery may be in the cervical and the lumbar region. As another non-limiting example, the sites of delivery may be in the cervical region. As another non-limiting example, the sites of delivery may be in the lumbar region.

[0355] In some embodiments, the AAV particles may be delivered to a subject via a single route of administration.

[0356] In some embodiments, the AAV particles may be delivered to a subject via a multi-site route of administration. For example, a subject may be administered the AAV particles at 2, 3, 4, 5, or more than 5 sites.

[0357] In some embodiments, a subject may be administered the AAV particles described herein using sustained delivery over a period of minutes, hours, or days. The infusion rate may be changed depending on the subject, distribution, formulation, or another delivery parameter known to those in the art.

[0358] In some embodiments, if continuous delivery (continuous infusion) of the AAV particles is used, the continuous infusion may be for 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, or more than 24 hours.

[0359] In some embodiments, the intracranial pressure may be evaluated prior to administration. The route, volume, AAV particle concentration, infusion duration and/or vector titer may be optimized based on the intracranial pressure of a subject.

[0360] In some embodiments, the AAV particles may be delivered by systemic delivery. In some embodiments, the systemic delivery may be by intravascular administration. In some embodiments, the systemic delivery may be by intravenous administration.

[0361] In some embodiments, the AAV particles may be delivered by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular administration.

[0362] In some embodiments, an AAV particle described herein is administered intravenously.

[0363] In some embodiments, the AAV particles may be delivered by direct (intraparenchymal) injection into the substance of an organ, *e.g.*, one or more regions of the brain.

[0364] In some embodiments, the AAV particles may be delivered by subpial injection into the spinal cord. For example, subjects may be placed into a spinal immobilization apparatus. A dorsal laminectomy may be performed to expose the spinal cord. Guiding tubes and XYZ manipulators may be used to assist catheter placement. Subpial catheters may be placed into the subpial space by advancing the catheter from the guiding tube and AAV particles may be injected through the catheter (Miyanohara *et al.*, Mol Ther Methods Clin Dev. 2016; 3: 16046). In some cases, the AAV particles may be injected into the cervical subpial space. In some cases, the AAV particles may be injected into the thoracic subpial space.

[0365] In some embodiments, the AAV particles may be delivered by direct injection to the CNS of a subject. In some embodiments, direct injection is intracerebral injection, intraparenchymal injection, intrathecal injection, intra-cisterna magna injection, or any combination thereof. In some embodiments, direct injection to the CNS of a subject comprises convection enhanced delivery (CED). In some embodiments, administration comprises peripheral injection. In some embodiments, peripheral injection is intravenous injection.

[0366] In some embodiments, the AAV particles may be delivered to a subject to increase a FXN protein level in the CNS (e.g., amygdala, brainstem, caudate, central grey, cerebellum (e.g., Purkinje cell layer and deep cerebellar nuclei), cortex (e.g., frontal cortex, motor cortex, perirhinal cortex, sensory cortex, and/or temporal cortex), external cuneate nucleus, geniculate nucleus, globus pallidus, gracile nucleus, hippocampus, inferior colliculus, inferior olivary complex, nucleus ambiguus, oculomotor nucleus, putamen, substantia nigra, thalamus, ventral palladium, vestibular nucleus, and/or spinal cord (e.g., cervical spinal cord region, lumbar spinal cord region, or thoracic spinal cord

region) as compared to a baseline level in the subject. The increase may be 0.1x to 5x, 0.5x to 5x, 1x to 5x, 2x to 5x, 3x to 5x, 4x to 5x, 0.1x to 4x, 0.5x to 4x, 1x to 4x, 2x to 4x, 3x to 4x, 0.1x to 3x, 0.5x to 3x, 1x to 3x, 2x to 3x, 0.1x to 2x, 0.5x to 2x, 0.1x to 1x, 0.5x to 1x, 0.1x to 0.5x, 1x to 2x, 0.1x, 0.2x, 0.3x, 0.4x, 0.5x, 0.6x, 0.7x, 0.8x, 0.9x, 1.0x, 1.1x, 1.2x, 1.3x, 1.4x, 1.5x, 1.6x, 1.7x, 1.8x, 1.9x, 2.0x, 2.1x, 2.2x, 2.3x, 2.4x, 2.5x, 2.6x, 2.7x, 2.8x, 2.9x, 3.0x, 3.1x, 3.2x, 3.3x, 3.4x, 3.5x, 3.6x, 3.7x, 3.8x, 3.9x, 4.0x, 4.1x, 4.2x, 4.3x, 4.4x, 4.5x, 4.6x, 4.7x, 4.8x, 4.9x or more than 5x as compared to a baseline level. In some embodiments, the increase may be 0.5x-3x as compared to a baseline level. In some embodiments, the increase may be 1.5-4x as compared to a baseline level.

[0367] In some embodiments, the AAV particles may be delivered to a subject to increase a FXN protein level in the CNS (e.g., amygdala, brainstem, caudate, central grey, cerebellum (e.g., Purkinje cell layer and deep cerebellar nuclei), cortex (e.g., frontal cortex, motor cortex, perirhinal cortex, sensory cortex, and/or temporal cortex), external cuneate nucleus, geniculate nucleus, globus pallidus, gracile nucleus, hippocampus, inferior colliculus, inferior olivary complex, nucleus ambiguus, oculomotor nucleus, putamen, substantia nigra, thalamus, ventral palladium, vestibular nucleus, and/or spinal cord (e.g., cervical spinal cord region, lumbar spinal cord region, or thoracic spinal cord region)) by transducing cells in these CNS regions. Transduction may also be referred to as the number of cells that are positive for FXN protein. The transduction may be greater than or equal to 1%, greater than or equal to 5%, greater than or equal to 10%, greater than or equal to 15%, greater than or equal to 20%, greater than or equal to 25%, greater than or equal to 30%, greater than or equal to 35%, greater than or equal to 40%, greater than or equal to 45%, greater than or equal to 50%, greater than or equal to 55%, greater than or equal to 60%, greater than or equal to 65%, greater than or equal to 70%, greater than or equal to 75%, greater than or equal to 80%, greater than or equal to 85%, greater than or equal to 90%, greater than or equal to 95%, or greater than or equal to 99% of cells in these CNS regions.

[0368] In some embodiments, delivery of AAV particles comprising a viral genome encoding FXN as described herein to neurons in the brain (e.g., amygdala, brainstem, caudate, central grey, cerebellum (e.g., Purkinje cell layer and deep cerebellar nuclei), cortex (e.g., frontal cortex, motor cortex, perirhinal cortex, sensory cortex, and/or temporal cortex), external cuneate nucleus, geniculate nucleus, globus pallidus, gracile nucleus, hippocampus, inferior colliculus, inferior olivary complex, nucleus ambiguus, oculomotor nucleus, putamen, substantia nigra, thalamus, ventral palladium, and/or vestibular nucleus) may lead to an increased expression of FXN protein in one or more of those neurons. In some embodiments, the increased FXN protein expression may lead to improved survival and/or function of various cell types in these CNS regions and/or improvement of at least one symptom of Friedreich's Ataxia.

[0369] In particular embodiments, the AAV particles may be delivered to a subject in order to establish widespread distribution of the FXN throughout the CNS by administering the AAV particles to the thalamus of the subject.

[0370] In some embodiments, the increased expression of FXN protein may lead to improved gait, improved ataxia-associated heart conditions, decreased feeling of exhaustion, improved symptoms relating to metabolic disorders such as diabetes, and/or improved quality of life.

Administration

[0371] In some embodiments, the present disclosure provides methods comprising administering viral vectors in accordance with the disclosure to a subject in need thereof. Viral vector pharmaceutical, diagnostic, or prophylactic compositions thereof, may be administered to a subject using any amount and any route of administration effective for treating, or diagnosing a disease, disorder, and/or condition associated with decreased FXN expression or FXN deficiency. In some embodiments, the disease, disorder, and/or condition is FA.

[0372] Compositions in accordance with the disclosure may be formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present disclosure may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific FXN employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[0373] In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses, *e.g.*, two or more administrations of the single unit dose. As used herein, a "single unit dose" is a dose of any therapeutic composition administered in one dose/at one time/single route/single point of contact, *i.e.*, single administration event. In some embodiments, a single unit dose is provided as a discrete dosage form (*e.g.*, a tablet, capsule, patch, loaded syringe, vial, *etc.*). As used herein, a "total daily dose" is an amount given or prescribed in 24-hour period. It may be administered as a single unit dose. The viral particles may be formulated in buffer only or in a formulation described herein.

[0374] In some embodiments, pharmaceutical composition described herein can be formulated into a topical, intranasal, pulmonary, intratracheal, or injectable dosage form. In some embodiments, a pharmaceutical composition described herein can be formulated in a dosage form suitable for intravenous, intraocular, intravitreal, intramuscular, intracardiac, intraperitoneal, and/or subcutaneous administration.

[0375] In some embodiments, delivery of the AAV particles described herein results in minimal serious adverse events (SAEs) as a result of the delivery of the AAV particles.

Combinations

[0376] The AAV particles may be used in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. The phrase "in combination with," is not intended to require that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, and/or modify their distribution within the body.

[0377] The therapeutic agents may be approved by the US Food and Drug Administration or may be in clinical trial or at the preclinical research stage. The therapeutic agents may utilize any therapeutic modality known in the art, with non-limiting examples including gene silencing or interference (*e.g.*., miRNA, siRNA, RNAi, shRNA), gene editing (*e.g.*., TALEN, CRISPR/Cas9 systems, zinc finger nucleases), and gene, protein or enzyme replacement.

[0378] In some embodiments, an AAV particle described herein, or a pharmaceutical composition comprising the AAV particle, may be administered in combination with at least one additional therapeutic agent and/or therapy. In some embodiments, the at least one additional therapeutic agent and/or therapy comprises an agent and/or therapy for treating the disorder associated with FXN deficiency (e.g., Friedreich's Ataxia). In some embodiments, the at least one additional therapeutic agent and/or therapy comprises omaveloxolone or idebenone. In some embodiments, the at least one additional therapeutic agent and/or therapy comprises CoQ10, IFN gamma, or a drug to treat comorbidities including diabetes, heart disease, and/or pain.

[0379] In some embodiments, the at least one additional therapeutic agent and/or therapy comprises an immunosuppressant. In some embodiments, the immunosuppressant may be administered to the subject prior to administration of an AAV particle or pharmaceutical composition described herein. In some embodiments, the immunosuppressant may be administered to the subject simultaneously with administration of an AAV particle or pharmaceutical composition described herein. In some embodiments, the immunosuppressant may be administered to the subject after administration of an AAV particle or pharmaceutical composition described herein. In some embodiments, the AAV particle or pharmaceutical composition is administered to a subject who is receiving or has received an immunosuppressant. In some embodiments, the immunosuppressant comprises a corticosteroid (e.g., prednisone, prednisolone, methylprednisolone, and/or

dexamethasone), rapamycin, mycophenolate mofetil, tacrolimus, rituximab, and/or eculizumab hydroxychloroquine.

Measurement of Expression

[0380] Expression of FXN from viral genomes may be determined using various methods known in the art such as, but not limited to immunochemistry (e.g., IHC), enzyme-linked immunosorbent assay (ELISA), affinity ELISA, ELISPOT, flow cytometry, immunocytology, surface plasmon resonance analysis, kinetic exclusion assay, liquid chromatography-mass spectrometry (LCMS), high-performance liquid chromatography (HPLC), BCA assay, immunoelectrophoresis, Western blot, SDS-PAGE, protein immunoprecipitation, PCR, and/or in situ hybridization (ISH). In some embodiments, transgenes encoding FXN delivered in different AAV capsids may have different expression levels in dorsal root ganglion (DRG).

[0381] In certain embodiments, the FXN polypeptide is detectable by Western blot.

[0382] In certain embodiments, the FXN polypeptide is detectable by a frataxin biofluid assay, such as the assay described in PCT/US2020/045687, the contents of which are hereby incorporated by reference in their entirety. In certain embodiments, a FXN gene, mRNA, and/or protein expression is measured in a cell or tissue of a subject who is receiving or has received an AAV particle described herein. In certain embodiments, the FXN gene, mRNA, and/or protein expression is measured in a cell or tissue of the CNS, such as the amygdala, brainstem, caudate, central grey, cerebellum (e.g., Purkinje cell layer and deep cerebellar nuclei), cortex (e.g., frontal cortex, motor cortex, perirhinal cortex, sensory cortex, and/or temporal cortex), external cuneate nucleus, geniculate nucleus, globus pallidus, gracile nucleus, hippocampus, inferior colliculus, inferior olivary complex, nucleus ambiguus, oculomotor nucleus, putamen, substantia nigra, thalamus, ventral palladium, vestibular nucleus, and/or spinal cord (e.g., cervical spinal cord region, lumbar spinal cord region, or thoracic spinal cord region). In certain embodiments, the FXN gene, mRNA, and/or protein expression is measured in a peripheral cell or tissue, such as the liver, heart, kidney, pancreas, and/or muscle.

VII. Kits and Devices

Kits

[0383] In some aspects, the present disclosure provides a variety of kits for conveniently and/or effectively carrying out methods of the present disclosure. Typically, kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

[0384] Any of the vectors, constructs, or FXN of the present disclosure may be comprised in a kit. In some embodiments, kits may further include reagents and/or instructions for creating and/or synthesizing compounds and/or compositions of the present disclosure. In some embodiments, kits may also include one or more buffers. In some embodiments, kits of the disclosure may include

components for making protein or nucleic acid arrays or libraries and thus, may include, for example, solid supports.

[0385] In some embodiments, kit components may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and suitably aliquoted. Where there is more than one kit component, (labeling reagent and label may be packaged together), kits may also generally contain second, third or other additional containers into which additional components may be separately placed. In some embodiments, kits may also comprise second container means for containing sterile, pharmaceutically acceptable buffers and/or other diluents. In some embodiments, various combinations of components may be comprised in one or more vial. Kits of the present disclosure may also typically include means for containing compounds and/or compositions of the present disclosure, e.g., proteins, nucleic acids, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which desired vials are retained.

[0386] In some embodiments, kit components are provided in one and/or more liquid solutions. In some embodiments, liquid solutions are aqueous solutions, with sterile aqueous solutions being particularly used. In some embodiments, kit components may be provided as dried powder(s). When reagents and/or components are provided as dry powders, such powders may be reconstituted by the addition of suitable volumes of solvent. In some embodiments, it is envisioned that solvents may also be provided in another container means. In some embodiments, labeling dyes are provided as dried powders. In some embodiments, it is contemplated that 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 micrograms or at least or at most those amounts of dried dye are provided in kits of the disclosure. In such embodiments, dye may then be resuspended in any suitable solvent, such as DMSO.

[0387] In some embodiments, kits may include instructions for employing kit components as well the use of any other reagent not included in the kit. Instructions may include variations that may be implemented.

Devices

[0388] In some embodiments, compounds and/or compositions of the present disclosure may be combined with, coated onto or embedded in a device. Devices may include, but are not limited to, dental implants, stents, bone replacements, artificial joints, valves, pacemakers and/or other implantable therapeutic device.

[0389] The present disclosure provides for devices which may incorporate viral vectors that encode one or more FXN molecules. These devices contain in a stable formulation the viral vectors which may be immediately delivered to a subject in need thereof, such as a human patient.

[0390] Devices for administration may be employed to deliver the viral vectors encoding FXN of the present disclosure according to single, multi- or split-dosing regimens taught herein.

[0391] Method and devices known in the art for multi-administration to cells, organs and tissues are contemplated for use in conjunction with the methods and compositions disclosed herein as embodiments of the present disclosure.

VIII. Definitions

[0392] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub-combination of the members of such groups and ranges. The following is a non-limiting list of term definitions.

[0393] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

[0394] The articles "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0395] The term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps.

[0396] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0397] *Adeno-associated virus:* As used herein, the term "adeno-associated virus" or "AAV" refers to members of the dependovirus genus or a functional variant thereof. Unless stated otherwise, "AAV" may refer to wildtype (i.e., naturally occurring) AAV or recombinant AAV.

[0398] *AAV Particle*: As used herein, an "AAV particle" refers to a particle comprising an AAV capsid, e.g., an AAV capsid variant (such as a parent capsid sequence with at least one peptide insert and/or with at least one substitution), and a polynucleotide, e.g., a viral genome or a vector genome. The AAV particle may be capable of delivering a polynucleotide to cells. The cells may be mammalian cells, e.g., human cells. In some embodiments, an AAV particle of the present disclosure may be produced recombinantly. In some embodiments, an AAV particle may be derived from any

serotype, described herein or known in the art, including combinations of serotypes (e.g., "pseudotyped" AAV) or from various genomes (e.g., single stranded or self-complementary). In some embodiments, the AAV particle may be replication defective and/or targeted. In some embodiments, the AAV particle may comprise a peptide present in, e.g., inserted into, the capsid to enhance tropism for a desired target tissue. It is to be understood that reference to the AAV particle of the disclosure also includes pharmaceutical compositions thereof, even if not explicitly recited.

[0399] *Administering*: As used herein, the term "administering" refers to providing a pharmaceutical agent or composition to a subject.

[0400] *Amelioration*: As used herein, the term "amelioration" or "ameliorating" refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of a neurodegenerative disorder, amelioration includes the reduction or stabilization of neuron loss.

[0401] *Approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to, i.e., within 10% of, a stated reference value.

[0402] *Baseline*: The term "baseline," when used to describe a measurement in a subject receiving or about to receive a treatment, refers to a measurement made before starting the treatment.

[0403] *Capsid*: As used herein, the term "capsid" refers to the exterior, e.g., a protein shell, of a virus particle, e.g., an AAV particle, that is substantially (e.g., >50%, >60%, >70%, >80%, >90%, >95%, >99%, or 100%) protein. In some embodiments, the capsid is an AAV capsid comprising an AAV capsid protein described herein, e.g., a VP1, VP2, and/or VP3 polypeptide. The AAV capsid protein can be a wild-type AAV capsid protein or a variant, e.g., a structural and/or functional variant from a wild-type or a reference capsid protein, referred to herein as an "AAV capsid variant." For example, and without limitation, an AAV capsid variant may refer to at least a VP1 protein, a VP2 protein, or a VP3 protein (e.g., all of the VP1, VP2, and VP3 proteins forming the AAV capsid) as will be clear from context. In some embodiments, the AAV capsid variant described herein may comprise a peptide insertion and/or substitution (i.e., replacement). In some embodiments, the AAV capsid variant described herein has the ability to encapsulate a viral genome and/or is capable of entry into mammalian cell. In some embodiments, the AAV capsid variant described herein may have modified tropism compared to that of a wild-type AAV capsid, e.g., the corresponding wild-type capsid.

[0404] *Cis-Elements*: As used herein, cis-elements or the synonymous term "cis-regulatory elements" refer to regions of non-coding DNA which regulate the transcription of nearby genes. The Latin prefix "cis" translates to "on this side." Cis-elements are found in the vicinity of the gene, or genes, they regulate. Examples of cis-elements include a Kozak sequence, SV40 introns, or a portion of the backbone.

[0405] *CNS structures:* As used herein, "CNS structures" refers to structures of the central nervous system and sub-structures thereof. Non-limiting examples of structures in the spinal cord may

include, ventral horn, dorsal horn, white matter, and nervous system pathways or nuclei within. Non-limiting examples of structures in the brain include, forebrain, midbrain, hindbrain, diencephalon, telencephalon, myelencephalon, metencephalon, mesencephalon, prosencephalon, rhombencephalon, cortices, frontal lobe, parietal lobe, temporal lobe, occipital lobe, cerebrum, thalamus, hypothalamus, tectum, tegmentum, cerebellum, pons, medulla, amygdala, hippocampus, basal ganglia, corpus callosum, pituitary gland, putamen, striatum, ventricles and sub-structures thereof.

[0406] *CNS Cells:* As used herein, "CNS cells" refers to cells of the central nervous system and sub-structures thereof. Non-limiting examples of CNS cells include, neurons and sub-types thereof, glia, microglia, oligodendrocytes, ependymal cells and astrocytes. Non-limiting examples of neurons include sensory neurons, motor neurons, interneurons, unipolar cells, bipolar cells, multipolar cells, pseudounipolar cells, pyramidal cells, basket cells, stellate cells, Purkinje cells, Betz cells, amacrine cells, granule cell, ovoid cell, medium aspiny neurons, large aspiny neurons, GABAergic neurons and/or glutamatergic neurons.

[0407] *Codon optimization*: As used herein, the term "codon optimization" refers to a process of changing codons of a given gene in such a manner that the polypeptide sequence encoded by the gene remains the same.

[0408] *Complementary and substantially complementary:* As used herein, the term "complementary" refers to the ability of polynucleotides to form base pairs with one another. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form a hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form a hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity. The term "complementary" as used herein can encompass fully complementary or partially (e.g., substantially) complementary. "Fully complementary", "perfect complementarity", or "100% complementarity" refers to the situation in which each nucleotide unit of one polynucleotide or oligonucleotide strand can base-pair with a nucleotide unit of a second polynucleotide or oligonucleotide strand. As used herein, the term "substantially complementary" means that >50% of the nucleotide units of a first polynucleotide strand can base pair with nucleotide units on a second polynucleotide strand. When used in the context of RNA silencing, "substantially complementary" refers to an siRNA that has a sequence (e.g., in the antisense strand) that is sufficient to bind the desired target mRNA and to trigger the RNA silencing of the target mRNA.

[0409] *Conservative substitution*: As used herein, a conservative substitution, as applied to an amino acid sequence, also referred to as a "conservative amino acid substitution," is one in which the amino acid residue is replaced with an amino acid residue having similar biochemical properties.

When used in reference to a nucleic acid sequence, the term "conservative substitution" refers to a nucleotide replacement that results in an amino acid residue having similar biochemical properties compared to a reference sequence. Families of amino acid residues having similar biochemical properties have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

[0410] *Corresponding to:* As used herein, the phrase "corresponding to" in the context of an amino acid sequence refers to the location of an amino acid in a reference sequence or the equivalent position in a modified sequence when aligned. For example, an amino acid corresponding to position 5 of SEQ ID NO: 36 refers to the amino acid at the fifth position from the N-terminus in SEQ ID NO: 36 or the equivalent position in an aligned sequence. As used herein, an amino acid at a position corresponding to that in a designated sequence may also be referred to as an amino acid at a particular position, numbered according to the designated sequence. For instance, an amino acid corresponding to position 5 of SEQ ID NO: 36 may also be referred to as an amino acid at position 5, numbered according to SEQ ID NO: 36, relative to a reference sequence of SEQ ID NO: 36, or as numbered according to a sequence corresponding to SEQ ID NO: 36.

[0411] *Derivative:* As used herein, the term "derivative" refers to a composition (*e.g.*, sequence, compound, formulation, *etc.*) that is derived from, or finds its basis in, a parent composition. Non-limiting examples of a parent composition include a wild-type or original amino acid or nucleic acid sequence, or an undiluted formulation. In some embodiments, a derivative is a variant of a parent composition. A derivative may differ from the parent composition by less than about 1%, less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, or less than about 50%. In certain embodiments, a derivative may differ from a parent composition by more than about 50%. In certain embodiments, a derivative may differ from a parent composition by more than about 75%. In some embodiments, a derivative may be a fragment or truncation of a parent amino acid or nucleotide sequence. As a non-limiting example, a derivative may be a sequence with a nucleotide, amino acid, or peptide substitution and/or insertion as compared to a parent nucleic acid or amino acid sequence (*e.g.*, as compared to AAV9).

[0412] *Effective amount:* As used herein, the term "effective amount" or "therapeutically effective amount" of an agent is that amount sufficient to effect beneficial or desired results. An effective amount is provided in a single dose or multiple doses to treat, improve symptoms of, delay progression of symptoms, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0413] *Excipient*: As used herein, the term "excipient" refers to an inactive substance that serves as the vehicle or medium for an active pharmaceutical agent or other active substance.

[0414] *Formulation*: As used herein, a "formulation" includes at least one active ingredient (e.g., an AAV particle) and at least one inactive ingredient (e.g., a pharmaceutically acceptable excipient).

[0415] *Fragment:* A "fragment," as used herein, refers to a contiguous portion of a reference sequence. A fragment may comprise a functional fragment that retains at least one activity of the reference sequence. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein isolated from cultured cells. A fragment may also refer to a truncation (*e.g.*, an N-terminal and/or C-terminal truncation) of a protein or a truncation (*e.g.*, at the 5' and/or 3' end) of a nucleic acid. A protein fragment may be obtained by expression of a truncated nucleic acid, such that the nucleic acid encodes a portion of the full-length protein.

[0416] *Healthy individual:* As used herein, the term "healthy individual" refers to an individual who does not have a disease or disorder associated with FXN protein deficiency, e.g., an individual who does not have Friedreich's Ataxia.

[0417] *Humanized*: As used herein, the term "humanized" refers to a non-human sequence of a polynucleotide or a polypeptide which has been altered to increase its similarity to a corresponding human sequence.

[0418] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between oligonucleotide molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, may be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference in its entirety. For example,

the percent identity between two nucleotide sequences can be determined using the algorithm of Myers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference in its entirety. Techniques for determining identity are codified in publicly available computer programs. Computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), the Basic Local Alignment Search Tool (BLAST, which includes, e.g., BLASTP for protein sequences and BLASTN for nucleic acid sequences), and FASTA Altschul, S. F. *et al.*, *J. Molecular Biol.*, 215, 403 (1990)), EMBOSS Needle, Clustal Omega, Benchling, and Geneious. In preferred embodiments, sequence identity may be determined using BLAST, Clustal Omega, or EMBOSS Needle.

[0419] *Inverted terminal repeat*: As used herein, the term "inverted terminal repeat" or "ITR" refers to a cis-regulatory element for the packaging of polynucleotide sequences into viral capsids.

[0420] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that is altered or removed from the natural state, e.g., altered or removed from at least some of component with which it is associated in the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature. In some embodiments, an isolated nucleic acid is recombinant, e.g., incorporated into a vector.

[0421] *miRNA binding site:* As used herein, a "miRNA binding site" or "miR binding site" refers either to a DNA sequence corresponding to an RNA sequence that is bound by a microRNA, or to the RNA sequence that is bound by the microRNA. The miR binding site is capable of binding, or binds, in whole or in part to a microRNA (miRNA, miR) through complete or partial hybridization. A miR binding site may be encoded or transcribed in series, also referred to as a "miR binding site series" or "miR BSs", which includes two or more miR binding sites having the same or a different nucleic acid sequence.

[0422] *Modification*: As used herein, the term "modification" or "modified," refers to any substance, compound, or molecule that has been changed in any way. For example, a modification in

an amino acid sequence may comprise a substitution (e.g., a conservative substitution), an insertion, and/or a deletion of one or more amino acids in the sequence.

[0423] *Neurological disease:* As used herein, a "neurological disease" is any disease associated with the central or peripheral nervous system and components thereof (e.g., neurons).

[0424] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[0425] *Payload*: As used herein, "payload," "payload sequence," or "payload region" refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, *e.g.*, a transgene, a polynucleotide encoding a polypeptide.

[0426] *Payload construct*: As used herein, "payload construct" is one or more polynucleotide regions encoding or comprising a payload that is flanked on one or both sides by an inverted terminal repeat (ITR) sequence. The payload construct is a template that is replicated in a viral production cell to produce a viral genome.

[0427] *Payload construct vector*: As used herein, "payload construct vector" is a vector encoding or comprising a payload construct, and regulatory regions for replication and expression in bacterial cells. The payload construct vector may also comprise a component for viral expression in a viral replication cell.

[0428] *Pharmaceutically acceptable*: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are suitable for use in contact with the tissues of human beings and animals.

[0429] *Pharmaceutically acceptable excipients:* As used herein, the term "pharmaceutically acceptable excipient," as used herein, refers to any ingredient other than active agents (*e.g.*, as described herein) present in pharmaceutical compositions that can function as vehicles for suspending and/or dissolving active agents.

[0430] *Pharmaceutically acceptable salts*: Pharmaceutically acceptable salts of the compounds described herein are forms of the disclosed compounds wherein the acid or base moiety is in its salt form (*e.g.*, as generated by reacting a free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

[0431] *Pharmaceutical Composition:* As used herein, the term "pharmaceutical composition" or pharmaceutically acceptable composition" comprises AAV polynucleotides, AAV genomes, or AAV particle and one or more pharmaceutically acceptable excipients, solvents, adjuvants, and/or the like.

[0432] *Position*: The term "position," as used herein in the context of an amino acid sequence, refers to the location of a particular amino acid or set of amino acids relative to a larger sequence. A position or positions of amino acids may interchangeably be referred to by an amino acid number or

numbers of a reference sequence. For example, and unless otherwise specified, "positions 1-742, as numbered according to SEQ ID NO: 982" is interchangeable with "amino acids 1-742, as numbered according to SEQ ID NO: 982."

[0433] *Preventing*: As used herein, the term "preventing" refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition. The term "prevention" or "preventing" of an infection, disease, disorder and/or condition may be considered a subset within the meaning with the term "treatment" or treating" of the infection, disease, disorder and/or condition.

[0434] *Region:* As used herein, the term "region" refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear sequence of amino acids along the protein or protein module or may comprise a three-dimensional area. In some embodiments, regions comprise terminal regions. As used herein, the term "terminal region" refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini. N-termini refer to the end of a protein comprising an amino acid with a free amino group. C-termini refer to the end of a protein comprising an amino acid with a free carboxyl group. N- and/or C-terminal regions may comprise the N- and/or C-termini as well as surrounding amino acids. When referring to a polynucleotide, a region may comprise a linear sequence of nucleic acids along the polynucleotide or may comprise a three-dimensional area, secondary structure, or tertiary structure. In some embodiments, regions comprise terminal regions. As used herein, the term "terminal region" refers to regions located at the ends or termini of a given agent. When referring to polynucleotides, terminal regions may comprise 5' and/or 3' termini.

[0435] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of tissues, cells, nucleic acids, or a component or part of the body (*e.g.*, a body fluid, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen).

[0436] *Self-complementary AAV*: As used herein, the term "self-complementary AAV" refers to an AAV comprising at least a protein capsid and a self-complementary viral genome.

[0437] *Serotype:* As used herein, the term "serotype" refers to distinct variations in a capsid of an AAV based on surface antigens which allow epidemiologic classifications of the AAVs at the sub-species level.

[0438] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization.

[0439] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[0440] *Spacer:* As used herein, a "spacer" is generally any selected nucleic acid sequence of, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. In some embodiments, spacers may also be more than 10 nucleotides in length, e.g., 20, 30, 40, or 50 or more than 50 nucleotides.

[0441] *Subject:* As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the disclosure may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Similarly, "subject" or "patient" refers to an organism who may seek, who may require, who is receiving, or who will receive treatment or who is under care by a trained professional for a particular disease or condition. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans). As used herein, a subject or patient may be susceptible to, suspected of having, or have a deficiency in frataxin protein, e.g., Friedreich's Ataxia (FA).

[0442] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0443] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[0444] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a

disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0445] *Target Cells:* As used herein, "target cells" refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a human patient.

[0446] *Target Tissue:* As used herein, "target tissue" refers to a tissue of interest that may be found *in vitro*, *in situ*, or as part of an animal, preferably a mammal, more preferably a human and most preferably a human patient.

[0447] *Therapeutic Agent:* The term "therapeutic agent" refers to any agent that, when administered to a subject, elicits a desired biological and/or pharmacological effect.

[0448] *Therapeutically Effective Outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, delay progression of symptoms, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0449] *Treating*: As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, reducing incidence of, and/or preventing one or more symptoms or features of a particular infection, disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0450] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild-type or native form of a biomolecule or entity. Molecules or entities may undergo a series of modifications whereby each modified product may serve as the "unmodified" starting molecule or entity for a subsequent modification.

[0451] *Variant:* The term "variant" refers to a polypeptide or polynucleotide that has an amino acid or a nucleotide sequence that has at least 90% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to a reference sequence. The variant may be a functional variant. As used herein, the term "functional variant" refers to a polypeptide variant or a polynucleotide variant that has at least one activity of the reference sequence.

[0452] *Vector*: As used herein, a "vector" is any molecule or moiety which transports, transduces, or otherwise acts as a carrier of a heterologous molecule. Vectors of the present disclosure may be

produced recombinantly and may be based on and/or may comprise adeno-associated virus (AAV) parent or reference sequence(s).

[0453] *Viral genome*: As used herein, a "viral genome", "vector genome", or "VG" is a polynucleotide comprising at least one inverted terminal repeat (ITR) and at least one nucleic acid sequence encoding a payload. A viral genome encodes at least one copy of the payload.

EXAMPLES

[0454] The present disclosure is further illustrated by the following non-limiting examples.

Example 1. High-throughput screen of TRACER AAV library in NHP and Mice

[0455] A TRACER based method as described in WO2020072683, WO 2021/202651, and WO2021230987, the contents of which are herein incorporated by reference in their entirety, was used to generate the AAV capsid variants described herein. An orthogonal evolution approach was combined with a high throughput screening by NGS. Briefly, the library of AAV capsid variants was generated using a sliding window approach, where 6 amino acid sequences were inserted into 8 different positions across loop IV of AAV9, including immediately subsequent to positions 453, 454, 455, 456, 457, 458, 459, and 460, relative to a reference sequence numbered according to SEQ ID NO: 138. The initial library was passed twice through non-human primates (NHP, 2-4 years of age). After the second passage (e.g., 28 days post injection into two NHPs), RNA was extracted from six brain regions. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate fold enrichment relative to an AAV9 wild-type control. Following these two passages, approximately 21195 variants were identified with an average fold change greater than wild-type. Of the 21195 variants, 1558 demonstrated a fold-change of greater than 6 compared to wild-type and were detected across all brain regions investigated. Of these 1558, approximately 1470 variants were selected for constructing a synthetic library and a third passage through two NHPs. Within the 1470 variants selected for further characterization and investigation, there was a relatively even distribution for each insertion position of the sliding window used to generate the initial library.

[0456] After creation of the synthetic library with the sub-selected variants, the synthetic library was screened (passage 3) in two NHPs (2-4 years of age) and two strains of mice, BALB/c (n=3, 6-8 weeks of age) and C57Bl/6 mice (n=3, 6-8 weeks of age), in a first cross-species evolution screen. The animals were injected intravenously with the synthetic library. After a period *in vivo*, (e.g., 28-days) RNA was extracted from nervous tissue, e.g., brain, spinal cord, and DRG of the NHPs and the brains of mice. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed, and the peptides comprised within the variants were identified and the capsid enrichment ratio for each variant compared to the wild-type AAV9 control was calculated (fold enrichment relative to wild-type AAV9) (Table 14). Values above 1 indicate an increase in expression relative to AAV9. All animals were dosed intravenously at 2-3 VG/kg across the screen.

[0457] As shown in Table 14, approximately 700 variants demonstrated an increase in expression relative to AAV9, and several variants demonstrated a greater than 10-fold enrichment relative to AAV9 in the brain of NHPs. Further, the variants demonstrating the greatest fold enrichment in the brain also demonstrated the greatest fold enrichment in the spinal cord relative to AAV9 in NHPs. These variants also demonstrated de-targeting in the DRG (data not shown). For instance, the variant comprising GSGSPHSKAQNQQT (SEQ ID NO: 200) demonstrated a 76.6 fold enrichment in the brain, a 29.4 fold enrichment in the spinal cord, and 0.4 fold enrichment in the DRG of NHPs relative to AAV9; and GHDSPHKSGQNQQT (SEQ ID NO: 201) demonstrated a 62.6 fold enrichment in the brain, a 15.6 fold enrichment in the spinal cord, and 0.0 fold enrichment in the DRG of NHPs relative to AAV9. Also, across the peptides comprised within the AAV capsid variants with the greatest fold-enrichment in the NHP brain relative wild-type AAV9, it was observed that each of these peptides comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138), regardless of the insertion position within the variant capsid, as well as a positive amino acid (e.g., K or R) in one of the next three residues subsequent to the SPH motif.

[0458] Those variants with the greatest fold enrichment in the brains of NHPs also had the greatest fold enrichment in the brains of both mouse species. Also, when comparing the fold enrichment relative to wild-type for each variant between the two species of mice investigated (C57Bl/6 and BALB/c mice), they were highly correlated (R^2= 0.8591).

Table 14. NGS fold-enrichment of AAV capsid variants in NHPs and mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in the brain of NHPs	Fold enrichment over AAV9 in the spinal cord of NHPs	Fold enrichment over AAV9 in the brain of Mice (C57Bl/6)	Fold enrichment over AAV9 in the brain of Mice (BALB/c)
GSGSPHSKAQNQQT	200	73.615	29.402	25.293	41.304
GHDSPHKSGQNQQT	201	62.612	15.641	63.993	49.760
GSGSPHARMQNQQT	202	56.138	22.690	7.795	4.164
GSGSPHVKSQNQQT	203	37.551	13.649	8.069	15.861
GQDSPHKSGQNQQT	204	24.569	3.548	57.344	42.615
GSGSPHASRQNQQT	205	18.265	7.804	28.028	36.577
GSGSPHASRQNKQT	206	17.520	35.029	13.096	18.114
GSGSPHVKIQNQQT	207	16.854	9.068	2.173	2.227
GSGSPHSKAKNQQT	208	14.458	0.049	21.494	23.556
GSGSPHKKNQNQQT	209	12.991	0.379	25.958	7.415
GSGSPHVRMQNQQT	210	11.574	6.764	9.121	10.076
GSGSPHASRQKQQT	211	11.417	0.005	7.413	12.400
GHSSPHRSGQNQQT	212	10.357	1.887	23.197	25.442
GMRTYHLSGQNQQT	213	9.241	1.939	2.033	1.586
GSGSPHTRGQNQQT	214	7.092	3.815	10.801	6.240
GSGIIPVSSQNQQT	215	6.352	0.000	0.642	0.253
GSEYGHKSGQNQQT	216	6.308	2.750	5.198	5.332
GRGQNVSSVHRQQT	217	5.404	0.000	1.206	0.691
GSSERFYGGQNQQT	218	4.732	0.000	0.787	0.110
GYFVAAWSGQNQQT	219	4.488	0.000	0.071	0.175
GSVLHSHAAQNQQT	220	4.150	6.448	0.675	0.423
GSGDLVVSTQNQQT	221	3.874	1.177	0.411	0.273
GSYGMAASGQNQQT	222	3.817	10.052	1.274	0.829
GLNEFGASGQNQQT	223	3.802	3.188	0.774	0.579

GSTGSHSAGQNQHT	224	3.717	0.285	1.190	0.850
GLAGHTVSGQNQQT	225	3.632	0.229	0.972	0.202
GIILGASSGQNQQT	226	3.630	4.868	1.378	0.865
GSGVSTYNIQNQQT	227	3.609	2.912	0.769	0.520
GSLVSVQTGQNQQT	228	3.534	6.043	0.903	0.469
GQSSPHRSGQNQQT	229	3.496	2.142	12.352	19.366
GREYGHKSGQNQQT	230	3.453	0.000	1.422	0.959
GHTLTLSSGQNQQT	231	3.405	5.648	0.648	0.606
GSITLIPSGQNQQT	232	3.361	3.917	0.326	0.435
GSNGFTALGQNQQT	233	3.361	2.663	0.830	0.332
GSGESSHSVQNQQT	234	3.339	3.318	0.942	0.424
GSGIPQRSGKNQQT	235	3.331	0.000	1.418	1.685
GSGDTLHMLQNQQT	236	3.317	1.174	0.393	0.482
GERITVLSGQNQQT	237	3.289	3.008	1.027	0.607
GSGMPQSHIQNQQT	238	3.289	11.609	0.514	0.334
GSGQLSGIGGNQQT	239	3.266	0.287	0.993	0.626
GSGQNRKPASFAQT	240	3.204	0.000	0.892	1.061
GSGSVSQLGQNQQT	241	3.184	2.307	0.596	0.375
GSDFLGTHGQNQQT	242	3.171	0.348	1.038	0.750
GQIVQNPSGQNQQT	243	3.133	0.406	1.446	0.635
GSGTQIPSQQNQQT	244	3.112	1.224	0.470	0.151
GSGQNQQSAREGLT	245	3.111	5.632	1.221	1.104
GSGLGMSTGQNQQT	246	3.110	5.499	0.458	0.660
GSGLPVLSGQNQQT	247	3.100	4.149	0.631	0.210
GSGESIRTDQNQQT	248	3.074	15.600	0.229	0.148
GSGQSVQTVVNQQT	249	3.057	5.441	0.582	0.240
GSGQNRAQSRFQQT	250	3.043	0.000	0.619	1.788
GGGDLGRSSQNQQT	251	3.036	4.830	0.916	0.539
GGGTKMDSGQNQQT	252	3.034	0.000	0.733	0.297
GSGSPHPSRQNQQT	253	3.017	1.993	1.869	0.975
GSGQFTNAGMNQQT	254	2.969	0.936	0.565	0.418
GGRNGHTVGQNQQT	255	2.965	3.732	1.105	1.003
GSGFGPQTGQNQQT	256	2.964	2.861	1.280	0.849
GRTDSHTSGQNQQT	257	2.913	1.510	1.299	0.704
GYEVLGSSGQNQQT	258	2.891	0.000	2.459	0.319
GSVELSVTGQNQQT	259	2.882	1.157	0.741	0.282
GFMSYKGSGQNQQT	260	2.865	0.209	1.808	0.569
GNIAGSVSGQNQQT	261	2.849	1.187	0.446	0.257
GSGSHRDVSQNQQT	262	2.843	4.022	0.626	0.550
GGLGSMSSGQNQQT	263	2.812	1.405	1.802	0.822
GSGHLPQSAQNQQT	264	2.803	7.828	0.826	0.496
GGVLVGGSGQNQQT	265	2.778	0.178	1.527	0.688
GTHPYTSSGQNQQT	266	2.775	1.684	0.758	0.471
GSGQNQQLKENRST	267	2.765	0.062	1.149	1.118
GSGQNQQTSPHNHT	268	2.761	3.132	1.524	0.845
GSGTLYPQSQNQQT	269	2.761	5.558	0.324	0.160
GSGQNQQSNWITKT	270	2.711	0.000	0.540	0.634
GSGYTSLFLQNQQT	271	2.710	0.010	0.490	1.044
GSGVMTHVLQNQQT	272	2.692	0.347	0.370	0.533
GSVSDVRAGQNQQT	273	2.661	1.647	0.267	0.747
GSGQSHMATLNQQT	274	2.657	0.724	1.173	0.504
GSGLSVHLAQNQQT	275	2.657	1.234	0.806	0.508
GSGLSHATQQNQQT	276	2.640	7.819	1.111	0.638
GSGLSVQSGQNQQT	277	2.637	2.929	1.695	1.005
GSGHMTYREKNQQT	278	2.633	5.267	1.257	0.540
GSKGVPTPGQNQQT	279	2.625	1.292	1.452	0.459
GSGLLPLSSQNQQT	280	2.612	1.130	0.501	0.293
GNGLYAVSGQNQQT	281	2.611	9.148	0.322	0.213
GFNGSPSSGQNQQT	282	2.609	12.197	2.338	0.924
GSGQTRHSDQNQQT	283	2.600	12.884	1.170	0.320
GGQVAPSSGQNQQT	284	2.581	2.427	1.433	0.709
GSFSMHTHGQNQQT	285	2.535	0.118	1.027	0.693
GSGQNQQVIQGSNT	286	2.521	8.778	0.935	0.810
GRVLHSHAGQNQQT	287	2.513	0.826	1.294	0.908

GSGQNQQTSLQDQT	288	2.505	0.500	0.315	0.968
GSGLGRAPVQNQQT	289	2.503	2.214	0.841	0.383
GNGFSSASGQNQQT	290	2.493	0.772	0.240	0.182
GSGQMASRESNQQT	291	2.492	0.300	0.341	0.288
GPGLPNHSGQNQQT	292	2.486	1.992	1.197	0.659
GNIQWQGSGQNQQT	293	2.468	6.266	1.182	0.837
GMSAHMSSGQNQQT	294	2.456	5.255	1.310	0.947
GHSFVNRSGQNQQT	295	2.447	11.148	1.305	0.756
GRAVMDHSGQNQQT	296	2.408	3.209	0.728	0.283
GALTVMQSGQNQQT	297	2.381	0.430	0.246	0.199
GSGQRSPVLPNQQT	298	2.369	6.230	0.434	0.526
GSGQNGHLSLKQQT	299	2.362	1.896	0.718	0.270
GSLPRGTSDQNQQT	300	2.362	0.000	0.453	0.495
GVAGSLVSGQNQQT	301	2.358	7.670	1.321	1.160
GRGGIPQSGQNQQT	302	2.352	8.683	1.639	1.181
GSGQYASSIPNQQT	303	2.346	3.321	1.022	0.489
GTDFGRQSSQNQQT	304	2.346	3.196	1.021	0.797
GIFMQTPSGQNQQT	305	2.344	6.198	0.938	0.252
GSGQNQQTRLVDLT	306	2.342	9.348	1.268	0.490
GTREMPLSGQNQQT	307	2.339	2.830	1.436	0.538
GSRLVHVHGQNQQT	308	2.334	1.174	1.277	0.934
GSGRLVPNGPNQQT	309	2.314	3.925	0.639	0.411
GSGYLRESPQNQQT	310	2.311	0.878	0.331	0.677
GARIQNASGQKQQT	311	2.300	2.103	1.220	1.039
GLSNPMPSGQNQQT	312	2.280	6.033	1.190	0.829
GSTVQDTRGQNQQT	313	2.270	4.979	0.576	0.473
GPFGMPSSGQNQQT	314	2.260	2.700	0.727	0.560
GSGQNHGVLSNQQT	315	2.254	1.603	1.113	0.701
GSGYSMSQAQNQQT	316	2.250	4.479	0.519	0.329
GSGMLTHTLQNQQT	317	2.246	2.272	0.496	0.199
GRGSPHASRQNQQT	318	2.241	0.000	5.050	5.856
GLSWPSTSGQNQQT	319	2.238	0.000	0.910	0.610
GNSMERTSGQNQQT	320	2.221	4.177	1.047	0.935
GSGMSPSTLQNQQT	321	2.216	3.053	0.318	0.153
GSGHGQVLSQNQQT	322	2.213	12.133	1.880	0.661
GRGQIYSTGGNQQT	323	2.210	11.629	1.329	0.743
GVVAAHNSGQNQQT	324	2.202	1.301	1.196	1.336
GDSSLRHSGQNQQT	325	2.194	0.000	0.662	0.412
GSLVSQGAGQNQQT	326	2.188	4.414	1.436	1.246
GSLLQAHSGQNQQT	327	2.182	1.008	0.575	0.748
GSGHIYVGIQNQQT	328	2.178	6.428	0.989	0.337
GHHTTVQSGQNQQT	329	2.177	6.245	0.851	0.755
GSRQSKRNELNQQT	330	2.177	0.000	1.325	0.232
GSGQNQQHVSSPRT	331	2.176	1.279	1.847	0.938
GSSKELLWGQNQQT	332	2.163	0.000	0.506	0.883
GSLSTPSSGQNQQT	333	2.159	1.279	1.094	0.669
GSIGYAGQGQNQQT	334	2.157	4.951	1.604	0.712
GSGQNQRVSNSQQT	335	2.146	0.492	1.086	0.985
GSGYASHVQQNQQT	336	2.146	3.038	1.157	0.758
GSGEYSRSGQNQQT	337	2.145	0.745	0.617	0.205
GSVSTHSSGQNQQT	338	2.145	3.446	1.198	0.918
GSGQNQHSLGNYQT	339	2.143	1.896	1.077	0.606
GSGGLDTRGQNQQT	340	2.139	6.216	0.236	0.197
GNILHATSGQNQQT	341	2.136	0.125	1.159	0.424
GSGQSYTMTQNQQT	342	2.136	6.755	0.297	0.231
GSGQNQHSAPNSQT	343	2.134	4.143	1.187	0.731
GSGQNQQTMDHNRT	344	2.130	4.944	0.642	0.440
GSNGGVGTGQNQQT	345	2.130	0.788	1.191	1.087
GAGSIIPSGQNQQT	346	2.129	7.164	0.595	0.249
GSGQTHGGQHNQQT	347	2.125	12.251	1.448	1.098
GSNLSFQSGQNQQT	348	2.122	5.853	1.087	0.719
GATLQVHSGQNQQT	349	2.122	2.219	0.623	0.545
GSGFNQRSEQNQQT	350	2.121	4.491	1.770	0.758
GSGSLRDFDQNQQT	351	2.120	6.846	0.586	0.272

GSGDSITGKQNQQT	352	2.112	1.295	0.793	0.306
GSGQDRNIVQNQQT	353	2.112	0.229	0.454	0.632
GSGLSHSHQQNQQT	354	2.109	5.852	1.256	0.592
GSGQNQQTGMSSVK	355	2.109	4.544	1.451	0.679
GSVTHGISGQNQQT	356	2.105	4.542	1.135	0.789
GVVAHQPSGQNQQT	357	2.103	0.152	0.910	2.267
GSGPILGQLQNQQT	358	2.097	2.058	0.470	0.123
GSGIVPNSGLNQQT	359	2.091	0.653	1.636	1.154
GDAGVRSSGQNQQT	360	2.068	3.918	1.033	1.193
GSGSQLMSLQNQQT	361	2.065	3.559	0.563	0.172
GSGLDYSQRQNQQT	362	2.056	0.837	0.484	0.217
GSGQSSGRLINKQT	363	2.055	28.135	0.543	0.277
GSSVSPSSGQNQQT	364	2.054	0.579	1.064	0.787
GSGQVVGLSGNQQT	365	2.052	7.212	0.785	0.881
GSNMGVPLGQNQQT	366	2.049	2.448	0.334	0.420
GSFYPSSTGQNQQT	367	2.047	2.374	0.420	0.277
GSGQNQQTRLTDLT	368	2.046	8.470	0.910	0.776
GPTNGRSSGQNQQT	369	2.034	8.903	0.936	1.308
GSGLLHGKLQNQQT	370	2.032	2.521	1.068	0.917
GANMGHVSGQNQQT	371	2.020	0.810	1.302	1.138
GSGQNQQSGRGDLT	372	2.019	6.919	0.524	1.152
GSHGHYASGQKQQT	373	2.016	0.000	0.895	0.685
GSGDLRISPQNQQT	374	2.012	16.207	0.620	0.237
GSGMPVILGQNQQT	375	2.005	0.150	0.840	0.287
GRGVITSSGQNHQT	376	2.004	0.864	1.656	0.669
GSGESVSGPQNQQT	377	1.993	6.259	1.370	0.619
GSRNGHTVGRNQQT	378	1.993	0.000	1.162	0.367
GAGVHMVSGQNQQT	379	1.987	6.488	1.055	0.791
GSGQNHRPSVLQQT	380	1.983	5.582	0.433	0.582
GSGSPRDSIQNQQT	381	1.981	4.914	0.171	0.446
GSGQGIHSSVNQQT	382	1.981	4.873	0.632	0.634
GSGQQLSITPNQQT	383	1.979	10.280	0.845	0.201
GGYESQTSGQNQQT	384	1.978	2.642	1.740	1.525
GSLEHDNHGQNQQT	385	1.976	0.980	0.968	0.463
GIMARDSSGQNQQT	386	1.972	3.486	1.320	0.904
GVVEITNSGQNQQT	387	1.969	0.504	0.794	0.846
GSGQNQHSAPFNQT	388	1.969	0.499	0.759	0.870
GSGQTSGLKQNQQT	389	1.968	3.927	0.394	0.334
GSGQNQQTSLSNTA	390	1.959	1.186	1.567	1.182
GSGQNQAVHNKSQT	391	1.956	3.791	1.465	1.083
GVHTHLPSGQNQQT	392	1.952	1.364	1.414	0.796
GHLTMHNSGQNHQT	393	1.938	1.798	1.030	0.586
GSGSSSRPYQNQQT	394	1.934	3.823	0.962	0.496
GILLATPSGQNQQT	395	1.931	8.205	1.341	0.288
GSGQNAGSFPNQQT	396	1.928	12.575	1.091	0.286
GSRDGHTVGQNQQT	397	1.928	7.089	0.495	0.661
GSLLISTSGQNQQT	398	1.919	5.763	1.488	0.808
GSGAMPSHGQNQQT	399	1.915	0.000	1.142	0.912
GALVSPISGQNQQT	400	1.912	1.051	0.640	0.347
GSLSSHGVGQNQQT	401	1.911	7.498	1.218	0.804
GSGQNQQASLAMRT	402	1.910	3.577	2.066	1.638
GPGLGSHSGQNQQT	403	1.906	14.563	0.880	1.195
GHDSQHKSGQNQQT	404	1.904	6.988	1.154	0.869
GSGLTLSATQNQQT	405	1.901	0.193	0.708	0.340
GSGQVVAHVGNQQT	406	1.901	0.833	0.800	0.321
GSGLRTMTTQNQQT	407	1.900	8.939	0.838	0.594
GSGQVGRLLQNQQT	408	1.899	1.762	0.773	0.748
GSGQLSHQSVNQQT	409	1.898	4.032	0.720	0.695
GSGDRYQTLQNQQT	410	1.897	1.075	0.645	0.318
GSGQNQQLKSSAQT	411	1.891	1.197	0.908	0.716
GSGQNQYSIPVAQT	412	1.891	1.194	0.511	0.297
GSGERLHLTQNQQT	413	1.885	1.456	0.387	0.245
GSGENQQVRTAPNT	414	1.885	1.022	1.006	0.580
GGLSHVMSGQNQQT	415	1.875	0.403	0.885	0.378

GSGQSHRDVLNQQT	416	1.872	15.082	0.138	0.280
GSGQNLAGRMDQQT	417	1.864	0.085	0.362	0.295
GSGQNQQTNRGNPM	418	1.860	3.402	1.349	1.098
GSGQSYQRDHNQQT	419	1.859	8.013	0.779	0.323
GSLLSAGMGQNQHT	420	1.856	6.168	0.589	0.342
GSGQNQQTAIYRNI	421	1.854	2.207	0.818	1.437
GSGQNQQTSGTTNC	422	1.854	8.161	1.040	0.806
GMTSHSVSGQNQQT	423	1.850	2.732	0.220	0.154
GSSQSTGYQPNQQT	424	1.847	3.388	0.522	0.577
GSLKPTTLGQNQQT	425	1.840	0.476	0.175	0.220
GRMFSLGSGQNQQT	426	1.836	8.429	1.630	1.174
GSGQNQQTALGVKC	427	1.835	1.343	1.378	1.014
GAMVSHSSGQNQQT	428	1.833	8.999	0.739	0.868
GSGQNQQRNSDSVT	429	1.829	0.000	1.238	0.842
GSGQSMTLHLNQQT	430	1.827	0.991	0.721	0.248
GSGQVHQAEVNQQT	431	1.825	0.152	0.436	0.287
GSGQNQSQNHLQQT	432	1.825	0.600	1.063	0.772
GSLLTTASGQNQQT	433	1.822	0.780	0.938	0.635
GSGLIRTAAQNQQT	434	1.822	8.339	0.808	0.998
GSGQNQQTVSRQST	435	1.820	0.472	1.330	0.796
GSGQYANHGINQQT	436	1.820	5.717	0.906	0.701
GSRSTGPSGQNQQT	437	1.819	2.479	0.440	0.466
GRGVQQKLQQNQQT	438	1.817	0.000	1.974	0.823
GSGQNQQVHLSTGT	439	1.811	0.266	1.011	0.455
GSGQNQQLSAKSST	440	1.809	1.567	1.224	1.115
GSGYKAARPQNQQT	441	1.803	0.000	1.418	0.337
GSAGISPSGQNQQT	442	1.797	1.812	0.784	0.622
GSGQNRAHAFLQQT	443	1.795	0.000	1.200	1.271
GSGLSGITMQNQQT	444	1.792	14.796	0.862	0.496
GPGSAHSSGQNQQT	445	1.785	4.392	1.099	0.872
GSSHTQALGQNQQT	446	1.784	0.143	0.882	0.874
GSGVHGVSSQNQQT	447	1.781	4.519	1.504	0.951
GSSGRDMGGQNQQT	448	1.778	2.177	1.052	0.595
GERAFPTSGQNQQT	449	1.775	6.515	0.972	0.362
GGRIVSLSGQNQQT	450	1.766	4.936	1.161	0.847
GSGQNSYSHTSQQT	451	1.765	2.262	1.130	0.658
GLGYPGSSGQNQQT	452	1.763	7.090	0.929	0.577
GSGPQSHTGQNQQT	453	1.757	9.490	0.958	0.447
GSGQNQQLSRDAST	454	1.754	3.716	1.877	0.611
GSGQILHSVPNQQT	455	1.752	1.316	0.398	0.240
GSGFHTDSRQNQQT	456	1.748	4.384	7.344	0.575
GSGQSHSLATNQQT	457	1.745	2.711	1.021	0.343
GSGQNQQTLSKPWT	458	1.743	0.253	0.845	0.733
GSGHAAISQQNQQT	459	1.742	2.373	1.211	0.520
GSGQNQQQIGGNST	460	1.741	6.169	0.877	0.576
GGGPMAGSGQNQQT	461	1.735	2.815	1.049	0.372
GMRMEYQSGQNQQT	462	1.729	3.695	0.644	0.632
GSGQNQQGTLLHQT	463	1.728	2.065	1.347	1.303
GSGQNQRSSGGVQT	464	1.723	2.056	1.805	1.165
GSGQNQRGALATQT	465	1.722	1.117	0.899	0.891
GSGTVHAATQNQQT	466	1.721	1.676	0.563	0.476
GSRMTQQFGQNQQT	467	1.720	25.798	1.233	0.976
GSSSPGASGQNQQT	468	1.717	1.244	1.378	0.660
GHPSPHVSGQNQQT	469	1.713	0.416	0.551	0.488
GSGSHHASRQNQQT	470	1.712	0.451	3.073	0.584
GAVGHSYSGQNQQT	471	1.706	0.808	0.306	0.536
GSRSQYDIGQNQQT	472	1.706	0.112	0.528	0.193
GSGQGPQERGNQQT	473	1.702	1.269	0.846	0.313
GSIAHVGTGQNQQT	474	1.696	1.264	0.837	1.045
GSGQNQQKQNHGNT	475	1.695	5.349	1.538	1.340
GSGQNQQALGSQRT	476	1.695	1.934	1.419	0.562
GSGAITHMPQNQQT	477	1.695	1.681	0.647	0.411
GSGQRNPLLLNQQT	478	1.693	0.144	0.662	0.740
GSSGIPVSHQNQQT	479	1.690	3.384	0.820	0.333

GVHSLTPSGQNQQT	480	1.687	4.104	0.475	0.215
GVIVLHGSGQNQQT	481	1.682	14.166	1.074	1.098
GGTRVVDSGQNQQT	482	1.676	9.735	0.676	0.370
GSGGVTYQSQNQQT	483	1.673	7.283	0.649	0.181
GSGQNQAGHGPGQT	484	1.670	2.861	1.040	0.887
GSGQLVTSGPNQQT	485	1.669	5.271	0.964	0.433
GSGIAAQRTQNQQT	486	1.665	2.691	1.062	0.754
GSTPAGVGGQNQQT	487	1.663	2.733	0.593	0.477
GSGQNQQTSTGVHS	488	1.660	8.271	1.039	1.075
GSGQIRQLVDNQQT	489	1.657	5.529	0.314	0.272
GSLIGMQSGQNQQT	490	1.656	6.783	0.797	0.392
GSGQIKGKMDNQQT	491	1.654	2.601	1.065	1.012
GSGSDMSSWQNQQT	492	1.651	0.175	0.281	0.303
GRGQNQQHTGLATT	493	1.650	6.174	1.134	0.691
GSGQNQQTLYSSNT	494	1.642	1.044	0.664	0.368
GSGQTQVLKSNQQT	495	1.640	3.031	1.599	0.975
GSRTLSNVGQNQQT	496	1.640	3.219	0.617	0.542
GSGVQHSLPQNQQT	497	1.639	0.764	0.440	0.387
GNYLHQASGQNQQT	498	1.635	1.454	0.816	0.181
GSGGTSVHQQNQQT	499	1.629	0.000	0.585	0.195
GMDESRPSGQNQQT	500	1.627	3.976	0.918	0.648
GSGQNQQSMGTFTT	501	1.625	0.000	1.792	0.399
GSGQNQQTPLRPPT	502	1.624	0.352	0.874	0.472
GSGQNQHHSVSQQT	503	1.623	3.700	0.605	0.334
GSGQLRSLSTNQQT	504	1.622	6.855	1.310	0.382
GSGSPRQLSQNQQT	505	1.621	0.873	0.520	0.273
GSGQNQQTTASSHT	506	1.618	7.404	0.745	0.678
GRGQVVSTHQNQQT	507	1.607	3.318	0.931	0.561
GSAQVSMVGQNQQT	508	1.601	1.332	0.500	0.285
GSSTLVTIGKNQQT	509	1.592	4.316	0.917	0.819
GFAHQASSGQNQQT	510	1.587	1.852	1.638	1.080
GSGQPVLSISNQQT	511	1.586	2.695	0.390	0.282
GSGQSHRSELNQQT	512	1.585	11.974	0.668	0.256
GSSVGSPIGQNQQT	513	1.584	3.574	1.059	0.706
GSGMPIRNVQNQQT	514	1.584	0.138	0.684	0.631
GSSTRVDSGQNQQT	515	1.584	2.774	0.704	0.660
GSGQNQQTAMRSTT	516	1.581	2.588	0.656	0.665
GSGQNQQHSSSHLT	517	1.581	2.782	1.091	0.859
GSRNGHAVGQNQQT	518	1.574	2.688	0.434	0.939
GLGAYQSSGQNQQT	519	1.574	0.696	1.407	0.688
GPGLSGHSGQNQQT	520	1.571	1.603	1.154	1.297
GSTGIVSSGQNQQT	521	1.570	0.927	2.141	1.046
GSRTTQVIGQNQQT	522	1.570	1.838	0.773	0.564
GSGLLHRAQQNQQT	523	1.569	0.724	1.583	0.646
GSGQNAQQAAAQQT	524	1.568	4.239	0.937	0.604
GSGQNQQSALRTQT	525	1.568	1.913	1.581	1.421
GSGFLSDTRQNQQT	526	1.566	45.953	0.473	0.575
GSGLLYHDQQNQQT	527	1.565	2.760	0.405	0.107
GSGQNQHYSLHKQT	528	1.563	3.399	1.485	1.273
GSGESPLPQQNQQT	529	1.562	0.556	0.387	0.247
GNGESMRPNQNQQT	530	1.560	2.341	0.693	0.376
GSGLKWSTLQNQQT	531	1.556	0.000	1.134	2.442
GSGQMGRQAVNQQT	532	1.554	1.529	0.535	0.411
GSGQNQQTSGVLTL	533	1.553	0.000	1.104	0.782
GSGQNQQALHNPHT	534	1.553	0.664	0.638	0.213
GSGQNQQVIPNSKT	535	1.548	1.036	0.844	0.376
GSPLQDRVGQNQQT	536	1.548	0.753	0.469	0.391
GSGQNQYSSTNPQT	537	1.542	2.251	0.544	0.535
GAMTVTISGQNQQT	538	1.542	6.249	0.443	0.257
GSGQNQQLQTLIRT	539	1.538	1.425	0.813	0.514
GSGLRQTSQQNQQT	540	1.537	2.067	0.978	0.705
GSGQNQQTGLRQQT	541	1.533	2.120	1.217	1.103
GSGQTRQMKDNQQT	542	1.530	11.079	0.841	0.214
GSGQNHGLQSGQQT	543	1.530	4.960	0.938	0.779

GSGQSHRQPENQQT	544	1.529	2.153	0.209	0.159
GSGQDRHIVQNQQT	545	1.527	11.068	0.285	0.162
GSGQNQQLPHSNLT	546	1.521	1.838	0.442	0.283
GSGQLSVPYDNQQT	547	1.521	0.000	0.622	0.111
GSGRNPQTQPLQQT	548	1.519	0.040	0.733	0.573
GSGQPYSTGLNQQT	549	1.519	1.403	0.612	0.376
GSGQNQQTHGGLRD	550	1.519	6.487	1.913	1.298
GAYGMVSSGQNQQT	551	1.518	3.469	0.732	0.773
GSGIQSSYSQNQQT	552	1.517	15.978	1.032	0.684
GPRLSDQSGQNQQT	553	1.511	0.364	0.640	0.579
GSGQNQQTHPSPCT	554	1.510	1.003	1.120	0.546
GSGQSFQMHTNQQT	555	1.504	9.770	0.503	0.325
GSGQNQQTGNPKHT	556	1.504	5.973	1.391	1.139
GFSSAVHSGQNQQT	557	1.502	1.234	0.218	0.210
GSGQNQQTSMSNAT	558	1.501	6.766	1.605	0.745
GSGQDMKQHHNQQT	559	1.501	1.638	0.358	0.239
GLRLSTPSGQNQQT	560	1.498	4.334	0.804	0.522
GSGQNQQTSVYMNT	561	1.498	0.613	0.640	0.983
GSGQNQYSQSSMQT	562	1.494	4.278	0.375	0.309
GSGQNQQSMADHTT	563	1.494	1.728	0.428	0.215
GWERSFVSGQNQQT	564	1.492	0.943	0.490	0.538
GLLAGKSSGQNQQT	565	1.491	2.981	0.999	0.946
GKSFVPQSGQNQQT	566	1.489	2.502	1.798	0.430
GSGQMQSAGSNQQT	567	1.482	0.116	1.034	1.128
GSDQNQRLTSSMQT	568	1.479	0.164	0.875	0.670
GESRAVLSGQNQQT	569	1.476	0.938	0.789	0.368
GSVFGVPSGQNQQT	570	1.474	1.248	0.685	0.213
GSGLPDRNLQNQQT	571	1.471	7.306	1.136	0.611
GSGTHNSAIQNQQT	572	1.469	0.570	0.762	0.574
GSGMIIASMQNQQT	573	1.469	6.722	1.135	0.415
GGITWTDSGQNQQT	574	1.462	4.535	1.472	0.468
GSGQNQQASGRQQT	575	1.458	3.179	0.943	0.991
GSGQNQQPHLKSLT	576	1.457	5.016	1.096	0.740
GPPQHMTSGQNQQT	577	1.457	1.547	0.509	0.677
GSGQNQQASLPSRT	578	1.456	0.389	0.930	0.673
GSGQIVSTQTNQQT	579	1.456	1.103	0.453	0.512
GSGKGHSAGQNQQT	580	1.453	0.936	1.035	1.173
GSGQNTRLQLGQQT	581	1.452	1.747	0.181	0.234
GSVGSRPVGQNQQT	582	1.442	11.363	1.182	0.716
GSSHTLALGQNQQT	583	1.441	7.071	0.851	0.406
GMYEYSQSGQNQQT	584	1.438	0.000	1.410	0.448
GNGQNQQHSILHGT	585	1.435	0.000	0.777	0.415
GSGYNQPHLQNQQT	586	1.435	4.512	0.711	0.395
GPLVNASSGQNQQT	587	1.434	5.239	0.831	0.343
GSGQNQQVLTTART	588	1.434	4.142	1.071	0.948
GSGQNQHSVHNDQT	589	1.428	0.000	0.521	0.515
GAGLIMHSGQNQQT	590	1.425	1.408	0.565	0.511
GMGRHSASGQNQQT	591	1.417	6.500	0.470	0.389
GSHSQSGHGQNQQT	592	1.413	1.240	0.696	0.318
GSSTTIVSGQNHQT	593	1.411	0.000	0.993	0.672
GRHLVTASGQNQQT	594	1.411	2.885	0.648	0.404
GSGQNQQHANLNQT	595	1.410	0.094	0.416	0.544
GSGSTHSKAQNQQT	596	1.410	0.515	0.921	0.801
GSGQNKQMLSGNTT	597	1.410	2.219	1.074	0.404
GSGQVHNPTQNQQT	598	1.410	2.488	1.021	0.542
GSGQNQQIPHVHQT	599	1.409	0.768	0.576	0.218
GSLHAGLSGQNQQT	600	1.408	1.739	1.286	0.936
GPAQHGTSGQNQQT	601	1.407	0.866	1.030	0.615
GEKAVTSSGQNQQT	602	1.402	0.998	0.558	0.327
GSGQNQQTMANGQR	603	1.394	0.216	1.169	1.230
GSGSPHSKDQNQQT	604	1.394	0.000	2.041	4.680
GSFSMGYGGQNQQT	605	1.393	18.476	1.908	1.030
GSGTHLVSLQNQQT	606	1.392	0.000	0.715	1.167
GSGQMQPHVQNQQT	607	1.389	9.381	0.387	0.153

GSGQNQQVAGLNNT	608	1.386	3.218	0.449	0.492
GSSQNQQHDMRLRT	609	1.386	2.645	0.669	0.552
GPASLPISGQNQQT	610	1.386	9.008	0.312	0.155
GSGQNQQPPLATRT	611	1.386	2.295	0.593	0.287
GSSRVPVSGQNQQT	612	1.385	13.191	0.870	0.485
GSGQNQQTNLGHTT	613	1.383	1.523	1.343	1.281
GSGQNQQLVSRVQT	614	1.381	1.195	0.656	0.466
GPNSYPVSGQKQQT	615	1.381	4.040	0.736	0.834
GHAEYQASGQNQQT	616	1.377	7.299	0.803	0.745
GSGQALLSTGNQQT	617	1.377	0.847	0.536	0.370
GSGQLPRQMTNQQT	618	1.376	3.550	0.400	0.562
GSGFPKSTEQNQQT	619	1.376	2.058	0.610	0.194
GSRETSLSGQNQQT	620	1.373	5.193	1.364	0.203
GSGQNQQGTGVSIT	621	1.371	4.295	1.417	0.749
GSRTVPVYGQNQQT	622	1.371	0.363	1.226	0.969
GSNAQSAHGQNQQT	623	1.371	0.888	0.976	0.245
GAFELAASGQNQQT	624	1.369	18.165	0.994	0.775
GSGQYRSSSDNQQT	625	1.369	6.209	0.681	0.409
GSGQVYISTPNQQT	626	1.367	0.000	0.859	0.282
GSGVSTQLLQNQQT	627	1.367	2.467	0.928	0.509
GSGQLGLSVTNQQT	628	1.364	6.906	1.395	0.376
GSGSNMRLSQNQQT	629	1.363	0.588	0.962	0.730
GSGQNLHSGLPQQT	630	1.363	1.594	1.054	0.592
GSSHTLALGQNKQT	631	1.362	2.160	0.838	0.643
GSGQNQHSLPAHRT	632	1.361	0.700	0.911	0.742
GSGQNQGTVYPNQT	633	1.358	7.648	0.835	0.815
GSGQNQQPSLRQST	634	1.356	2.905	1.315	0.554
GSGQNARLKDNQQT	635	1.354	2.395	0.580	0.938
GHAGSTGSGQNQQT	636	1.352	2.829	1.332	1.233
GSGQALSSSGNQQT	637	1.351	6.860	0.894	0.931
GSGASESHRQNQQT	638	1.350	0.850	0.325	0.313
GVGVITSSGQNQQT	639	1.348	0.918	1.296	0.777
GSLYGQSLGQNQQT	640	1.348	11.248	0.894	0.843
GSGQMSDVHGNQQT	641	1.346	7.172	0.408	0.548
GSGQNQQHSSKATT	642	1.345	12.248	1.350	1.401
GSGQNQQTSVSQQT	643	1.342	1.614	1.030	0.913
GSGQKMWKLDNQQT	644	1.341	0.000	0.990	1.418
GSGQNVSMQVNQQT	645	1.341	0.000	0.357	0.251
GSGQNQRATLSNQT	646	1.339	1.084	0.947	0.723
GSGQASSKSANQQT	647	1.339	1.138	0.500	0.175
GSGKNQTPIPKGQT	648	1.339	5.077	1.306	1.154
GSGQNQQTRQEGST	649	1.339	0.000	0.645	0.718
GASSLATSGQNQQT	650	1.337	0.703	0.423	0.217
GSGQRGSLTENQQT	651	1.337	2.482	0.300	0.567
GSEQTRQRGQNQQT	652	1.333	2.172	0.574	0.815
GSGQNQQTLTASKE	653	1.333	1.152	0.981	1.172
GSGTSGKTGKNQQT	654	1.333	4.033	0.358	0.676
GQLVTFTSGQNQQT	655	1.331	11.282	0.819	0.294
GSGQNQQSANKILT	656	1.331	3.789	0.894	1.236
GSGQNQQHHSSHTT	657	1.328	2.158	0.957	0.452
GSGQNQKGMQPNQT	658	1.326	3.139	0.775	1.059
GSGQLVSGLYNQQT	659	1.325	0.000	0.842	0.733
GSSVGVPSGQNQQT	660	1.322	4.867	0.336	1.157
GSGQNQQWDSRRQT	661	1.321	0.531	1.059	0.825
GSEQTRQSGQNQQT	662	1.321	0.514	0.734	0.900
GSGIGSHIPQNQQT	663	1.319	0.173	0.822	0.597
GSGQNQRLHGVDQT	664	1.318	4.655	0.459	0.341
GEVSRVLSGQNQQT	665	1.318	0.437	1.150	0.440
GSGQNQQKVSPLLT	666	1.314	1.602	0.755	0.806
GSGLALERSQNQQT	667	1.311	0.486	0.618	0.096
GPDRIGSSGQNQQT	668	1.308	0.426	0.654	0.342
GSGQNQDHQNKQQT	669	1.308	1.470	0.510	0.761
GSGQNQQTALYNNT	670	1.307	0.862	0.660	0.726
GSGAVHLTAQNQQT	671	1.306	1.668	0.541	0.466

GSLVSTQSGQNQQT	672	1.305	1.293	1.282	0.650
GSGVSARMVQNQQT	673	1.299	0.624	0.870	0.697
GSGQTRMPLANQQT	674	1.296	0.790	0.447	0.273
GSGISSRNMQNQQT	675	1.291	6.328	1.671	0.560
GSGEKVHSGQNQQT	676	1.289	0.062	0.862	0.671
GSGQNQQKLSSMST	677	1.286	1.586	1.160	1.052
GSGQNQQTGQHMRV	678	1.286	4.161	1.839	1.635
GSGMIIITTAQNQQT	679	1.285	0.105	0.678	0.276
GSGQNWPALKGQQT	680	1.284	2.031	1.101	1.222
GASHMSISGQNQQT	681	1.284	0.462	0.404	0.374
GSDQNQQLGYSKQT	682	1.283	0.000	0.853	0.660
GIPSIRESGQNQQT	683	1.282	0.166	0.484	0.254
GSGIPSVKFQNQQT	684	1.281	0.061	0.364	0.561
GSGQNQQTSVSQNV	685	1.281	0.750	0.788	0.715
GSGQNQQIGESRMT	686	1.279	0.103	0.890	0.453
GSGSSSMSFQNQQT	687	1.279	0.540	0.466	0.095
GSGQKQERAVSKQT	688	1.277	0.000	1.174	0.732
GCTTRLNSGQNQQT	689	1.276	0.000	0.184	0.618
GSGQNQQIISTKIT	690	1.275	0.000	0.951	0.710
GSGQNQQKSLNGNT	691	1.275	8.573	0.586	0.851
GSGIPAPRLQNQQT	692	1.273	4.162	0.583	0.396
GSGQIRESMGNQQT	693	1.270	1.676	0.833	0.523
GSGQNSGVHFNQQT	694	1.268	0.587	0.871	0.377
GSGQNIGHSLPQQT	695	1.264	6.183	0.740	0.478
GSGERSISVQNQQT	696	1.264	1.619	0.598	0.173
GSGLKPNVLQNQQT	697	1.263	0.975	0.701	0.268
GSGQVAYAQGNQQT	698	1.259	1.309	0.734	0.313
GSGQSSYGSGNQQT	699	1.257	1.686	1.161	0.456
GSGQNQAMTHGDQT	700	1.257	1.878	0.357	0.259
GSGQNQALVSMGQT	701	1.255	1.876	0.987	0.560
GSGQNPSFMRGQQT	702	1.252	1.454	1.293	1.094
GSGQNQQSHLRTNT	703	1.251	4.583	1.022	0.718
GYTRLETSGQNQQT	704	1.250	1.323	0.841	0.297
GSGQSYDMRGNQQT	705	1.248	0.567	0.588	0.368
GSRTTQDIGQNQQT	706	1.247	0.000	0.685	0.280
GSGEPYKAAQNQQT	707	1.246	0.000	0.872	0.507
GRLSNAHGGQNQQT	708	1.245	0.839	1.036	0.725
GSGQNQRAVLNDQT	709	1.242	3.023	0.556	0.259
GGSETYGGGQNQQT	710	1.241	13.065	0.982	0.730
GSSVNSMIGQNQQT	711	1.239	0.000	0.976	0.580
GNSSMMGSGQNQQT	712	1.239	3.856	0.656	0.364
GNRDRPSSGQNQQT	713	1.239	3.947	0.298	0.178
GSGNMHASRQNQQT	714	1.238	3.878	0.782	0.687
GFIFPKVSGQNQQT	715	1.237	0.000	1.764	0.692
GSGQNQQLKNSTST	716	1.235	1.703	1.063	0.538
GSGQNQQSQYMPRT	717	1.234	0.401	0.549	0.520
GSGQRMADIGNQQT	718	1.233	2.539	0.352	0.427
GSGQNQSHYPSQQT	719	1.228	4.315	0.644	0.402
GSDGKMHRGQNQQT	720	1.227	0.000	1.826	0.776
GSGSVGFIGQNQQT	721	1.227	8.261	0.689	0.445
GLHGMTLSGQNQQT	722	1.226	3.552	0.470	0.338
GSDQSKRGDSNQQT	723	1.225	0.639	0.479	0.267
GSLFLATGGQNQQT	724	1.220	0.000	0.775	0.485
GSGQNQQPSAFSKT	725	1.220	4.906	1.309	0.754
GSGQLPQSGLNQQT	726	1.218	1.504	0.641	0.318
GSGSKQNALQNQQT	727	1.216	2.010	0.941	0.594
GSGQRRELSQNQQT	728	1.215	1.791	0.622	0.396
GSGQREPKASNQQT	729	1.214	2.793	0.399	0.520
GSGQNQQHPSTQQT	730	1.205	1.552	1.017	0.680
GSQSTLGLGQNQQT	731	1.204	3.246	0.594	0.400
GSGQNQQMPGLSST	732	1.204	1.887	0.234	0.181
GSGQNQQTVGGKNL	733	1.203	0.128	0.777	1.051
GSSREFHSGQNQQT	734	1.203	1.591	0.688	0.474
GSGQNQQTVPSNLV	735	1.201	0.791	0.434	0.281

GSGQNAYSSQAQQT	736	1.201	12.096	0.629	0.216
GSGQNKDHSTRRQT	737	1.197	0.000	0.384	0.477
GQLGSVGSGQDQQT	738	1.196	0.000	1.020	0.437
GSGQHAAPGHNQQT	739	1.195	5.999	0.600	0.199
GSGQNQQTSQSPPT	740	1.194	1.208	0.851	0.478
GSGNYRDHEQNQQT	741	1.193	7.389	0.287	0.222
GSGQHSNQHVNQQT	742	1.192	1.453	0.955	0.558
GSGQTARNGINQQT	743	1.192	2.030	1.002	0.472
GSGQNQQHYGSQGT	744	1.189	0.453	1.345	0.379
GSGSPQASRQNQQT	745	1.189	6.782	0.923	0.542
GSGFSHSMGKNQQT	746	1.188	9.809	1.381	0.611
GSGQSHSLETNQQT	747	1.188	1.319	0.520	0.363
GTEQTRQSGQNQQT	748	1.188	0.132	0.756	0.756
GSGRHLASVQNQQT	749	1.187	1.024	0.654	0.606
GLGSKNHSGQNQQT	750	1.187	5.046	0.825	0.224
GSGQNQQTSHFPSA	751	1.185	0.325	0.969	0.907
GSGQLSGTPQNQQT	752	1.185	1.382	1.025	0.643
GSGQNQQAPHKKET	753	1.180	0.598	0.994	0.689
GSGQNQQTLRGSLE	754	1.179	1.812	0.853	0.354
GSIAMTSHGQNQQT	755	1.178	1.435	0.551	0.438
GSPGVSPSGQNQQT	756	1.178	3.006	0.853	1.160
GSGQNQQTGSSSRV	757	1.176	0.580	0.995	1.128
GSGQHLPLLGNQQT	758	1.175	1.739	0.519	0.347
GSDESHRGGQNQQT	759	1.174	0.504	0.818	0.331
GSGIVTKLGQNQQT	760	1.174	10.571	0.599	0.242
GSGQDVTKTGNQQT	761	1.173	4.523	0.531	0.035
GSGQNQQSHGRIGT	762	1.173	5.117	0.607	0.455
GSGQNQQINHRSPT	763	1.173	0.748	0.259	0.220
GSGDDSRVGQNQQT	764	1.172	0.191	0.466	0.156
GSGQSTLKRINQQT	765	1.168	13.442	0.534	1.184
GSGSQHSKAQNQQT	766	1.168	0.312	0.638	0.916
GSGQNQQHASSNNT	767	1.166	7.155	0.789	0.896
GSRTYQVSGQNQQT	768	1.164	1.853	0.638	0.641
GSGQNQGLLSSPQT	769	1.164	0.000	0.707	0.417
GSGGGLQHNQNQQT	770	1.163	4.098	1.137	0.778
GSGQNQQTTAATRM	771	1.163	3.925	0.947	1.005
GSGQNQRASILVQT	772	1.162	3.632	0.531	0.569
GSGQNLGLLGAQQT	773	1.161	1.458	0.524	0.226
GSLDLGRSGQNQQT	774	1.160	3.283	1.002	0.505
GNSQVKVSGQNQQT	775	1.158	4.930	1.422	0.728
GSSGSHQYGQNQQT	776	1.155	0.000	1.129	0.794
GSGQNQQQRDGTLT	777	1.152	0.387	0.760	0.730
GRGQHVSVANNQQT	778	1.152	1.896	1.032	0.589
GDSSSRISGQNQQT	779	1.151	3.787	0.916	0.348
GSGQNQQHSLSSQT	780	1.150	3.844	0.700	0.730
GSLMDVHRGQNQQT	781	1.150	0.387	1.009	0.238
GSIQYQSSGQNQQT	782	1.147	2.601	1.074	1.191
GLGSKNPSGQNQQT	783	1.147	1.629	1.184	0.424
GSGQLVLTLQNQQT	784	1.143	0.000	0.336	0.336
GSGQNQQTSQPLPG	785	1.141	0.080	0.748	0.530
GSGQNQQNLGKLNT	786	1.141	0.000	0.919	0.687
GTTAHQPSGQNQQT	787	1.138	0.211	0.726	0.275
GSGQNRAQIGTQQT	788	1.138	0.469	0.776	0.654
GSGQYVHVSSNQQT	789	1.137	1.803	0.739	0.366
GSGQNQQTAHAFNI	790	1.132	3.404	0.699	0.729
GSGQNQRTMVATQT	791	1.130	1.122	0.649	0.554
GSGQNPIRGAMQQT	792	1.126	1.327	1.296	0.427
GSGYVITGSQNQQT	793	1.125	6.271	0.971	0.248
GRGPKQSNIQNQQT	794	1.125	0.737	0.771	2.490
GSGQNQQTMLGKPC	795	1.125	0.047	1.090	0.992
GSGQNQQVGSTVRT	796	1.124	2.040	0.918	0.614
GNVTTQKSGQNQQT	797	1.122	2.546	1.215	0.922
GSGNPVSHLQNQQT	798	1.121	1.037	0.583	0.310
GSLSHMESGQNQQT	799	1.120	0.829	0.489	0.265

GRAPTNLSGQNQQT	800	1.118	0.687	0.757	0.169
GSGQNQQTVMTARA	801	1.117	1.535	0.995	0.843
GSGMPASRLQNQQT	802	1.117	1.689	0.790	0.372
GVVRNHQSGQNQQT	803	1.116	5.801	0.899	0.868
GSGQNQHSVQVRQT	804	1.116	1.909	0.782	0.916
GSGQNTGHLTMQQT	805	1.114	0.078	1.026	0.595
GSGQNQQYAGKILT	806	1.112	0.300	1.078	0.431
GSGNPIIVRNQNQQT	807	1.112	0.873	0.732	0.755
GSGQNGGSSNRQQT	808	1.109	2.594	1.255	0.844
GSGQRLSQGVNHQT	809	1.108	3.394	0.931	1.141
GSGQNAHAKEGQQT	810	1.108	0.000	0.875	1.179
GSSPAPNSGQNQQT	811	1.106	2.229	0.719	0.368
GLAHKTSSGQNQQT	812	1.106	0.915	0.427	0.690
GSGQNQQTPGAIIKT	813	1.105	3.827	0.957	0.277
GSGQNQQSLSGSFT	814	1.105	0.735	0.745	0.883
GSGQNQQSTGTSRT	815	1.103	4.054	1.209	0.935
GSGQNQQTVQSNLV	816	1.103	2.350	0.577	0.698
GSGQNQQLGSRQCT	817	1.102	0.183	0.987	0.407
GSGQNQYLRLELQT	818	1.101	0.000	0.416	0.839
GSGQNQQTSPRLQT	819	1.100	0.795	1.156	1.091
GSGQNQQTTSSNMT	820	1.099	0.569	0.638	0.698
GTASTYNSGQNQQT	821	1.099	2.560	0.250	0.625
GSGQNQQTMPQHKI	822	1.097	2.394	0.479	0.197
GSGQSHLHTGNQQT	823	1.096	2.584	0.721	0.295
GVKGVGHSGQNQQT	824	1.096	2.485	0.994	0.783
GSGKVTKQSQNQQT	825	1.095	0.000	0.928	1.035
GSGQNQQTALEKSL	826	1.092	0.000	0.625	0.702
GSGYKDTYGQNQQT	827	1.091	0.854	0.717	0.448
GSGQNQQSGTFLST	828	1.090	5.673	1.021	0.742
GSGQNTGQHMMQQT	829	1.090	1.058	1.147	0.917
GSGKNQQRPGLDQT	830	1.089	1.557	0.583	0.385
GSGQSREISLNQQT	831	1.088	6.954	0.594	0.282
GTPTSPSSGQNQQT	832	1.086	4.558	0.833	0.662
GKPAGGLSGQNQQT	833	1.085	2.805	0.708	0.739
GSGQNHRSADMQQT	834	1.084	12.001	0.417	0.212
GSGQNQQTLPSLSL	835	1.084	1.758	0.527	0.175
GSPYMGATGQNQQT	836	1.083	5.364	0.918	0.254
GSGEAKAVGQNQQT	837	1.081	4.357	0.703	0.824
GHMKGVTSGQNQQT	838	1.081	2.814	0.807	0.413
GSGQNQKILTLDQT	839	1.080	0.371	0.291	0.314
GSGQNQQTKVGHSA	840	1.079	1.256	0.669	1.019
GIARTTISGQNQQT	841	1.078	1.783	0.819	0.330
GSGQNQQTSVGFRT	842	1.077	3.737	0.648	0.534
GSGQNQQTMIANIR	843	1.076	0.000	0.379	0.458
GDMTRSSSGQNQQT	844	1.075	0.802	1.145	1.038
GSGHMSDLRQNQQT	845	1.073	4.291	0.555	0.328
GRGAVMASGQNQQT	846	1.072	0.923	0.783	0.605
GSGQNQQLSGKSVT	847	1.070	1.524	1.276	0.930
GSHTLVVSGQNQQT	848	1.069	1.535	0.671	0.748
GSGPWSAGLQNQQT	849	1.067	0.947	0.700	0.539
GSGQHSPHALNQQT	850	1.064	1.412	0.885	0.573
GSGQNQQPNSGSMT	851	1.064	0.925	0.588	0.339
GSGLAHLGGQNQQT	852	1.064	2.191	0.749	0.794
GSSVRYEPKQNQQT	853	1.063	1.564	0.450	0.501
GSGQNQQARPLELT	854	1.061	0.059	0.389	0.252
GSGQPRSTGINQQT	855	1.061	0.693	0.650	0.542
GSGQNQANWVKVQT	856	1.059	0.126	0.683	0.532
GSGHLFQSGQNQQT	857	1.057	0.615	0.751	0.386
GSGQNRGISISQQT	858	1.057	2.166	0.686	0.566
GSGTHYDNRQNQQT	859	1.054	0.072	0.612	0.486
GSGQNQQTSTTPLP	860	1.052	2.823	0.828	0.741
GSGQVHASQVNQKT	861	1.049	0.503	0.855	0.767
GSSGHRESGQNQQT	862	1.048	4.398	0.641	0.691
GLSAEKSSGQNQQT	863	1.047	7.203	0.629	0.303

GSGQEHRSLANQQT	864	1.046	0.000	0.507	0.344
GSGQTVVRIANQQT	865	1.046	4.156	0.661	0.390
GSGQNVSSVHRQQT	866	1.045	0.712	0.383	0.271
GSGASRMSIQNQQT	867	1.045	0.111	0.801	0.417
GVAFIGSSGQNQQT	868	1.043	0.000	0.744	0.648
GSGQNQQTVPTRQT	869	1.040	1.207	0.629	0.138
GSGQAAKSSQNQQT	870	1.036	0.681	0.778	0.737
GSGQNQQVAIRTST	871	1.035	2.447	0.963	0.370
GSVHMQNAGQNQQT	872	1.034	3.608	1.004	0.625
GSGMRQAGVQNQQT	873	1.032	0.811	0.736	0.775
GSGQNQQVGGKTVT	874	1.032	6.195	1.094	0.821
GVHDMRVSGQNQQT	875	1.032	8.083	1.171	0.818
GSGQHVSVANNQQT	876	1.029	5.734	0.974	0.577
GSAAMSVRGQNQQT	877	1.029	2.386	0.202	0.287
GVSRGGPSGQNQQT	878	1.028	1.611	0.750	0.591
GSGQMVHTIGNQQT	879	1.026	1.328	0.406	0.430
GRGGSMAETQNQQT	880	1.024	2.853	0.799	0.669
GSGETNPTRQNQQT	881	1.021	0.688	0.726	0.807
GSGEAARYEQNQQT	882	1.020	0.000	0.107	0.125
GSGQNERHLVLQQT	883	1.019	5.354	0.416	0.150
GSGQNQQSKQQVLT	884	1.019	1.494	1.428	1.256
GSGQARAHRGNQQT	885	1.017	0.000	0.254	0.386
GSGQNQQPLDTSRT	886	1.015	0.775	0.491	0.376
GSGQNQQLANMVTT	887	1.014	1.739	1.253	0.987
GSGQMKDLHRNQQT	888	1.014	1.068	0.587	0.506
GSGQNQHLSSFVQT	889	1.013	0.110	1.090	0.364
GSGQNQQPSSRVTT	890	1.012	2.179	0.784	0.504
GSGQNQQLAITLGT	891	1.011	0.000	0.877	0.143
GSGQNQQTVGNPAT	892	1.008	3.014	0.856	0.395
GSGQNQGRAHPMQT	893	1.007	2.364	0.684	0.453
GSGQLIASVVNQQT	894	1.005	0.086	0.197	0.359
GSSVRSLVGQNQQT	895	1.004	3.840	0.412	0.608
GGAGSAHSGQNQQT	896	1.003	6.108	0.474	1.092
GSDQNQQTMSSTRT	897	1.003	2.428	1.306	0.835
GSGQNQQMAGAFRT	898	1.003	1.784	1.307	0.762
GSLGNLQRGQNQQT	899	1.003	0.895	0.947	0.385
GSGPSISHGQNQQT	900	1.000	0.000	0.614	0.665
GSGQNQQT	6406	1.000	1.000	1.000	1.000
GSGQNQQSSFNVQT	901	0.998	0.000	1.307	0.675
GSGQNQQTGQATHN	902	0.996	2.199	0.877	0.527

[0459] A second cross-species evolution screen was performed using an AAV capsid variant library with a modification in loop IV introduced as described above and passaging it once through NHPs (passage 1) and then subsequently injected it into two different strains of mice (passage 2), C57Bl/6 and BALB/c. The fold-enrichment for each variant in the brain of each mouse species was calculated by systematic NGS enrichment analysis following RNA recovery and RT-PCR amplification. The fold enrichment values in the second passage in mice were compared to those fold enrichment values from the second pass that was performed in NHPs as described above. As shown in Table 15, when comparing the second pass fold enrichment values in the mice versus NHPs, 12 variants were identified that had a fold-enrichment value greater than 10 in all three animal groups. Further, 10 of these 12 variants comprised the SPH motif and a positive residue in one of the next three subsequent residues (Table 15).

Table 15. NGS fold-enrichment of AAV capsid variants from a second passage (P2) in NHPs or mice (C57Bl/6 or BALB/c) following a first passage in NHPs

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in NHP P2	Fold enrichment over AAV9 in BALB/c P2	Fold enrichment over AAV9 in C57Bl/6 P2
VSGSPHSKAQNQQT	903	99.76	92.99	34.29
CSGSPHSKAQNQQT	904	85.1	66.74	22.19
GSGSPHSKAQNQQT	200	56.33	44.58	14.48
GSGSPHRKAQNQQT	905	46.39	42.47	14.11
GRGSPHSKAQNQQT	906	43.68	59.65	28.13
GHDSPHKSGQNQQT	201	33.96	59.14	27.15
GSGSPHSKAKNQQT	208	31.27	41.51	14
GSGSPHSKAQNKQT	907	29.52	44.1	13.69
GSGSPHSKAQTQQT	908	24.27	41.75	18
GQDSPHKSGQNQQT	204	22.7	32.37	16.02
GSGSTHASRQNQQT	909	11.04	23.71	10.67
GHDSQHKSGQNQQT	404	10.36	21.3	13.55

[0460] Following the second passage in mice, a synthetic library was generated using those variants that demonstrated a fold-change in enrichment relative to wild-type AAV9 that was above 10 in the brain of either strain of mice, as measured by systematic NGS enrichment analysis following RNA recovery and RT-PCR amplification. There were approximately 500 variants in this synthetic library. This synthetic library was then injected back into both strains of mice (C57Bl/6 and BALB/c; passage 3). RNA was recovered from the mouse brains, RT-PCR amplification was performed, and fold-enrichment relative to wild-type AAV9 was calculated by NGS analysis, which is provided in Table 16. As shown in Table 16, the variants with the greatest fold-enrichment in the brain in each strain, were highly correlated across strains (R^2=0.8458).

Table 16. NGS fold-enrichment of AAV capsid variants in the brain from a third passage (P3) in mice (C57Bl/6 or BALB/c) following a first and second passage in mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in BALB/c	Fold enrichment over AAV9 in C57Bl/6	Average
GSGSPHKYGQNQQT	910	150.445	103.488	126.966
GSGSPHKFGQNQQT	911	73.364	60.304	66.834
GHDSPHKSGQNQQT	201	82.460	51.125	66.792
GSGSPHSKAQNQQT	200	60.312	65.853	63.083
VSGSPHKFGQNQQT	912	60.186	59.142	59.664
GSGSPHSKAQNHQT	913	63.486	51.647	57.566
VSGSPHSKAQNQQT	903	73.555	37.429	55.492
GQDSPHKSGQNQQT	204	63.898	43.752	53.825
GSGSPHSKAQHQQT	914	45.309	45.600	45.454
GSGSPHKTYQNQQT	915	50.283	35.460	42.871
GSGSPHSKAQTQQT	908	43.120	39.098	41.109
VSGSPHASRQNQQT	916	46.572	32.480	39.526
GSGSPHSKAQNKQT	907	39.848	35.596	37.722
GSGSPHKFGKNQQT	917	31.948	34.899	33.423
GSGSPHASRQNQHT	918	28.145	30.928	29.537

GSHSPHKSGQNQQT	919	22.948	35.412	29.180
GSGQNQQRRMSPST	920	4.576	53.520	29.048
GSGSPHASRQNQQT	205	28.866	29.139	29.003
GSGSPHSKPQNQQT	921	26.958	28.599	27.779
GSGSPHKFGQKQQT	922	39.597	14.927	27.262
VSGSPHGARQNQQT	923	30.985	22.634	26.810
GSGSPHSKAQKQQT	924	25.052	27.459	26.256
GHSSPHRSGQNQQT	212	16.982	35.081	26.032
GSGSPHSKAKNQQT	208	21.069	25.711	23.390
GSHSPHKRGQNQQT	925	24.054	20.262	22.158
GRGSPHSKAQNQQT	906	20.939	22.720	21.830
GQSSPHRSGQNQQT	229	9.916	26.608	18.262
GSGQNRQRLKGLET	926	3.937	31.022	17.480
GSGSPHKLGQNQQT	927	18.905	14.732	16.818
GSGSPHKTSKNQQT	928	14.654	17.606	16.130
GSGSPHKIGQNQQT	929	16.999	14.794	15.897
GSGSPHKKNQNQQT	209	25.633	5.605	15.619
GSGSPHASRQNKQT	206	10.738	20.347	15.542
GSGSPHTRGQNQQT	214	16.899	13.869	15.384
GSGQDSPHVRNQQT	930	15.340	14.646	14.993
GSGSPHKTSQNQQT	931	20.428	8.818	14.623
GSGSPHASRKNQQT	932	13.799	12.749	13.274
GSGSPHASRQKQQT	211	13.624	11.188	12.406
GSHSPHKSGQKQQT	933	6.700	17.736	12.218
GSGSPHKTSQKQQT	934	12.621	11.720	12.170
GSGSPHVRGQNKQT	935	13.174	11.017	12.095
GSGSPHKTTQNQQT	936	9.722	13.381	11.552
CSGSPHSKAQNQQT	904	11.772	9.447	10.610
GSGPVRALRQNQQT	937	3.369	17.431	10.400
GSGSPHVRGQKQQT	938	7.573	12.498	10.036
GSGSPHRKAQNQQT	905	12.308	7.349	9.828
GRGSPHASRQNQQT	318	11.903	6.780	9.342
CSGSPHKTSQNQQT	939	11.167	6.631	8.899
CSHSPHKSGQNQQT	940	11.356	6.304	8.830
GSGSPHSKDQNQQT	604	3.492	10.236	6.864

[0461] Taken together, these results demonstrate that after 3 rounds of screening of this AAV9 variant library with loop IV modifications in NHP and mice, many AAV capsid variants outperformed the wild-type AAV9, for example, in penetration of the blood brain barrier (BBB) and spinal cord expression. These capsid variants were able to cross-species, evidenced by expression and tropism in the NHP brain/spinal cord as well as in the brain of two different mouse species.

Example 2. Individual Capsid Characterization in Mice

[0462] The goal of these experiments was to determine the transduction level, tropism, ability to cross the blood brain barrier, and overall spatial distribution in the central nervous system (CNS) of 2 capsid variants selected from the study described in Example 1 relative to AAV9 following intravenous injection in mice. The 2 capsid variants were TTM-001 (SEQ ID NO: 981 (amino acid)

and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2), as outlined in Table 3 above. The amino acid and DNA sequences of TTM-001 and TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0463] AAV particles were generated with each of these capsid variants encapsulating a luciferase-EGFP transgene driven by a CMV/chicken beta actin promoter in a single stranded viral genome. Each capsid variant and AAV9 control were tested by intravenously administering by tail vein injection, the AAV particle formulation at 5e11 VG/dose (2.5E13 vg/kg) to three female BALB/c mice. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA, transgene protein, and viral DNA (biodistribution).

[0464] At 28 days post-injection of the AAV particles encapsulated in the TTM-001 capsid variant (AAV_TTM-001), mice were injected with luciferin and their brains were harvested for IVIS imaging. Robust luciferase signal was observed in mice injected with AAV particles encapsulated in the TTM-001 capsid variant, and this was greatly increased relative to AAV particles encapsulated in the wild-type AAV9 control capsid.

[0465] The brains isolated from mice injected with the AAV particles encapsulated in the TTM-001 capsid variant (AAV_TTM-001) or the TTM-002 capsid variant (AAV_TTM-002) were assayed by qPCR for the presence of transgene RNA as a measure of transgene expression, and the presence of viral DNA as a measure of viral genome levels. Data were provided as fold over AAV9 (**Table 17**). As shown in **Table 17**, when compared to the wild-type AAV9 capsid control, TTM-001 and TTM-002 demonstrated a 30-fold and 66-fold increase, respectively, in transgene mRNA levels and expression in the brain, indicative of enhanced payload delivery. This correlated with a 32-fold (TTM-001) and 47-fold (TTM-002) increase, respectively, in viral genome (DNA) concentrations in the brain relative to the AAV9 capsid control, which is indicative of enhanced CNS tropism and transduction (**Table 17**).

Table 17. Transgene mRNA and viral genome levels (DNA) in mice relative to the AAV9 control

Measure	Tissue	AAV9	TTM-001	TTM-002
mRNA (transgene expression)	Brain	1.0	30.4503	66.2161
DNA (viral genome quantification)	Brain	1.0	32.0315	47.2810
mRNA (transgene expression)	Liver	1.0	1.2356	0.2016
DNA (viral genome quantification)	Liver	1.0	0.4802	0.0277

[0466] The brain tissues and spinal cords of the mice were also subjected to anti-GFP immunohistochemistry staining to evaluate overall CNS tropism and biodistribution. Immunohistochemical staining correlated with the qPCR analysis, as TTM-001 and TTM-002 showed significantly stronger staining and payload expression in the brain and spinal cord, as compared to the AAV9 control. More specifically, TTM-001 and TTM-002 demonstrated localization and strong payload expression and transduction in the mid-brain region, with increased staining observed in the hippocampus and thalamus, as well as in the brain stem, compared to AAV9. Less staining was

observed in the cortical regions of the brain compared to the midbrain. However, staining in these cortical regions was stronger for TTM-001 and TTM-002 compared to the AAV9 control. It also appeared that the TTM-001 and TTM-002 capsid variants were able to transduce non-neuronal cells, including glial cells and oligodendrocytes. With respect to the spinal cord, staining and payload expression for TTM-01 and TTM-002 were localized to the ventral horns of the grey matter.

[0467] Peripheral tissues were also isolated from the mice intravenously injected with the AAV particles encapsulated in the TTM-001 capsid variant or the TTM-002 capsid variant for analysis by qPCR and/or GFP immunohistochemical staining. Transgene mRNA levels and viral genome DNA levels were quantified in the liver by qPCR and the fold over AAV9 was calculated for each capsid variant (Table 17). TTM-001 resulted in similar levels of payload expression (mRNA levels) as compared to wild-type AAV9, but only half as much viral genome DNA was quantified in the liver compared to AAV9. TTM-002 demonstrated greatly reduced mRNA and viral genome DNA levels in the liver compared to AAV9. GFP immunohistochemical staining of the spleen, heart, skeletal muscle, kidneys, and lungs of mice injected with AAV particles encapsulated in the TTM-001 capsid variant or the TTM-002 capsid variant showed similar levels of payload expression as compared to those mice injected with AAV particles encapsulated in the wild-type AAV9 control capsid.

[0468] Taken together, these data demonstrate that TTM-001 and TTM-002 are enhanced CNS tropic capsids in mice that can infect non-neuronal cells. Additionally, these capsid variants were able to successfully penetrate the blood brain barrier following intravenous injection.

Example 3. Maturation of TTM-001 and TTM-002 Capsid in Mice

[0469] This Example describes maturation of the TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variants to further enhance their transduction and biodistribution in the central nervous system and evolve the AAV capsid variants to provide further cross-species compatibility. Two approaches were used to mature the TTM-001 and TTM-002 capsid sequences in order to randomize and mutate within and around the peptide insert comprised within loop IV of the capsid variant. As many of the AAV capsid variants that demonstrated the greatest fold-enrichment in the NHP brain relative wild-type AAV9 comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138) (see **Example 1**), the SPH motif was not mutated in either approach to mature the TTM-001 and TTM-002 capsid variants. In the first maturation approach, sets of three contiguous amino acids were randomized across the mutagenesis region in the TTM-001 and TTM-002 sequences, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 981 and 982. In the second maturation approach, mutagenic primers were used to introduce point mutations at a low frequency, scattered across the mutagenesis region in the TTM-001 and TTM-002 sequences ranging from position 449 to position 466, numbered

according to SEQ ID NO: 981 and 982. AAV capsid variants arising from each maturation approach for TTM-001 were pooled together and AAV capsid variants arising from each maturation approach for TTM-002 were also pooled together, for subsequent testing and characterization in mice.

[0470] The library of pooled matured AAV capsid variants generated from TTM-001 or library of pooled matured AAV capsid variants generated from the TTM-002 matured AAV capsid variant each were intravenously injected into the tail vein of three female CD-1 Outbred mice (Charles River) at a dose of 1.0×10^{12} VG/dose. After 14-days in life, the brains of the mice were isolated and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the corresponding TTM-001 or TTM-002 control, and the peptides comprised within the variants were identified. The data for the TTM-001 matured capsid variants is provided in **Table 18** and the data for the TTM-002 matured capsid variants is provided in **Table 19**.

[0471] As shown in **Table 18**, approximately 714 TTM-001 matured capsid variants demonstrated at least a 2-fold increase in expression relative to the non-matured TTM-001 control, and several variants demonstrated greater than a four-fold enrichment relative to the non-matured TTM-001 control. Also, across the peptides comprised within the TTM-001 matured capsid variants with the greatest fold-enrichment relative to the non-matured TTM-001 capsid in the brain, it was observed that the modifications in the variant sequences appeared in the region C-terminal to the SPH motif present within the capsid variant. This indicates that modifications that appeared to improve TTM-001 capsid tropism in the CNS of mice were skewed to the C-terminal portion of the peptide insertion in loop IV of the sequence. Additionally, a number of these C-terminal modifications were the incorporation of an arginine (R) or leucine (L) residue.

Table 18. NGS fold-enrichment of TTM-001 matured AAV capsid variants in the brain of CD-1 Outbred mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-001	Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-001
KTINGSGSPHSLLWNQQT	1008	7.983	KTINGRPSPHVKAQNQQT	1365	2.419
KTINGSGSPHSKAQYYVT	1009	6.283	KTINGSGSPHSMFPNQQT	1366	2.419
KTINGSGSPHSKLRRQQT	1010	6.231	KTINGMKSPHSKAQNQQT	1367	2.413
KTINGSGSPHSIWQNQQT	1011	5.883	KTINGSGSPHSKVRAQQT	1368	2.412
KTINGSSSPHCTAQNQQT	1012	5.607	KGLVGSGSPHSKAQNQQT	1369	2.412
KTINGSGSPHSKAGCGQT	1013	5.341	KTINGSRSPHVRAQNQQT	1370	2.412
KSMNGSGSPHSRAQNQQT	1014	5.145	KTIRLRGSPHSKAQNQQT	1371	2.408
KTINGSGSPHSKRLRQQT	1015	5.034	KPRLGSGSPHSKAQNQQT	1372	2.406
KTINGSGSPHSLRRNQQT	1016	4.985	KTINGSGSPHSKAWYPQT	1373	2.406
KTINGSGSPHSRGRNQQT	1017	4.961	KTINGSCSPHVRAQNQQT	1374	2.406
KTINGSGSPHSEIVNQQT	1018	4.931	KTINGSGSPHSKRNVQQT	1375	2.404
KTINGSGSPHSSRRNQQT	1019	4.920	KTINGSGSPHSKRGLQQT	1376	2.402
KTINGSGSPHCLLQNQQT	1020	4.898	KTINGSGSPHSKRLAQQT	1377	2.397
KTIMRVGSPHSKAQNQQT	1021	4.875	KTINGSGSPHSKVTRQQT	1378	2.397

KTINGSGSPHSKAFRLQT	1022	4.849	KTINGSGSPHTWLQNQQT	1379	2.397
KTINGSGSPHCLAQNQQT	1023	4.847	KTINGSGSPHSKQRSQQT	1380	2.395
KTINGSCSPHRKAQNQQT	1024	4.801	KTINGSGSPHSKAQRCST	1381	2.393
KTINGSGSPHFLRQNQQT	1025	4.777	KTINGSPSPHYLAQNQQT	1382	2.391
KTINGSGSPHSLRFNQQT	1026	4.765	KTINGRRSPHLKAQNQQT	1383	2.391
KTINGSGSPHSYLRNQQT	1027	4.566	KTINGSGSPHWSLQNQQT	1384	2.389
KTINGSGSPHCSLQNQQT	1028	4.540	KTINGVTSPHWKAQNQQT	1385	2.387
KTINGSGSPHVLWQNQQT	1029	4.533	KTINGSGSPHSKAQTTRT	1386	2.385
KTINGSGSPHSKWLLQQT	1030	4.521	KTINGSGSPHSKAQLFKT	1387	2.385
KTINGSGSPHSLWSNQQT	1031	4.467	KTINGSGSPHSKARSYQT	1388	2.382
KTINGSGSPHSKRRLQQT	1032	4.451	KTINGSGSPHSKLSRQQT	1389	2.380
KTINGSGSPHSVYLNQQT	1033	4.426	KTINGSGSPHLVFQNQQT	1390	2.376
KTINGSGSPHSLWLNQQT	1034	4.412	KTINGSGSPHSKAQLVKT	1391	2.376
KTINGSGSPHSKAQRKLT	1035	4.339	KTINGSGSPHSKAQTGRT	1392	2.371
KTINGSGSPHSKALRRQT	1036	4.330	KTINGSGSPHSKARYSQT	1393	2.369
KTINGSGSPHSKAQRLRT	1037	4.322	KTINGRHSPHLKAQNQQT	1394	2.369
KYLSGSGSPHSKAQNQQT	1038	4.264	KTINGSGSPHSFARNQQT	1395	2.367
KTINGSGSPHSKAQRRLT	1039	4.227	KTINGSGSPHSSCQNQQT	1396	2.365
KTINGSGSPHSKARRQQT	1040	4.218	KTINGSGSPHSLFANQQT	1397	2.365
KTINGSGSPHSKARRLQT	1041	4.210	KTINGSGSPHSKRLTQQT	1398	2.363
KTINGSGSPHSKSRRQQT	1042	4.175	KTINGSGSPHSKAQTART	1399	2.363
KTINGLLSPHWKAQNQQT	1043	4.173	KTINGSGSPHFLNQNQQT	1400	2.359
KTINGSGSPHSKARLRQT	1044	4.155	KTINGSGSPHSKAQLILT	1401	2.358
KTINGSGSPHSKASKRQT	1045	4.117	KEVGGSGSPHSKAQNQQT	1402	2.358
KTINGSGSPHVRRQNQQT	1046	4.114	KTINGSRSPHIRAQNQQT	1403	2.356
KTINGSGSPHSKAQLYRT	1047	4.108	KTINGSGSPHSSWLNQQT	1404	2.354
KGLSGSGSPHSKAQNQQT	1048	4.056	KTINGSMSPHLYAQNQQT	1405	2.354
KTINGSGSPHSLFRNQQT	1049	4.037	KTINGMSSPHRKAQNQQT	1406	2.352
KTINGSGSPHSKAQLTVT	1050	4.026	KTINGSGSPHSKPRPQQT	1407	2.352
KTINGSRSPHTRAQNQQT	1051	3.989	KTINGSGSPHSGLWNQQT	1408	2.350
KTINGSGSPHSKAKLRQT	1052	3.976	KTINGSGSPHRWAQNQQT	1409	2.350
KTINGSGSPHSKLIRQQT	1053	3.968	KTINGSGSPHSKIRLQQT	1410	2.348
KTINGSGSPHSKALRFQT	1054	3.894	KTINGSGSPHSKFSCQQT	1411	2.348
KTINGSGSPHSKRTFQQT	1055	3.879	KTINGSGSPHSKSCAQQT	1412	2.348
KTINGSGSPHSKAQKRLT	1056	3.872	KTINGSGSPHSKRLMQQT	1413	2.345
KTINGSGSPHLWSQNQQT	1057	3.857	KTSRCSGSPHSKAQNQQT	1414	2.345
KTINGSGSPHLLWQNQQT	1058	3.855	KTINGSGSPHSFLLNQQT	1415	2.341
KTINGSGSPHSRLRNQQT	1059	3.851	KTINGSGSPHCSAQNQQT	1416	2.339
KTINGSGSPHSKRAAQQT	1060	3.838	KTINGSGSPHSKAQPSKT	1417	2.339
KTINGSGSPHSKRSWQQT	1061	3.838	KTINGSGSPHSYVRNQQT	1418	2.339
KTINGSGSPHSKAQLRRT	1062	3.825	KTINGSGSPHSKAQQSRT	1419	2.337
KTINGSGSPHYLVQNQQT	1063	3.819	KTINGSGSPHSFVVNQQT	1420	2.335
KTINGSGSPHSKLFRQQT	1064	3.806	KTINGFRSPHSKAQNQQT	1421	2.333
KTINGSGSPHSKRAMQQT	1065	3.801	KTINGSGSPHSKWLVQQT	1422	2.333
KTINGSGSPHSKTLRQQT	1066	3.788	KTINGSGSPHSKRTAQQT	1423	2.331
KTINGSGSPHSRSRNQQT	1067	3.784	KTINGLFSPHRKAQNQQT	1424	2.331
KTINGSGSPHRRRQNQQT	1068	3.754	KTINTIESPHSKAQNQQT	1425	2.331
KTINGSGSPHSKTCLQQT	1069	3.717	KRLFGSGSPHSKAQNQQT	1426	2.330
KTINGSGSPHSKSRWQQT	1070	3.698	KTINGSGSPHSKAPNHLT	1427	2.324
KTINGSGSPHRFRQNQQT	1071	3.698	KTINGSGSPHLFRQNQQT	1428	2.324
KTINGLRSPHRKAQNQQT	1072	3.676	KTINGSGSPHSKASRHQT	1429	2.324
KTRSRSGSPHSKAQNQQT	1073	3.669	KTINGSGSPHSKLSWQQT	1430	2.322
KTINGSGSPHSKAQLVVT	1074	3.654	KETAGSGSPHSKAQNQQT	1431	2.320

KTINGSGSPHSRKLNQQT	1075	3.646	KTINGHRSPHLKAQNQQT	1432	2.320
KTINGSGSPHSLLCNQQT	1076	3.644	KTINGSGSPHSKGCLQQT	1433	2.320
KTINGKRSPHSKAQNQQT	1077	3.611	KTINGSGSPHSKAQVLIT	1434	2.317
KTINGSRSPHLFAQNQQT	1078	3.601	KTINGSGSPHSKLRSQQT	1435	2.309
KSINGSGSPHSKAHDQQT	1079	3.592	KTINGTLSPHRKAQNQQT	1436	2.307
KTINGSGSPHSKAQRSRT	1080	3.585	KTINGSGSPHSTWTNQQT	1437	2.307
KTINGSGSPHSTWLNQQT	1081	3.583	KTINGSGSPHSKAQCRLT	1438	2.304
KTINGSGSPHSKASRRQT	1082	3.577	KTINNLRSPHSKAQNQQT	1439	2.302
KTINGSGSPHSKRSMQQT	1083	3.561	KTINGSGSPHSKARANQT	1440	2.300
KTINGSGSPHSCLQNQQT	1084	3.559	KTINGRQSPHTKAQNQQT	1441	2.294
KTINGSGSPHSKRLWQQT	1085	3.529	KTINSARSPHSKAQNQQT	1442	2.292
KTINGSGSPHSWLSNQQT	1086	3.495	KTINGCSSPHRKAQNQQT	1443	2.291
KTINGSGSPHLRRQNQQT	1087	3.493	KTINGSVSPHFMAQNQQT	1444	2.287
KTINGSGSPHSKARRSQT	1088	3.493	KTINGSGSPHSLCQNQQT	1445	2.285
KTINGSGSPHSKHLRQQT	1089	3.438	KTINGSLSPHLFAQNQQT	1446	2.285
KTINGSGSPHSCSQNQQT	1090	3.428	KTINGSGSPHSKACPLQT	1447	2.285
KTINGSGSPHSKSFRQQT	1091	3.426	KTINGRTSPHRKAQNQQT	1448	2.285
KTINGSGSPHLCLQNQQT	1092	3.425	KTINGSGSPHSKRATQQT	1449	2.283
KTINGSGSPHSKAQTSRT	1093	3.421	KTINGSGSPHSKARIMQT	1450	2.283
KTINGSGSPHSLCSNQQT	1094	3.413	KTINGSGSPHVTWQNQQT	1451	2.281
KTINGSRSPHLRAQNQQT	1095	3.410	KTINGSGSPHSKRLPQQT	1452	2.279
KTINGSGSPHSKAQVSKT	1096	3.406	KTINGSGSPHSKAQGFRT	1453	2.279
KTINGSGSPHSKAQRHVT	1097	3.404	KTINGSGSPHLYGQNQQT	1454	2.277
KTINGSSSPHLCAQNQQT	1098	3.402	KTINGSGSPHLSCQNQQT	1455	2.277
KTINGSGSPHSFLRNQQT	1099	3.384	KTINGSGSPHSKAQFTLT	1456	2.277
KTINGSGSPHSFVLNQQT	1100	3.382	KTINGSRSPHFKAQNQQT	1457	2.277
KTINGSGSPHSKMRAQQT	1101	3.382	KTINGRPSPHSKAQNQQT	1458	2.276
KTINGSGSPHRPRQNQQT	1102	3.380	KTINGFSSPHRKAQNQQT	1459	2.276
KTINGSGSPHSKCLLQQT	1103	3.374	KTINGRASPHVKAQNQQT	1460	2.272
KTINGSGSPHSKAQSRRT	1104	3.372	KTINGSGSPHSKAQNEVH	1461	2.272
KTINGSGSPHSRWQNQQT	1105	3.372	KTINGSGSPHSKRSLQQT	1462	2.270
KYSVGSGSPHSKAQNQQT	1106	3.365	KTINGSGSPHRSRQNQQT	1463	2.270
KTINGSGSPHSKRFLQQT	1107	3.359	KPPTGSGSPHSKAQNQQT	1464	2.270
KTINGSGSPHSLFLNQQT	1108	3.358	KTINGSGSPHSKAARTQT	1465	2.266
KTINGSGSPHSKAYLRQT	1109	3.356	KTINGSGSPHSSWANQQT	1466	2.264
KTINGSGSPHSKRNGQQT	1110	3.350	KTINGSGSPHSKAQRHAT	1467	2.264
KTINGSGSPHTRRQNQQT	1111	3.350	KTINSPRSPHSKAQNQQT	1468	2.264
KTINGSGSPHSKPRLQQT	1112	3.337	KTINGSGSPHSKSERQQT	1469	2.263
KTINFLRSPHSKAQNQQT	1113	3.331	KTINGSGSPHALFQNQQT	1470	2.261
KTINGSGSPHLLCQNQQT	1114	3.328	KTINGSGSPHSKAQCYVT	1471	2.261
KTINGSGSPHSKARIVQT	1115	3.287	KTINGVASPHRKAQNQQT	1472	2.261
KTINGSKSPHFKAQNQQT	1116	3.285	KTINGSGSPHSALWNQQT	1473	2.261
KTINGSGSPHSKAQIRLT	1117	3.279	KTINGSGSPHSKSVRQQT	1474	2.259
KTINGSSSPHWVAQNQQT	1118	3.277	KTINGSGSPHSHMENQQT	1475	2.259
KTINGSGSPHSKATRRQT	1119	3.277	KTINGSGTPHSKAQNQQT	1476	2.259
KTINGSLSPHSCAQNQQT	1120	3.268	KTINGSGSPHSKTGRQQT	1477	2.259
KTINGSGSPHSLYLNQQT	1121	3.264	KTINGSGSPHSKAQANRT	1478	2.255
KTINGSGSPHSKVGRQQT	1122	3.255	KTINGSGSPHSKARFSQT	1479	2.253
KTINGSGSPHSRRLNQQT	1123	3.251	KYLLGSGSPHSKAQNQQT	1480	2.253
KTINGSGSPHSKAQHSRT	1124	3.227	KTINGSGSPHCSSQNQQT	1481	2.253
KTINGSGSPHSKAFPRQT	1125	3.220	KTINGSMSPHRKAQNQQT	1482	2.251
KTINGSPSPHRRAQNQQT	1126	3.216	KTINGNLSPHRKAQNQQT	1483	2.250
KTINGSGSPHSKRNLQQT	1127	3.210	KEVAGSGSPHSKAQNQQT	1484	2.250

KTINGSGSPHSKPTRQQT	1128	3.201	KTINLSRSPHSKAQNQQT	1485	2.246
KTINGSGSPHSKLWLQQT	1129	3.199	KTINGSGSPHSKARQQQT	1486	2.244
KTINGSGSPHWLAQNQQT	1130	3.192	KTINGTPSPHRKAQNQQT	1487	2.244
KTINGSGSPHRTRQNQQT	1131	3.190	KTINGSGSPHSKFKLQQT	1488	2.244
KTINGSGSPHSKLNKQQT	1132	3.181	KTINGSGSPHSKAWLLQT	1489	2.240
KTINGSGSPHSSLWNQQT	1133	3.179	KTINGLRSPHSKAQNQQT	1490	2.238
KTINGSGSPHSKAQITLT	1134	3.177	KTINGRLSPHRKAQNQQT	1491	2.238
KTINGSGSPHSKFLFQQT	1135	3.173	KTINGSPSPHLFAQNQQT	1492	2.238
KTINGSGSPHSKRTPQQT	1136	3.169	KDLRGSGSPHSKAQNQQT	1493	2.238
KTINGSGSPHSKAQNSRR	1137	3.168	KTINGSGSPHSKAQLAKT	1494	2.238
KTINGSGSPHSRLKNQQT	1138	3.156	KTINGSGSPHSKPRSQQT	1495	2.235
KTINGSGSPHSCLLNQQT	1139	3.127	KTINGSGSPHSKKMSQQT	1496	2.235
KTINGSGSPHTLYQNQQT	1140	3.117	KTINGSGSPHSKAQLIVT	1497	2.235
KTINGSGSPHSKYPSQQT	1141	3.114	KTINGSGSPHSKARFTQT	1498	2.233
KTINGSGSPHSKLRNQQT	1142	3.112	KTINGSGSPHPLFQNQQT	1499	2.233
KTINGSGSPHLNWQNQQT	1143	3.112	KTINGSGSPHSKAQRGMT	1500	2.231
KTINGVVSPHRKAQNQQT	1144	3.106	KTINGSGSPHSKAQNLRR	1501	2.231
KTINGSGSPHSYRPNQQT	1145	3.095	KTINGSGSPHSKAQFRVT	1502	2.231
KTINGSTSPHRRAQNQQT	1146	3.089	KTINGSGSPHSKAFVRQT	1503	2.225
KTINGSCSPHPLAQNQQT	1147	3.086	KTINGSGSPHSKARLTQT	1504	2.223
KTINGSGSPHSKAFARQT	1148	3.082	KTINGSGSPHRFKQNQQT	1505	2.223
KTINGSGSPHSKALRYQT	1149	3.076	KTINGSGSPHSKEETQQT	1506	2.223
KTINGSKSPHRLAQNQQT	1150	3.073	KTINGSGSPHSKTRAQQT	1507	2.223
KTINMRVSPHSKAQNQQT	1151	3.073	KTINGSGSPHSVSWNQQT	1508	2.223
KTINGSGSPHMYLQNQQT	1152	3.061	KTINGSGSPHTKWQNQQT	1509	2.222
KTINGSGSPHSKLARQQT	1153	3.054	KTINGSNSPHRKAQNQQT	1510	2.218
KTINGSGSPHSKARPYQT	1154	3.050	KTINGSGSPHSKAQNKRS	1511	2.214
KTINGSGSPHSKRVPQQT	1155	3.048	KTINGSGSPHSTRQNQQT	1512	2.212
KTINGSGSPHLSWQNQQT	1156	3.047	KTINGTRSPHTKAQNQQT	1513	2.203
KTINGRSSPHGKAQNQQT	1157	3.035	KTINGSGSPHVLFQNQQT	1514	2.203
KTINGSGSPHLWTQNQQT	1158	3.034	KTINGSVSPHYLAQNQQT	1515	2.203
KTINGLLSPHRKAQNQQT	1159	3.026	KTINGALSPHRKAQNQQT	1516	2.203
KTINGSGSPHRLRQNQQT	1160	2.998	KTINGSGSPHSKARLYQT	1517	2.201
KTINGSCSPHSGAQNQQT	1161	2.994	KTINGSGSPHEHNQNQQT	1518	2.199
KTINGSGSPHSKAQRRST	1162	2.993	KTINGVLSPHWKAQNQQT	1519	2.199
KTINGSGSPHSKLCSQQT	1163	2.989	KTINGSGSPHSKASRQQT	1520	2.197
KTINGSGSPHSKAQLLKT	1164	2.985	KTINGSGSPHSKRSFQQT	1521	2.197
KTINGRKSPHSKAQNQQT	1165	2.985	KTINGSGSPHSKRVSQQT	1522	2.196
KTINGSGSPHLLYQNQQT	1166	2.983	KTINGSGSPHSYSRNQQT	1523	2.196
KTINGSGSPHSKLLRQQT	1167	2.981	KTINGSGSPHSTVWNQQT	1524	2.196
KTINGSGSPHSLRHNQQT	1168	2.980	KTINGSGSPHSVLFNQQT	1525	2.194
KTINGSGSPHSSKRNQQT	1169	2.978	KTINGPLSPHCKAQNQQT	1526	2.194
KTINGSGSPHSKARSRQT	1170	2.972	KTINGSGSPHSKRVGQQT	1527	2.190
KTINGRSSPHRKAQNQQT	1171	2.965	KTINGSGSPHSKLWSQQT	1528	2.190
KTINGSKSPHRTAQNQQT	1172	2.950	KTINGSGSPHSKAQGVRT	1529	2.188
KTINGMRSPHVKAQNQQT	1173	2.937	KTINGSVSPHRRAQNQQT	1530	2.186
KTINGSGSPHSKRMSQQT	1174	2.931	KTINGSGSPHLRFQNQQT	1531	2.186
KTINGSGSPHSKVPKQQT	1175	2.924	KTINGSASPHVFAQNQQT	1532	2.186
KTINLIRSPHSKAQNQQT	1176	2.920	KTWVRSGSPHSKAQNQQT	1533	2.186
KTINGSGSPHPFLQNQQT	1177	2.916	KTINGSGSPHSKARMQQT	1534	2.184
KTINGSGSPHSKARLWQT	1178	2.914	KTINGSGSPHSKASRGQT	1535	2.182
KTINGSGSPHSRTRNQQT	1179	2.912	KTINGSGSPHSKAQVCLT	1536	2.182
KTINGSGSPHSKRSNQQT	1180	2.886	KTINGSGSPHSKARGVQT	1537	2.181

KTINGSLSPHSWAQNQQT	1181	2.885	KTINGSGSPHGLWQNQQT	1538	2.181
KTINGSRSPHYKAQNQQT	1182	2.879	KTINGSGSPHSKAQVWFT	1539	2.181
KTINRHSSPHSKAQNQQT	1183	2.877	KTINGSGSPHSKAQVTLT	1540	2.179
KTINGSGSPHSKRRNQQT	1184	2.877	KTINGSGSPHSKAQLRIT	1541	2.179
KTINGSGSPHSKAKHLQT	1185	2.870	KDSLGSGSPHSKAQNQQT	1542	2.175
KTINGSGSPHSKRTYQQT	1186	2.870	KTINGSGSPHSKRASQQT	1543	2.173
KTINGVLSPHRKAQNQQT	1187	2.868	KTINGSGSPHSKRINQQT	1544	2.173
KTINGSGSPHSFITNQQT	1188	2.868	KTINGSGSPHSKASKNQT	1545	2.171
KTINGSGSPHSTRLNQQT	1189	2.860	KTINGSGSPHSKAQLPWT	1546	2.169
KTINGSGSPHSKRTSQQT	1190	2.857	KTINGSGSPHSKLTRQQT	1547	2.169
KTINGSGSPHSRRSNQQT	1191	2.851	KTINGSGSPHSKTNRQQT	1548	2.169
KTINGHLSPHRKAQNQQT	1192	2.851	KTINRVISPHSKAQNQQT	1549	2.169
KTINGSGSPHSKAQFSRT	1193	2.847	KTINGSGSPHTLWQNQQT	1550	2.168
KTINGSGSPHSKAQTFRT	1194	2.847	KTINGSGSPHSRRQNQQT	1551	2.166
KTINGSGSPHSKPLRQQT	1195	2.844	KTINGSGSPHSKGGRQQT	1552	2.164
KTINGSGSPHSKASCRQT	1196	2.840	KTINGSESPHDSAQNQQT	1553	2.164
KTINGSGSPHSKILWQQT	1197	2.838	KTINGSGSPHSRPRNQQT	1554	2.164
KTINGSGSPHSKALKRQT	1198	2.836	KTINGSGSPHSRKQNQQT	1555	2.162
KTINGSGSPHSKAHRSQT	1199	2.819	KTINGSGSPHSKAQEELT	1556	2.162
KTINGSGSPHSMLYNQQT	1200	2.808	KTINGWRSPHSKAQNQQT	1557	2.160
KTINGSGSPHSKCTLQQT	1201	2.808	KTINGSGSPHSLLYNQQT	1558	2.158
KTINGSGSPHSKAQNRMR	1202	2.804	KTINGSGSPHSFRLNQQT	1559	2.158
KTINGSGSPHSKLVRQQT	1203	2.801	KTINGSGSPHSKAQFLRT	1560	2.156
KTINGSGSPHSKRILQQT	1204	2.801	KTINGSGSPHSKQSRQQT	1561	2.156
KTINGSGSPHSKAQWLRT	1205	2.795	KTINGSRSPHSKAQNRQT	1562	2.155
KTINGSGSPHSLTCNQQT	1206	2.795	KTINGRPSPHIKAQNQQT	1563	2.155
KTINGIRSPHTKAQNQQT	1207	2.793	KTINGSGSPHSKRLVQQT	1564	2.151
KTINGSGSPHSKAQRWLT	1208	2.788	KGHEGSGSPHSKAQNQQT	1565	2.151
KTINGSGSPHSKAQLSIT	1209	2.784	KTINGSGSPHSKAQKRST	1566	2.151
KTINGSGSPHIYRQNQQT	1210	2.782	KTINGSGSPHSYLLNQQT	1567	2.147
KTINGSGSPHSLRSNQQT	1211	2.778	KTINGSGSPHSKPRGQQT	1568	2.147
KTINGSGSPHSKVKPQQT	1212	2.778	KTINGSGSPHSKTRLQQT	1569	2.145
KTINGSGSPHSKATRHQT	1213	2.777	KTINGSGSPHSKSHRQQT	1570	2.145
KTINGSLSPHLCAQNQQT	1214	2.775	KEIKGSGSPHSKAQNQQT	1571	2.140
KTINGSGSPHSKACASQT	1215	2.775	KTINGSGSPHSKARGIQT	1572	2.140
KWSPGSGSPHSKAQNQQT	1216	2.764	KTINGYRSPHSKAQNQQT	1573	2.140
KTINGYLSPHRKAQNQQT	1217	2.762	KTINGSGSPHSKLWTQQT	1574	2.140
KTINGSGSPHSKVIRQQT	1218	2.760	KTINGSGSPHSKPWLQQT	1575	2.138
KTINGSGSPHFLLQNQQT	1219	2.758	KTINGSGSPHWSVQNQQT	1576	2.138
KTINGSGSPHSKARSKQT	1220	2.758	KTINGSGSPHSKVARQQT	1577	2.136
KTINGVPSPHWKAQNQQT	1221	2.758	KTINGSGSPHTLFQNQQT	1578	2.136
KTINGSGSPHSKATRNQT	1222	2.756	KTINGSCSPHLAAQNQQT	1579	2.134
KTINGSGSPHSKACSAQT	1223	2.754	KTINGSGSPHSKTSRQQT	1580	2.132
KTINGSGSPHSKARYVQT	1224	2.749	KTINGSGSPHSKAQNARH	1581	2.127
KTINGSRSPHARAQNQQT	1225	2.745	KTINGSGSPHSKAQLKLT	1582	2.125
KTINGSGSPHSKAQHLRT	1226	2.741	KTINGSGSPHSKAQNWRT	1583	2.125
KTINGSGSPHSKAKSRQT	1227	2.739	KTINGSGSPHFLPQNQQT	1584	2.123
KTINGSGSPHSKIGRQQT	1228	2.739	KTINGSGSPHSKNVRQQT	1585	2.123
KTINGLASPHRKAQNQQT	1229	2.737	KTINGSGSPHFMRQNQQT	1586	2.123
KTINGSGSPHSKARTRQT	1230	2.737	KTINGSGSPHGWAQNQQT	1587	2.121
KTINGSGSPHSKSIRQQT	1231	2.728	KTINGSGSPHFHLQNQQT	1588	2.121
KTINGSGSPHSKRLYQQT	1232	2.721	KTINGSASPHWSAQNQQT	1589	2.121
KTINGLPSPHRKAQNQQT	1233	2.719	KTINGSSSPHSWAQNQQT	1590	2.119

KTINGSLSPHRRAQNQQT	1234	2.717	KTINGSGSPHSKAHRQQT	1591	2.117
KTINGKTSPHGKAQNQQT	1235	2.717	KTINGSGSPHSKQRVQQT	1592	2.117
KTINGSRSPHRLAQNQQT	1236	2.698	KTLRRSGSPHSKAQNQQT	1593	2.117
KTINGSGSPHSLTWNQQT	1237	2.698	KTINGSGSPHSKGVRQQT	1594	2.115
KTINGSKSPHRKAQNQQT	1238	2.696	KTINGSLSPHTWAQNQQT	1595	2.115
KTINGSGSPHSKAQLRKT	1239	2.689	KTINGSGSPHSKRALQQT	1596	2.114
KTINGSGSPHSKSRHQQT	1240	2.685	KTINGSGSPHCLSQNQQT	1597	2.114
KTINRRLSPHSKAQNQQT	1241	2.678	KTINGSGSPHSKAQSLKT	1598	2.110
KTINGSGSPHSRRVNQQT	1242	2.676	KTINGSGSPHSFVRNQQT	1599	2.110
KTINGSGSPHSHWQNQQT	1243	2.676	KTINGSGSPHSIFSNQQT	1600	2.110
KTTHCSGSPHSKAQNQQT	1244	2.672	KTINGSGSPHSKVSRQQT	1601	2.108
KTINGSGSPHSWLQNQQT	1245	2.665	KTINGSGSPHSKARNKQT	1602	2.108
KTINGSTSPHYLAQNQQT	1246	2.665	KTINASGSPHSKAQGQQT	1603	2.108
KTINGLTSPHRKAQNQQT	1247	2.663	KTINGSGSPHSKLRMQQT	1604	2.106
KTINGSGSPHSKRLLQQT	1248	2.659	KTINGSWSPHMLAQNQQT	1605	2.106
KTINGSGSPHSKLCVQQT	1249	2.659	KTINGSGSPHSLFPNQQT	1606	2.106
KTINGFLSPHRKAQNQQT	1250	2.654	KPPLGSGSPHSKAQNQQT	1607	2.102
KTINGSGSPHSKMRPQQT	1251	2.652	KTINGIASPHRKAQNQQT	1608	2.099
KTINGSGSPHSKQTRQQT	1252	2.650	KTINGSCSPHSLAQNQQT	1609	2.099
KTINGSGSPHSYLINQQT	1253	2.650	KTINGRLSPHFKAQNQQT	1610	2.097
KTINGSGSPHSKALRSQT	1254	2.648	KTINGSGSPHSKARMTQT	1611	2.091
KTINGMLSPHRKAQNQQT	1255	2.646	KTINGSGSPHSKARLQQT	1612	2.089
KTINGSGSPHSKCLTQQT	1256	2.644	KTINGSGSPHSKWVSQQT	1613	2.089
KTINGSGSPHSKAQLTLT	1257	2.641	KTINGSGSPHSKKVSQQT	1614	2.088
KTINGHSSPHRKAQNQQT	1258	2.639	KTINGSGSPHSKAQSYRT	1615	2.088
KTINGSGSPHLTWQNQQT	1259	2.637	KAFNGSGSPHSKAPNQQT	1616	2.088
KTINGSGSPHSKAQYCLT	1260	2.628	KTINGSGSPHSKAQYRLT	1617	2.088
KTINGSGSPHSFLVNQQT	1261	2.624	KTINGSWSPHLVAQNQQT	1618	2.084
KTINMSRSPHSKAQNQQT	1262	2.622	KTINGSGSPHSWTQNQQT	1619	2.084
KTINGSGSPHSKAQLHRT	1263	2.618	KTINGSGSPHSKAQSHRT	1620	2.084
KTINGSGSPHLYMQNQQT	1264	2.615	KGINGSGSPHGKAQNQQT	1621	2.084
KTINGSRSPHRRAQNQQT	1265	2.615	KTINGSGSPHSKAQNRKL	1622	2.084
KTINGSGSPHSKAQNRRS	1266	2.613	KTINGRYSPHSKAQNQQT	1623	2.080
KTINLRFSPHSKAQNQQT	1267	2.611	KTINGSGSPHSKGRSQQT	1624	2.080
KTINGSGSPHSKAQRLWT	1268	2.611	KTINGSGSPHCVAQNQQT	1625	2.080
KTINGSGSPHSKGRAQQT	1269	2.607	KTINGSGSPHSKIRPQQT	1626	2.080
KTINGSGSPHSLSCNQQT	1270	2.605	KTINGSGSPHSKAQSSKT	1627	2.078
KTINGLVSPHCKAQNQQT	1271	2.605	KTINGSGSPHSKRPFQQT	1628	2.076
KTINGSSSPHLWAQNQQT	1272	2.605	KTINGSSSPHCLAQNQQT	1629	2.074
KTINGSGSPHSKAHRLQT	1273	2.603	KTINGTRSPHAKAQNQQT	1630	2.071
KTINGSGSPHPYAQNQQT	1274	2.598	KTINGSGSPHLLFQNQQT	1631	2.069
KTINGSGSPHSTRPNQQT	1275	2.598	KTINGRRSPHTKAQNQQT	1632	2.069
KTINGRSSPHPKAQNQQT	1276	2.596	KTINGSGSPHSKASKQQT	1633	2.069
KTINGSGSPHSKAQSWRT	1277	2.596	KTINGSGSPHSKAQLGRT	1634	2.069
KTINGQRSPHVKAQNQQT	1278	2.596	KTINGSGSPHSVFLNQQT	1635	2.069
KTINGSGSPHSKAQFVRT	1279	2.596	KTINGSGSPHSKSARQQT	1636	2.067
KTINGSGSPHSKCLNQQT	1280	2.594	KTINGSGSPHSKLRLQQT	1637	2.065
KTINGSGSPHSSLCNQQT	1281	2.592	KTRKSSGSPHSKAQNQQT	1638	2.065
KTINGQRSPHSKAQNQQT	1282	2.590	KTINGFRSPHLKAQNQQT	1639	2.063
KTINGSGSPHSLSWNQQT	1283	2.588	KTINGSGSPHSKRSIQQT	1640	2.063
KTINGSGSPHSSRKNQQT	1284	2.585	KTINGSGSPHSKGRIQQT	1641	2.061
KTINGSGSPHSKRTLQQT	1285	2.583	KTINGSRSPHRPAQNQQT	1642	2.061
KTINGSLSPHCLAQNQQT	1286	2.577	KTINGSGSPHSKLRPQQT	1643	2.060

KTINGSGSPHSKAQSSRT	1287	2.575	KTINGSGSPHMYAQNQQT	1644	2.060
KTINGSGSPHLKRQNQQT	1288	2.564	KTINGRTSPHAKAQNQQT	1645	2.060
KTINGSGSPHSKARMGQT	1289	2.564	KTINGSGSPHSKAGRGQT	1646	2.058
KTINGSGSPHSKAQVKLT	1290	2.564	KTINGSGSPHSKLMRQQT	1647	2.056
KTINGSGSPHSKLPRQQT	1291	2.562	KTINGSGSPHSKANKSQT	1648	2.056
KTINGSGSPHSKLCLQQT	1292	2.562	KTINGSGSPHSKAVRQQT	1649	2.052
KTINGSGSPHSPLWNQQT	1293	2.562	KTINGSGSPHSKCLSQQT	1650	2.052
KTINGSVSPHSWAQNQQT	1294	2.562	KTINGSGSPHSKAQWVLT	1651	2.052
KTIRSKGSPHSKAQNQQT	1295	2.559	KTINGSGSPHSKAQFWVT	1652	2.050
KTINGSRSPHSWAQNQQT	1296	2.559	KTINGSGSPHSKALCRQT	1653	2.048
KTINGSGSPHSKILRQQT	1297	2.557	KEVMGSGSPHSKAQNQQT	1654	2.047
KTINGRQSPHVKAQNQQT	1298	2.557	KTINGSGSPHSKNTRQQT	1655	2.047
KTINGSGSPHSKAQSIKT	1299	2.555	KTINGSGSPHTWTQNQQT	1656	2.045
KTINGSGSPHSKAQASKT	1300	2.546	KTINGSTSPHWSAQNQQT	1657	2.043
KTINGSGSPHSRLFNQQT	1301	2.542	KTINGNVSPHRKAQNQQT	1658	2.043
KTINGSGSPHIYLQNQQT	1302	2.542	KTINGSTSPHLFAQNQQT	1659	2.041
KTINGSGSPHSRVRNQQT	1303	2.540	KTINGSGSPHSKAQNYRA	1660	2.039
KTINGSGSPHSKAVRAQT	1304	2.538	KTINGSGSPHSKARGQQT	1661	2.039
KTINGSGSPHSKPARQQT	1305	2.538	KTINGSGSPHSKAQNRIR	1662	2.039
KTINGSGSPHSRYSNQQT	1306	2.536	KTINGSGSPHSKWTLQQT	1663	2.039
KTINGSRSPHRSAQNQQT	1307	2.536	KTINGSGSPHSKAQMKCT	1664	2.039
KTINGSLSPHIYAQNQQT	1308	2.536	KTINGSGSPHSLWQNQQT	1665	2.037
KTINGSGSPHSKPVRQQT	1309	2.529	KTINGSGSPHSKAQLSKT	1666	2.035
KTINGMRSPHGKAQNQQT	1310	2.527	KTINLIWSPHSKAQNQQT	1667	2.035
KTINGSGSPHSKARITQT	1311	2.525	KTINGSGSPHSKRVLQQT	1668	2.035
KTINGSGSPHSWSLNQQT	1312	2.523	KTINGSGSPHSKVRVQQT	1669	2.034
KTINTSRSPHSKAQNQQT	1313	2.520	KTINSRFSPHSKAQNQQT	1670	2.032
KTINGSGSPHSKAFTRQT	1314	2.518	KRSKGSGSPHSKAQNQQT	1671	2.030
KTINGSGSPHSKAVRNQT	1315	2.516	KTINGSGSPHRRLQNQQT	1672	2.030
KTINGSGSPHSKAQTNRT	1316	2.510	KTINGSGSPHSCAQNQQT	1673	2.030
KTINGSGSPHSKANRMQT	1317	2.508	KTINGPLSPHRKAQNQQT	1674	2.028
KTINGSGSPHSKAQLVLT	1318	2.508	KTINGSVSPHLYAQNQQT	1675	2.028
KTINGSGSPHSKATRQQT	1319	2.505	KTINGRISPHLKAQNQQT	1676	2.028
KTINGSGSPHSKARGTQT	1320	2.505	KTINGSHSPHRKAQNQQT	1677	2.028
KTINGSGSPHSKAQWSVT	1321	2.501	KTINGSGSPHSKAQVSIT	1678	2.028
KTINGSGSPHSKAWLIQT	1322	2.499	KTINGSMSPHRRAQNQQT	1679	2.028
KTINGSGSPHSKAFRPQT	1323	2.499	KTINGRQSPHAKAQNQQT	1680	2.026
KTINGSGSPHRRSQNQQT	1324	2.497	KTINGSGSPHSKAVWRQT	1681	2.026
KTINGSGSPHSKGIRQQT	1325	2.497	KQPLGSGSPHSKAQNQQT	1682	2.024
KTINGSGSPHCTLQNQQT	1326	2.497	KTINGSGSPHSKAQNVKL	1683	2.024
KPLPGSGSPHSKAQNQQT	1327	2.495	KTINGSGSPHSKRGTQQT	1684	2.022
KTINGSGSPHLVCQNQQT	1328	2.493	KTINGSVSPHYVAQNQQT	1685	2.022
KTINGSGSPHSKARGYQT	1329	2.492	KTINGSGSPHSKNLRQQT	1686	2.022
KTINGRISPHGKAQNQQT	1330	2.492	KTINGSGSPHSKAQAFRT	1687	2.022
KTINGSSSPHWLAQNQQT	1331	2.490	KTINGSGSPHSKCSNQQT	1688	2.020
KTINGSGSPHSKARMAQT	1332	2.488	KELVGSGSPHSKAQNQQT	1689	2.019
KPLDGSGSPHSKAQNQQT	1333	2.488	KTINGSGSPHSLVFNQQT	1690	2.019
KPLRGSGSPHSKAQNQQT	1334	2.486	KTINGSGSPHSKAQATRT	1691	2.019
KTINGSGSPHSKAQNAKL	1335	2.486	KTINGTSSPHCKAQNQQT	1692	2.017
KTINGSGSPHSKLSKQQT	1336	2.482	KTINGSGSPHSKALWRQT	1693	2.015
KTINGSGSPHSKARNGQT	1337	2.482	KTINGSGSPHSKAQFSVT	1694	2.015
KTINGSGSPHSKAQRRQT	1338	2.479	KTINGSGSPHSKLYMQQT	1695	2.015
KTINGSGSPHSKWPGQQT	1339	2.477	KTINGSLSPHYMAQNQQT	1696	2.015

KTINGSGSPHAFLQNQQT	1340	2.475	KTINGSGSPHSKAWLMQT	1697	2.015
KTINGILSPHRKAQNQQT	1341	2.475	KTINGSGSPHSKSLKQQT	1698	2.013
KTINGSGSPHSWGSNQQT	1342	2.473	KTINGSGSPHSKAQNTRR	1699	2.013
KTINGSGSPHSSCLNQQT	1343	2.471	KTINGSGSPHYLLQNQQT	1700	2.011
KTINGSGSPHSKAQSVKT	1344	2.464	KTINGSGSPHTWSQNQQT	1701	2.011
KTINGSGSPHSLRYNQQT	1345	2.462	KTINGSGSPHSKTRMQQT	1702	2.011
KTINGSGSPHSKARKLQT	1346	2.458	KTINTRPSPHSKAQNQQT	1703	2.011
KHRSGSGSPHSKAQNQQT	1347	2.456	KTINGSGSPHSKAQILVT	1704	2.009
KTINGSGSPHSKWSLQQT	1348	2.453	KTINGSGSPHSKAQNAKS	1705	2.009
KTINGSGSPHSKAQTMRT	1349	2.453	KTINGSGSPHSRTYNQQT	1706	2.009
KTINGSGSPHSKTIRQQT	1350	2.453	KTINGSGSPHSKKGGQQT	1707	2.009
KTINGKLSPHMKAQNQQT	1351	2.449	KTINGYSSPHRKAQNQQT	1708	2.007
KTINGSGSPHSKARPFQT	1352	2.443	KTINGSGSPHWVSQNQQT	1709	2.007
KTINGSGSPHSKPRVQQT	1353	2.441	KTINGSGSPHSKARLAQT	1710	2.007
KTINGSGSPHSKAQVVLT	1354	2.438	KTINGMCSPHSKAQNQQT	1711	2.006
KTRRSSGSPHSKAQNQQT	1355	2.438	KTINGSGSPHSKSNKQQT	1712	2.006
KTINGSGSPHSKPSRQQT	1356	2.438	KTINGSGSPHSKAQFVLT	1713	2.006
KTINGSGSPHSVYRNQQT	1357	2.432	KTINGSISPHFVAQNQQT	1714	2.006
KTINGSGSPHSKTCSQQT	1358	2.430	KTINGSGSPHRRMQNQQT	1715	2.004
KTINGSPSPHRKAQNQQT	1359	2.430	KTINGSGSPHSKAWILQT	1716	2.004
KTINGRSSPHFKAQNQQT	1360	2.428	KTINGSGSPHSKAQGVKT	1717	2.002
KTINGSGSPHSKAQMVRT	1361	2.426	KTINGSGSPHSKAQFSLT	1718	2.000
KTINGSRSPHCSAQNQQT	1362	2.426	KTINMLRSPHSKAQNQQT	1719	2.000
KTINGSCSPHLRAQNQQT	1363	2.423	KTINGSGSPHSKAQLGKT	1720	2.000
KTINGSGSPHSKAQCLFT	1364	2.421	KTINGSGSPHSMYLNQQT	1721	2.000

[0472] As shown in **Table 19**, approximately 72 TTM-002 matured capsid variants demonstrated at least a 2-fold increase in expression relative to the non-matured TTM-002 control, with a few variants demonstrating greater than a three- to five-fold enrichment relative to the non-matured TTM-002 control. Also, across the peptides comprised within the TTM-002 matured capsid variants with the greatest fold-enrichment relative to the non-matured TTM-002 capsid in the brain, it was observed that the modifications in the variant sequences appeared in the region N-terminal to the SPH motif present within the capsid variant. This indicates that modifications that appeared to improve TTM-002 capsid tropism in the CNS of mice were skewed to the N-terminal portion of the peptide insertion in loop IV of the sequence. Additionally, a number of these N-terminal modifications that were incorporated into the matured TTM-002 capsid variants were negatively charged amino acids (particularly glutamic acid (E)).

Table 19. NGS fold-enrichment of TTM-002 matured AAV capsid variants in the brain of CD-1 Outbred mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-002	Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-002
KTINGHDSPHVTDQNQQT	1722	5.20	KAEVGHDSPHKSGQNQQT	1760	2.15
KTINGHDSPHKRGQHRQT	1723	4.20	KMDAGHDSPHKSGQNQQT	1761	2.15
KMPEGHDSPHKSGQNQQT	1724	3.18	KVEWGHDSPHKSGQNQQT	1762	2.15
KMEGGHDSPHKSGQNQQT	1725	2.72	KAEQGHDSPHKSGQNQQT	1763	2.14
KMEYGHDSPHKSGQNQQT	1726	2.71	KLEWGHDSPHKSGQNQQT	1764	2.14

KAEWGHDSPHKSGQNQQT	1727	2.69	KTINGHPSPHYLGQNQQT	1765	2.14
KCEWGHDSPHKSGQNQQT	1728	2.68	KTINGHLSPHYYGQNQQT	1766	2.13
KANNGQDSPHKSGQNQQT	1729	2.67	KMELGHDSPHKSGQNQQT	1767	2.13
KTINGHDSPHLCGQNQQT	1730	2.59	KMETGHDSPHKSGQNQQT	1768	2.12
KIPEGHDSPHKSGQNQQT	1731	2.54	KMEAGHDSPHKSGQNQQT	1769	2.12
KADMGHDSPHKSGQNQQT	1732	2.48	KTINGHDSPHLLWQNQQT	1770	2.12
KTINGHLSPHYFGQNQQT	1733	2.41	KTINRQRSPHKSGQNQQT	1771	2.11
KIEYGHDSPHKSGQNQQT	6409	2.41	KIESGHDSPHKSGQNQQT	1772	2.11
KADYGHDSPHKSGQNQQT	1735	2.40	KTAKDHDSPHKSGQNQQT	1773	2.11
KIETGHDSPHKSGQNQQT	1736	2.38	KMEVGHDSPHKSGQNQQT	1774	2.11
KTINGHDSPHTNGQKQQT	1737	2.38	KCEIGHDSPHKSGQNQQT	1775	2.10
KMEWGHDSPHKSGQNQQT	6410	2.38	KATNGHDSPHKSGLNQQT	1776	2.10
KTINGHDSPHWLLQNQQT	1739	2.37	KMDGGHDSPHKSGQNQQT	1777	2.09
KCEYGHDSPHKSGQNQQT	6411	2.36	KQEVGHDSPHKSGQNQQT	1778	2.07
KRINGHDSPHKSGQKQQN	1741	2.34	KADQGHDSPHKSGQNQQT	1779	2.07
KMEIGHDSPHKSGQNQQT	6412	2.34	KTINGHESPHKSAQNHQT	1780	2.07
KLEYGHDSPHKSGQNQQT	6413	2.33	KTINGHDSPHKSAQNQWT	1781	2.07
KADWGHDSPHKSGQNQQT	1744	2.32	KNMNGHDSPHKSGQNTHS	1782	2.06
KIEIGHDSPHKSGQNQQT	1745	2.30	KTPWEHDSPHKSGQNQQT	1783	2.05
KTIKDNDSPHKSGQNQQT	1746	2.27	KTINGHSSPHYFGQNQQT	1784	2.05
KDIMGHDSPHKSGQNQQT	1747	2.23	KIEMGHDSPHKSGQNQQT	1785	2.05
KFEQGHDSPHKSGQNQQT	1748	2.22	KTANEHDSPHKSGQNQQT	1786	2.05
KMEFGHDSPHKSGQNQQT	1749	2.21	KTINGHDSPHKSGRRRQT	1787	2.04
KCDQGHDSPHKSGQNQQT	6414	2.21	KISNGHDSPHKSAQNQQT	1788	2.03
KLPEGHDSPHKSGQNQQT	1751	2.19	KTGNGHDSPHKSGQYQQT	1789	2.03
KIENGHDSPHKSGQNQQT	1752	2.19	KTINGHYSPHLFGQNQQT	1790	2.02
KMESGHDSPHKSGQNQQT	1753	2.18	KTINGNYSPHKIGQNQQT	1791	2.02
KAEIGHDSPHKSGQNQQT	1754	2.17	KTINGHDSPHKSRQNDQT	1792	2.01
KVEYGHDSPHKSGQNQQT	1755	2.17	KQQQGHDSPHKSGQNQQT	1793	2.01
KIINGHDSPHKSGLTQQT	1756	2.17	KTPQDHDSPHKSGQNQQT	1794	2.00
KTSNGDDSPHKSGRNQQT	1757	2.17	KHDWGHDSPHKSGQNQQT	1795	2.00
KIEVGHDSPHKSGQNQQT	1758	2.16	KIEGGHDSPHKSGQNQQT	1796	2.00
KMEMGHDSPHKSGQNQQT	1759	2.16			

[0473] These data demonstrate that following two maturation approaches, matured TTM-001 and TTM-002 capsid variants with loop IV modifications were generated with significantly enhanced CNS tropism in mice compared to the corresponding non-matured TTM-001 and TTM-002 capsid variants, which already exhibited a significant fold enrichment over AAV9 in the mouse brain.

Example 4. Maturation of TTM-001 and TTM-002 Capsid in NHPs

[0474] This Example describes maturation of the AAV9 capsid variants, TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941 (encoded by SEQ ID NO: 942)) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2 (encoded by SEQ ID NO: 3)) in NHPs to further enhance their transduction and biodistribution in the central nervous system as well as other tissues, and evolve the AAV capsid variants to provide further cross-species compatibility. Two approaches were used to mature the TTM-001 and TTM-002 capsid sequences in order to randomize and mutate within and around the peptide insert comprised within loop IV of the capsid variant. As many of the AAV capsid variants that demonstrated the greatest

fold-enrichment in the NHP brain relative wild-type AAV9 comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138) (see **Example 1**), the SPH motif was not mutated in either approach to mature the TTM-001 and TTM-002 capsid variants. In the first maturation approach, sets of three contiguous amino acids were randomized across the mutagenesis region in the TTM-001 and TTM-002 sequences, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 981 and 982. In the second maturation approach, mutagenic primers were used to introduce point mutations at a low frequency, scattered across the mutagenesis region in the TTM-001 and TTM-002 sequences ranging from position 449 to position 466, numbered according to SEQ ID NO: 981 and 982. AAV capsid variants arising from each maturation approach for TTM-001 and TTM-002 were pooled together, for subsequent testing and characterization in NHPs.

[0475] The library of pooled matured AAV capsid variants generated using the first maturation approach and the second maturation approach for the TTM-001 and TTM-002 AAV capsid variants were injected into two NHPs. After a period in life, the brains, heart, liver, muscle, and DRG of the NHPs were isolated and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to an AAV9 control, and the peptides comprised within the variants were identified.

[0476] Following the RNA recovery and NGS analysis from the second maturation approach, approximately 680,000 capsid variants were identified. The 680,000 matured capsid variants were then filtered based on samples with a raw virus count greater than 10 and a coefficient of variance (CV) of less than 1, which was calculated for each peptide across the brain samples taken from the two NHPs. Those that had a CV value <1 were identified, as these were the peptides that were reliably detected in the majority of samples isolated from the brains of the two NHPs. Using this filtering criteria, this led to approximately 64,000 matured capsid variants.

[0477] **Table 20** provides the peptide sequences of the matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the brain samples isolated, and that also demonstrated a 50-fold or greater fold-increase in expression in the brain relative to the AAV9 control in both mice and NHPs. The matured variants in **Table 20**, were also those variants that had a fold-change in expression that was less than 2 relative to the AAV9 control in the liver and the DRG. Applying these criteria, approximately 350 matured capsid variants were identified that demonstrated high transduction in the brain in NHPs and mice, cross-species compatibility in mice and NHPs, and were de-targeted in the liver and DRG, relative to the AAV9 control. Several variants as shown in **Table 20**, led to greater than 100-fold increase in expression relative to AAV9 in the NHP and/or mouse brain, with one variant resulting in a greater than 200-fold increase in expression relative to AAV9 in both species.

[0478] Fold-change in expression for the TTM-001 and TTM-002 matured variants in **Table 20** that showed increased expression in the brain of the NHPs and mice, were also calculated for the DRG, muscle, liver (RNA and DNA), and heart of the NHPs following each maturation approach. As shown in **Table 20**, many variants were de-targeted in the peripheral tissues with a lower fold-change in expression relative to the AAV9 control, demonstrating CNS-specific tropism and a preferential transduction of the brain and CNS. Some variants demonstrated increased expression to AAV9 in multiple tissues, including the brain and peripheral tissues, demonstrating pan-tropism.

Table 20. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the brain of NHPs and mice

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTIIGSGSPHSKAQNRHT	3239	217.176	0.000	0.000	0.000	0.000	0.000	210.515
KTFPGSGSPHSKVQNQQT	3240	199.720	0.000	0.000	0.000	0.000	0.967	97.703
KTEKMSGSPHSKAQNQQT	3241	169.461	0.523	0.000	0.000	0.000	0.158	109.161
KEINGRGSPHSKAQNQQT	3527	134.390	0.239	0.000	0.000	0.000	0.232	52.311
KTVNRNGSPHSKAQNQQT	3528	133.016	0.000	0.416	0.000	0.000	0.000	85.361
KTVNGSGSPHSKARDQQT	3242	124.789	0.123	0.039	0.312	0.569	0.454	132.137
KTFNGSGSPHSKAPNLQT	3243	121.436	0.000	0.167	0.000	0.000	0.015	168.920
KTEKTSGSPHSKAQNQQT	3244	120.337	0.000	0.355	0.000	0.000	0.119	101.467
KTINGSGSPHSKAHVRQT	3245	119.798	0.000	0.000	0.262	0.694	1.039	165.590
KTVNGSGSPHSKAPNQHT	3246	117.207	0.000	0.109	0.000	0.000	0.074	51.008
KTEKISGSPHSKAQNQQT	3247	116.603	0.000	0.000	0.000	0.000	0.426	102.978
KTINGPGSPHSKAHNQQT	3529	115.742	0.146	0.000	0.235	0.000	0.513	52.508
KTVNGSGSPHSKTQSQQT	3248	115.086	0.000	0.726	0.000	0.000	0.340	63.248
TTINGSGSPHSKAQNQQT	3249	114.856	1.340	14.856	0.827	1.281	0.957	72.058
KSINESGSPHSKAQNQQI	3250	113.833	0.000	0.000	0.000	0.000	0.000	67.649
KTERTSGSPHSKAQNQQT	3251	112.957	0.000	0.009	0.000	1.128	0.207	117.374
KTINGSGSPHSKAQPAKT	3252	111.472	0.331	0.000	1.089	0.044	1.796	215.275
KTEKSSGSPHSKAQNQQT	3253	107.470	0.000	0.016	0.014	0.977	0.179	100.177
KTSYGNGSPHSKAQNQQT	3530	105.937	0.000	0.000	0.000	0.000	0.114	105.894
KTEKGSGSPHSKAQNQQT	3254	105.614	0.053	0.031	0.000	0.586	0.169	84.653
KTINGSGSPHSKSQTQQN	3255	104.474	0.000	0.131	0.000	0.084	0.038	54.021
KTERISGSPHSKAQNQQT	3256	103.692	0.000	0.000	0.000	0.062	0.370	89.637
KTERASGSPHSKAQNQQT	3257	103.669	0.000	0.000	0.000	0.127	0.070	115.550
KELHGSGSPHSKAQNQQT	3258	102.680	0.000	0.000	0.000	1.634	0.592	96.554
KAINGSGSPHSKAQNLAT	3259	101.954	0.000	10.954	8.655	0.298	0.239	116.685
KTVNGSGSPHSKSQNQLT	3260	101.327	0.000	0.035	0.000	0.000	0.025	80.716
KTERNSGSPHSKAQNQQT	3261	99.892	0.000	0.000	0.000	0.000	0.107	87.392
KSVNGNGSPHSKAQNQQT	3531	99.385	0.000	1.329	0.000	0.359	0.079	51.016
KTFNGSGSPHSKAQGQQT	3262	99.253	0.000	0.208	0.000	0.128	0.099	81.459
KTINGSGSPHGWVQNQQT	3532	97.122	0.000	0.000	0.000	1.240	1.975	290.720
KTERVSGSPHSKAQNQQT	3263	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KTINGSGSPHSKALNRQS	3264	96.843	0.136	0.532	0.000	0.042	0.178	55.945
KTERLSGSPHSKAQNQQT	3265	95.857	0.000	0.004	0.005	0.126	0.260	102.372
KTDNGSGSPHSKAHNQQT	3266	95.164	0.000	0.000	0.000	0.000	0.027	55.313
KTFHGSGSPHSKTQNQQT	3267	94.714	0.000	0.210	0.120	0.000	0.000	51.119
KTINGGGSPHSKAQTQQI	3533	92.345	0.000	0.000	0.000	0.000	0.023	54.199
KTSNGSGSPHSKAQNPPT	3268	91.528	0.000	0.000	0.000	0.000	0.039	51.541
ETINGSGSPHSKAQNLQT	3269	90.969	0.221	1.023	0.197	0.179	0.813	107.216
KTVHGNGSPHSKAQNQQT	3534	90.073	0.000	0.000	0.000	0.000	0.304	97.003
NTINGSGSPHSKAQNQQT	3270	90.017	1.712	1.261	1.171	0.923	0.540	55.179

KTINGGGSPHSKAQNQQC	3535	89.301	0.219	0.000	0.000	0.287	0.319	53.840
KTENMSGSPHSKAQNQQT	3271	89.247	0.000	0.000	0.000	0.000	0.260	130.568
KTENVSGSPHSKAQNQQT	3272	88.506	0.000	0.000	0.000	0.964	0.112	108.591
KTSSGSGSPHSKAQYQQT	3273	87.304	0.000	0.000	0.000	0.000	0.299	58.143
KTIDGGGSPHSKAQNKQT	3536	85.019	0.000	0.000	0.000	0.000	0.477	55.517
KTEKVSGSPHSKAQNQQT	3274	84.558	0.000	0.022	0.000	0.873	0.424	112.185
KAINGSGSPHSKAQDQET	3275	84.080	0.000	0.000	0.000	0.194	0.027	87.637
KTCNKSGSPHSKAQNQQT	3276	83.992	0.000	0.000	0.165	0.283	0.000	119.496
KTINGGGSPHSKAQNQLI	3537	83.881	0.000	0.000	0.000	0.046	0.387	78.383
KNINGGGSPHSKAQNQQT	3538	83.083	0.000	0.042	0.000	0.000	0.000	75.913
KTEHLSGSPHSKAQNQQT	3277	83.080	0.000	0.000	0.012	0.021	0.189	69.494
KAEMGSGSPHSKAQNQQT	3278	83.049	0.000	0.020	0.000	0.768	0.112	135.019
KATNGSGSPHSKAQNHQT	3279	82.627	0.000	0.176	0.000	0.155	0.057	66.207
KAIKGSGSPHSKAQDQQT	3280	82.258	0.000	0.000	0.000	0.108	0.000	85.178
KTINGGGSPHSKSQNQLT	3539	82.231	0.000	0.070	0.000	0.000	0.498	126.986
KTVNGNGSPHSKAQNKQT	3540	81.481	0.000	0.000	0.000	0.000	0.122	69.455
KTINGSGSPHSKGHWQQT	3281	81.434	0.000	0.000	0.000	0.000	1.011	65.252
KTDKTSGSPHSKAQNQQT	3282	81.430	0.000	0.000	0.000	1.362	0.291	169.515
KTFKGSGSPHSKAPNQQT	3283	80.890	0.000	0.000	0.000	0.000	0.017	71.144
KTVNGSGSPHSKAQNQLI	3284	80.509	0.000	0.000	0.000	0.000	0.166	71.156
KTINGSGSPHSKRPEQQT	3285	80.418	0.000	0.013	0.000	0.149	0.361	50.319
KTINGSGSPHSKAQRTMT	3286	80.388	0.000	0.022	0.170	1.812	1.025	100.248
KTEKASGSPHSKAQNQQT	3287	80.285	0.000	0.041	0.000	0.000	0.261	90.390
KSDQGSGSPHSKAQNQQT	3288	80.076	0.000	0.000	0.000	0.993	0.124	151.911
KTEITSGSPHSKAQNQQT	3289	79.620	0.000	0.163	0.000	0.332	0.074	76.686
KTDKSSGSPHSKAQNQQT	3290	79.470	0.055	0.012	0.000	1.437	0.367	141.351
KTIDGSGSPHSKAQNQQH	3291	79.090	0.000	0.000	0.000	0.136	0.049	57.914
KTVNGNGSPHSKAQNQHT	3541	78.849	0.000	0.000	0.000	0.000	0.045	54.086
KNTNGSGSPHSKAQNQQT	3292	78.445	0.000	0.000	0.000	0.571	0.177	89.719
KTETHSGSPHSKAQNQQT	3293	77.974	0.000	0.067	0.000	0.000	0.512	57.287
KTINGGGSPHSKALNQQN	3542	77.822	0.000	0.131	0.000	0.000	0.274	69.884
KTINGSGSPHSKALHQHT	3294	77.502	0.000	0.052	0.041	0.000	0.188	68.196
KTINGTGSPHSKAQNHQI	3543	77.089	0.171	0.000	0.000	0.000	0.166	54.281
KTINGSGSPHSKAQHRIT	3295	76.849	0.105	0.499	0.170	1.424	0.214	127.000
KTINGSGSPHSKAQYIHT	3296	76.170	0.000	0.014	0.033	1.523	0.168	59.649
KTENISGSPHSKAQNQQT	3297	76.072	0.000	0.000	0.000	0.115	0.132	83.118
KTIIGGGSPHSKAHNQQT	3544	75.872	0.000	0.050	0.000	0.000	0.235	65.492
KTINGSGSPHSKAQKFET	3298	75.788	0.000	0.000	0.028	0.108	0.093	65.588
KTSNESGSPHSKAQNHQT	3299	75.720	0.000	0.000	0.000	0.169	0.217	70.590
KTINGSGSPHSKAQFPST	3300	75.677	0.000	0.004	0.000	0.849	0.127	119.712
KTERPSGSPHSKAQNQQT	3301	75.669	0.000	0.029	0.000	0.000	0.156	73.894
KTINGNGSPHSKAQNPLT	3545	75.269	0.000	0.000	0.000	0.366	0.000	53.583
KSIKGNGSPHSKAQNQQT	3546	75.196	0.000	0.000	0.000	0.000	0.000	90.251
KTERMSGSPHSKAQNQQT	3302	74.910	0.000	0.000	0.000	0.100	0.151	122.812
KTERSSGSPHSKAQNQQT	3303	74.853	0.000	0.071	0.000	1.036	0.056	125.538
KTELHSGSPHSKAQNQQT	3304	74.620	0.000	0.000	0.000	0.021	0.089	53.124
KTELTSGSPHSKAQNQQT	3305	74.548	0.000	0.000	0.000	0.537	0.421	100.311
KTINGSGSPHSKAHNQQR	3306	74.272	0.562	0.486	0.047	0.956	0.057	107.301
KTINGGGSPHSKAQSQQI	3547	74.264	0.000	0.000	0.000	0.000	0.235	67.651
KTINGSGSPHSKAQAIKT	3307	74.261	0.255	0.000	0.000	0.186	0.132	73.560
KTENTSGSPHSKAQNQQT	3308	74.061	0.000	0.000	0.218	0.233	0.730	96.249
KTIDGSGSPHSKGQNRQT	3309	73.930	0.000	0.000	0.000	0.106	0.091	63.626
KNINGSGSPHSKAQSQQT	3310	73.757	0.000	0.000	0.000	0.000	0.041	57.432
KTINGSVSPHGKAQNQLT	3548	73.525	0.000	0.061	0.067	0.000	0.053	51.358
KTSNASGSPHSKAQNQLT	3311	73.501	0.000	0.000	0.297	0.000	0.313	150.401
KTEARSGSPHSKAQNQQT	3312	73.349	0.000	0.000	0.000	0.695	0.118	62.903
KTEKNSGSPHSKAQNQQT	3313	73.347	0.000	0.000	0.044	0.159	0.021	74.393
KTANGSGSPHSKAQYQQT	3314	73.038	0.000	0.000	0.000	0.153	0.160	139.451

KTVNGSGSPHSKAQYQHT	3315	72.847	0.000	0.000	0.000	0.000	0.130	54.158
KTINGSGSPHTKAQNPQS	3316	72.594	0.000	0.000	0.000	0.000	0.130	62.508
KTINGSGSPHSKGQNPPT	3317	72.339	0.000	0.206	0.000	0.000	0.041	134.808
KTIIGSGSPHSKAQHQLT	3318	72.291	0.000	0.000	0.000	0.000	0.000	100.144
KTINGSGSPHSKAQSPPT	3319	71.632	0.069	0.047	0.274	0.179	0.425	97.111
NTIYGSGSPHSKAQNQQT	3320	71.267	1.739	0.000	273.69	0.000	0.209	59.707
KTINGSGSPHSKAQAKLT	3321	71.154	0.000	0.273	0.017	1.591	0.777	130.132
KTDKNSGSPHSKAQNQQT	3322	70.964	0.000	0.000	0.000	0.070	0.123	62.932
KTINGSGSPHSKTKSQQT	3323	70.891	0.000	0.568	0.045	0.418	0.496	83.923
KTINGSGSPHSKAQDRPT	3324	70.831	0.132	0.006	0.000	0.039	0.379	66.800
KTINGIGSPHSKAQNLGT	3549	70.543	0.000	0.071	0.000	0.000	0.135	104.769
KTINGSGSPHSKAQSQQL	3325	70.539	0.000	0.000	0.000	0.000	0.041	51.126
KTENLSGSPHSKAQNQQT	3326	70.303	0.070	0.000	0.000	0.395	0.470	107.385
KTINGSGSPHSKAQAFHT	3327	70.159	0.033	0.000	0.058	0.762	0.119	86.268
KTINGSGSPHSKAQKQQD	3328	70.116	0.000	0.024	0.000	0.064	0.083	110.196
KTFSGSGSPHSKAQNLQT	3329	70.035	0.000	0.327	0.303	0.000	0.228	70.917
KAINGSGSPHSKAQNAQT	3330	69.651	0.000	0.000	0.000	0.023	0.142	72.160
KTESWSGSPHSKAQNQQT	3331	69.144	0.000	0.000	0.000	0.000	0.019	67.699
KTTNGSGSPHSKAHNQLT	3332	69.062	0.000	0.000	0.000	0.708	0.000	65.505
KTVNGNGSPHSKAQNHQT	3550	68.889	0.000	0.000	0.000	0.000	0.030	52.482
KTEDKSGSPHSKAQNQQT	3333	68.813	0.000	0.000	0.000	0.000	0.000	70.071
KTESASGSPHSKAQNQQT	3334	68.651	0.000	0.000	0.000	0.274	0.084	80.500
KTNNGSGSPHSKAQNQQY	3335	68.530	0.000	0.040	0.000	0.000	0.059	82.656
KTSNGGGSPHSKAQNLQT	3551	68.311	0.000	0.052	0.000	0.000	0.000	124.871
KTDKMSGSPHSKAQNQQT	3336	68.167	0.000	0.000	0.000	0.017	0.205	88.234
KEVHGSGSPHSKAQNQQT	3337	67.901	0.000	0.000	0.000	0.727	0.000	100.111
KTINGSGSPHSKAQKLNT	3338	67.782	0.073	0.092	0.000	1.232	0.201	68.637
KTINGGGSPHSKSQNQHT	3552	67.773	0.000	0.057	0.000	0.000	0.220	100.748
KTVNGGGSPHSKAQSQQT	3553	67.634	0.000	0.055	0.000	0.000	0.210	160.711
KTTNGSGSPHSKAQYQHT	3339	67.325	0.000	0.000	0.000	1.378	0.080	83.337
KTISGSGSPHSKAQYQHT	3340	66.739	0.000	0.000	0.000	0.000	0.191	59.822
KTESTSGSPHSKAQNQQT	3341	66.649	0.000	0.009	0.000	1.688	0.176	95.861
KTINGSGSPHSKSQNVQT	3342	66.627	0.000	0.190	0.000	0.202	0.188	56.672
KSINGSGSPHSKAQAQQT	3343	66.464	0.000	0.711	0.000	0.148	0.111	78.451
KTVNGSGSPHSKAQNLQA	3344	66.379	0.000	0.000	0.000	0.000	0.132	50.934
KTVRDSGSPHSKAQNQQT	3345	66.056	0.000	0.025	0.000	0.129	0.461	142.600
KTFNASGSPHSKAPNQQT	3346	65.392	0.208	0.000	0.000	0.215	0.156	66.275
KTDRMSGSPHSKAQNQQT	3347	65.143	0.000	0.000	0.000	0.332	0.103	104.890
KTINGSGSPHSKAQTPPT	3348	64.657	0.010	0.015	0.014	0.200	0.207	54.179
ETIKGSGSPHSKAQNQQT	3349	64.609	0.000	0.000	0.144	0.000	0.024	67.201
KNHIGSGSPHSKAQNQQT	3350	64.535	0.000	0.000	0.000	1.253	0.187	70.356
KTINGSGSPHSKAQYQHA	3351	64.435	0.000	0.000	0.024	0.993	0.097	57.278
KTIPIDGSPHSKAQNQQT	3554	64.421	0.000	0.047	0.000	0.234	0.936	76.826
KTINGSGSPHSKAQGQQA	3352	64.128	0.000	0.185	0.000	0.063	0.195	64.116
KTFNGSGSPHNKAQNHQT	3353	64.060	0.000	0.000	0.035	0.094	0.317	67.757
KESDGSGSPHSKAQNQQT	3354	63.766	0.000	0.000	0.000	0.567	0.146	115.231
KTINGSGSPHSKAQPPAT	3355	63.510	0.048	0.030	0.031	0.126	0.302	117.453
KTINGSGSPHSKAQERPT	3356	63.460	0.000	0.011	0.000	0.810	0.173	57.506
KTIKGSGSPHSKAQDLQT	3357	63.260	0.000	0.000	0.000	0.000	0.218	58.576
KTDLKSGSPHSKAQNQQT	3358	63.152	0.000	0.000	0.012	0.285	0.377	62.687
KTINGGGSPHSKAQNPPT	3555	63.041	0.000	0.082	0.000	0.000	0.057	64.045
KTINGSGSPHSKAQAMHT	3359	62.756	0.000	0.000	0.010	0.976	0.393	84.056
KTVPNSGSPHSKAQNQQT	3360	62.540	0.000	0.000	0.011	0.202	0.161	93.793
KTVIGSGSPHSKALNQQT	3361	62.358	0.000	0.310	0.000	0.062	0.245	60.369
KTINGSGSPHSKAQHPST	3362	62.255	0.000	0.044	0.000	1.345	0.301	101.103
KTINGLGSPHSKSQNQQT	3556	62.170	0.000	0.157	0.000	0.146	0.107	64.139
KTINGTGSPHSKAQNQQM	3557	62.151	0.000	0.000	0.000	0.000	0.000	62.376
KTINGSGSPHSKAPGLQT	3363	62.043	0.007	0.000	0.005	0.651	0.210	144.610

KTINGSGSPHSKAQGIRT	3364	61.952	0.041	0.000	0.012	0.897	0.502	155.013
KTESHSGSPHSKAQNQQT	3365	61.947	0.000	0.000	0.000	1.480	0.106	52.506
KTINGSGSPHSKAQAPAT	3366	61.934	0.000	0.169	0.015	0.696	0.197	127.420
KTINGSGSPHSKSQSQQI	3367	61.870	0.000	0.000	0.000	0.200	0.175	64.027
KAEHGSGSPHSKAQNQQT	3368	61.830	0.000	0.000	0.000	0.772	0.184	116.201
KTEDRSGSPHSKAQNQQT	3369	61.756	0.000	0.000	0.000	1.004	0.408	66.887
KNCLGSGSPHSKAQNQQT	3370	61.442	0.000	0.036	0.000	1.849	0.026	82.488
KTDRGSGSPHSKAQNQQT	3371	61.419	0.000	0.004	0.000	0.211	0.316	74.256
KTINGSGSPHSKAQIPPT	3372	61.258	0.000	0.000	0.000	0.758	0.115	87.661
KTVKGSGSPHSKAQDQQT	3373	61.175	0.000	0.041	0.000	0.432	0.090	58.114
KNADGSGSPHSKAQNQQT	3374	60.944	0.000	0.000	0.000	1.239	0.085	104.503
KTDKVSGSPHSKAQNQQT	3375	60.935	0.000	0.015	0.000	0.765	0.128	146.657
KTITGSGSPHSKAQTQLT	3376	60.846	0.160	8.992	0.000	0.000	0.000	55.640
KTINGSGSPHSKAQAPST	3377	60.696	0.200	0.005	0.000	0.751	0.263	115.528
KNCVGSGSPHSKAQNQQT	3378	60.535	0.000	0.000	0.000	0.018	0.282	96.175
KTIRDAGSPHSKAQNQQT	3558	60.346	0.000	0.000	0.000	0.141	0.251	113.179
KTVKDSGSPHSKAQNQQT	3379	60.216	0.000	0.019	0.000	0.443	0.251	87.334
KNALGSGSPHSKAQNQQT	3380	60.014	0.000	0.003	0.000	0.682	0.213	137.222
KVINGSGSPHSKGQNQQT	3381	60.001	0.000	0.000	0.031	0.264	0.157	68.532
KTVNGGGSPHSKAQNQQS	3559	59.871	0.062	0.020	0.000	0.080	0.185	61.847
KTIQDGGSPHSKAQNQQT	3560	59.865	0.000	0.000	0.116	1.435	0.789	87.522
KTISGGGSPHSKAQNQQN	3561	59.801	0.000	0.000	0.000	0.722	0.039	87.761
KTSNASGSPHSKAHNQQT	3382	59.607	0.000	0.078	0.067	0.031	0.050	67.967
KTINGSGSPHSKAQNTYA	3383	59.603	0.000	0.000	0.000	0.425	0.346	101.715
KTINGSGSPHSKSQNQHI	3384	59.438	0.000	0.099	0.000	0.111	0.108	76.025
KTINGGGSPHSKAQDKQT	3562	59.322	0.000	0.000	0.000	0.000	0.093	50.764
KTEFVSGSPHSKAQNQQT	3385	59.306	0.000	0.000	0.000	0.196	0.276	69.788
KTVNGSGSPHSKAQNHLT	3386	59.239	0.133	0.034	0.000	0.000	0.156	70.786
KTREISGSPHSKAQNQQT	3387	59.027	0.000	0.042	0.224	0.356	0.269	51.696
KTINGSGSPHSKAQIGMT	3388	59.013	0.081	106.528	0.000	1.003	0.248	134.585
KTIDGSGSPHSKALNKQT	3389	58.992	0.000	0.267	0.000	0.000	0.056	74.626
KTIIGGGSPHSKAQNPQT	3563	58.924	0.000	0.202	0.000	0.000	0.126	53.992
KQGEGSGSPHSKAQNQQT	3390	58.752	0.000	0.000	0.000	0.000	0.151	135.300
KTINGTGSPHSKAPNQLT	3564	58.738	0.000	0.000	0.000	0.229	0.035	86.939
KTVNGSGSPHSKAQLQQT	3391	58.681	0.315	0.465	0.045	0.529	0.333	81.201
KTFNGGGSPHSKAQYQQT	3565	58.609	0.000	0.000	0.000	0.163	0.045	72.618
KSINGSGSPHSKTQSQQT	3392	58.608	0.000	3.017	0.000	0.155	0.017	71.397
KTVNGGGSPHSKAQHQQT	3566	58.602	0.729	0.000	0.000	0.000	0.043	138.544
KSEKGSGSPHSKAQNQQT	3393	58.566	0.000	0.010	0.011	1.601	0.059	158.931
KNVNGSGSPHSKAQNQQT	3394	58.481	0.000	0.000	0.000	0.917	0.166	53.379
KGGEGSGSPHSKAQNQQT	3395	58.472	0.000	0.034	0.000	0.037	0.066	91.023
KTINGSGSPHSKAQRMST	3396	58.435	0.192	0.037	0.000	1.707	0.882	53.414
KTINGSGSPHSKAQGILT	3397	58.418	0.000	0.005	0.010	0.569	0.192	102.631
KEFVGSGSPHSKAQNQQT	3398	58.374	0.000	0.046	0.000	0.088	0.326	128.675
KTIIGSGSPHSKAQDRQT	3399	58.258	1.393	0.230	0.219	0.000	0.045	53.981
KSDKGSGSPHSKAQNQQT	3400	58.248	0.000	0.000	0.000	0.076	0.166	146.566
KTEQVSGSPHSKAQNQQT	3401	58.247	0.000	0.000	0.000	0.000	0.081	88.487
KTEHVSGSPHSKAQNQQT	3402	58.228	0.000	0.024	0.000	0.433	0.141	71.410
KTINGSGSPHSKARDWQT	3403	58.216	0.000	0.005	0.000	0.800	0.259	120.704
KTENASGSPHSKAQNQQT	3404	58.187	0.000	0.038	0.000	0.371	0.129	88.439
KEVQGSGSPHSKAQNQQT	3405	58.125	0.000	0.000	0.000	0.657	0.000	168.220
KTINGSGSPHSKAQNTHD	3406	58.108	0.000	0.027	0.000	0.410	0.126	81.189
KTINGSGSPHSKAPNLQI	3407	58.022	0.000	0.044	0.000	1.548	0.243	55.714
KTINGSGSPHSKAQERST	3408	58.021	0.000	0.011	0.005	0.829	0.409	87.656
KTSNGSGSPHSKAQNYQT	3409	57.894	0.000	0.082	0.000	0.000	0.110	63.681
KTEYISGSPHSKAQNQQT	3410	57.891	0.000	0.000	0.000	0.076	0.075	57.620
KTINGSGSPHSKAQRTCT	3411	57.863	0.000	0.140	0.129	1.855	1.716	90.146
KTINGSGSPHSKAQIGHT	3412	57.769	0.024	0.000	0.000	0.281	0.154	99.262

KNCWGSGSPHSKAQNQQT	3413	57.756	0.000	0.000	0.000	0.000	0.092	59.888
KTINGSGSPHSKAQGAIT	3414	57.627	0.000	0.000	0.000	0.594	0.161	95.696
KTDVNSGSPHSKAQNQQT	3415	57.593	0.000	0.000	0.000	0.000	0.331	66.127
KSDIGSGSPHSKAQNQQT	3416	57.592	0.000	0.000	0.000	0.844	0.128	107.342
KTINGSGSPHSKAQVPPT	3417	57.316	0.000	0.012	0.000	0.257	0.200	90.220
KTINGSGSPHSKAQVQQI	3418	57.308	0.000	1.113	0.000	0.000	0.113	61.957
KTINGSGSPHSKALMRQT	3419	57.234	0.060	0.036	0.100	1.798	0.517	81.332
KTINGSGSPHSKAQYSVT	3420	57.130	0.000	0.093	0.000	1.235	0.302	60.023
KNSIGSGSPHSKAQNQQT	3421	57.101	0.000	0.052	0.000	0.083	0.074	97.381
KTINGSGSPHSKVPNLQT	3422	57.046	0.000	0.029	0.000	0.459	0.082	50.474
KAINGSGSPHSKAQSQQI	3423	56.976	0.000	0.000	0.000	0.000	0.000	57.052
KTINGSGSPHSKAQAITT	3424	56.924	0.000	0.000	0.000	1.239	0.438	75.250
KTINGSGSPHSKAQKTLT	3425	56.844	0.000	0.017	0.009	1.800	1.400	66.415
KTVNGSGSPHSKAQNQWT	3426	56.823	0.000	0.000	0.299	0.000	0.219	69.906
KTINGSGSPHSKAQLHHT	3427	56.815	0.025	0.000	0.010	0.712	0.368	58.418
KTEQTSGSPHSKAQNQQT	3428	56.683	0.000	0.045	0.000	0.792	0.430	59.360
KTINGSGSPHSKAQNIII	3429	56.630	0.000	0.062	0.123	0.099	0.056	76.742
KNSLGSGSPHSKAQNQQT	3430	56.621	0.000	0.028	0.000	0.308	0.162	101.942
KTIPMEGSPHSKAQNQQT	3567	56.560	0.000	0.000	0.000	1.824	0.371	89.951
KTINGSGSPHSKAQGHHT	3431	56.559	0.000	0.000	0.000	0.632	0.117	71.050
KTDRTSGSPHSKAQNQQT	3432	56.466	0.000	0.000	0.000	0.062	0.160	148.498
KTINGSGSPHSKAQSKVT	3433	56.373	0.000	0.050	0.014	1.021	0.390	76.115
KEVVGSGSPHSKAQNQQT	3434	56.371	0.000	0.000	0.000	0.000	0.323	116.964
KTINGSGSPHSKAQLPST	3435	56.238	0.005	4.258	0.001	1.040	0.185	84.918
KTINGSGSPHSKAIGKQT	3436	56.158	0.000	0.000	0.000	0.887	0.088	110.132
KTEPTSGSPHSKAQNQQT	3437	56.134	0.000	0.000	0.000	0.061	0.527	143.397
KTVNGGGSPHSKSQNQQT	3568	56.114	0.116	0.000	0.000	0.000	0.040	170.548
KTINGSGSPHSKAQAIHT	3438	56.047	0.000	0.000	212.32	0.887	0.890	81.908
KTINGSGSPHSKAQHGLT	3439	55.999	0.000	0.000	0.101	1.913	0.244	117.191
KSELGSGSPHSKAQNQQT	3440	55.997	0.000	0.005	0.000	0.881	0.239	120.521
KTINGSGSPHSKAQFMCT	3441	55.916	0.000	0.000	0.000	0.078	0.448	81.959
KTINVSGSPHSKAQGQQT	3442	55.870	0.000	0.191	0.000	0.592	0.040	87.211
KTINGGGSPHSKAQNQMT	3569	55.778	0.000	0.000	0.000	0.866	0.012	73.177
KTVNGSGSPHSKAQHLQT	3443	55.739	0.091	0.036	0.000	0.062	0.409	62.743
KTIRENGSPHSKAQNQQT	3570	55.605	0.000	0.000	0.016	0.131	0.257	95.931
KTINGSGSPHSKTQNHQN	3444	55.551	0.000	0.048	0.000	0.000	0.099	64.846
KTINGSGSPHSKAQPART	3445	55.513	0.000	0.000	0.328	1.294	0.991	127.301
KTVNGSGSPHSKAQSLQT	3446	55.497	0.000	0.060	0.000	0.000	0.143	69.033
KTINGSGSPHSKSQSQLT	3447	55.430	0.000	0.035	0.000	0.050	0.013	125.577
KTINGSASPHSKAHSQQT	3571	55.293	0.000	0.000	0.000	0.000	0.166	66.252
KTWQNSGSPHSKAQNQQT	3448	55.245	0.000	0.000	0.000	0.111	0.265	114.258
KTINGSGSPHSKAQDRQS	3449	55.137	1.146	0.016	0.106	0.644	0.086	55.701
KTINGSGSPHSKAQMPST	3450	54.986	1.691	0.039	0.028	0.450	0.202	114.331
KTNNGGGSPHSKAQNLQT	3572	54.963	0.000	0.000	0.000	0.000	0.089	80.506
KTINGSGSPHSKAQGSLT	3451	54.717	0.000	0.006	0.013	0.480	0.298	142.786
KTEVTSGSPHSKAQNQQT	3452	54.663	0.000	0.000	0.000	0.323	0.185	81.482
KSINGGGSPHSKAQYQQT	3573	54.612	0.000	0.000	0.000	0.105	0.010	65.952
KTVIGSGSPHSKSQNQQT	3453	54.603	0.000	0.000	0.000	0.000	0.106	69.121
KAVNVSGSPHSKAQNQQT	3454	54.586	0.000	0.000	0.000	0.000	0.023	57.835
KTVNGNGSPHSKSQNQQT	3574	54.586	0.000	0.000	0.000	0.256	0.168	95.384
KTDRNSGSPHSKAQNQQT	3455	54.495	0.000	0.000	0.000	0.823	0.241	85.823
KTINGSGSPHSKAQVPAT	3456	54.475	0.000	0.002	0.000	0.782	0.223	137.743
KGVLGSGSPHSKAQNQQT	3457	54.472	0.000	0.007	0.027	0.359	0.189	145.740
KTLNGNGSPHSKAQNLQT	3575	54.458	0.668	0.000	0.000	0.161	0.172	159.134
KAINGSGSPHSKAQDKQT	3458	54.452	0.000	0.000	0.057	0.044	0.223	56.004
KTSNGSGSPHSKAHYQQT	3459	54.414	0.000	0.251	0.000	0.249	0.204	54.162
KTINGSGSPHSKAQVPST	3460	54.366	0.000	1.001	0.000	0.202	0.139	117.223
KTINGSGSSHSKAQNQQT	3576	54.292	1.709	1.870	1.287	1.075	0.458	67.731

KTELRSGSPHSKAQNQQT	3461	54.289	0.000	0.007	0.040	0.790	0.239	57.814
KNINGSGSPHSKAQNHQT	3462	54.248	0.000	0.034	0.000	0.340	0.075	74.979
KTVNGGGSPHSKAQNHQT	3577	54.246	0.375	0.024	0.000	0.000	0.146	67.188
KTINGSGSPHSKARGEQT	3463	54.207	0.025	0.006	0.005	0.309	0.327	128.098
KTINGGGSPHSKAQYQHT	3578	54.188	0.000	0.000	0.000	0.000	0.223	82.256
KTEDLSGSPHSKAQNQQT	3464	54.156	0.000	0.000	0.000	1.193	0.132	70.198
KTINGSGSPHSKAPGQQT	3465	54.071	0.065	0.000	0.004	0.542	0.179	73.440
KTIPKNGSPHSKAQNQQT	3579	53.824	0.000	0.032	0.000	0.115	0.178	77.458
KTINGSGSPHSKAQSLQI	3466	53.778	0.000	0.186	0.000	0.022	0.047	51.543
KTINGSGSPHSKRLEQQT	3467	53.512	0.000	0.118	0.003	0.161	0.292	71.704
KTERGSGSPHSKAQNQQT	3468	53.475	0.000	0.030	0.000	1.416	0.175	85.368
KTVNGSGSPHSKAPNQQT	3469	53.444	0.833	2.206	0.006	0.156	0.178	58.080
KTSNGSGSPHSKAQNQST	3470	53.353	0.000	0.000	0.000	0.000	0.014	120.897
KTINGSGSPHSKAQKVIT	3471	53.273	0.000	0.000	0.000	0.357	0.402	95.147
KTEGISGSPHSKAQNQQT	3472	53.270	0.000	0.000	0.000	0.000	0.010	78.303
KTINGSGSPHSKAQNNDQ	3473	53.226	0.000	0.000	0.000	0.593	0.046	59.664
KTINGSGSPHSKAQSVHT	3474	53.226	0.000	0.004	0.000	0.446	0.217	76.110
KTINGSGSPHSKAQPLGT	3475	53.049	0.015	0.004	0.001	0.515	0.222	68.656
KTINKEGSPHSKAQNQQT	3580	53.006	0.000	0.029	0.000	0.177	0.111	64.520
KTCNASGSPHSKAQNQQT	3476	52.998	0.000	0.011	0.000	0.897	0.141	67.934
KAINGSGSPHSKAHNQET	3477	52.973	0.000	0.030	0.000	0.035	0.058	71.809
KTEGLSGSPHSKAQNQQT	3478	52.891	0.000	0.000	0.020	0.104	0.155	104.529
KTRDASGSPHSKAQNQQT	3479	52.861	0.000	0.000	0.010	1.062	0.402	52.089
KTSNGSGSPHSKAQNLQI	3480	52.843	0.000	0.000	1.605	0.178	0.214	74.823
KTGNGSGSPHSKAQIQQT	3481	52.809	0.000	0.000	0.000	0.000	0.012	98.291
KTVNGGGSPHSKAQNLQT	3581	52.788	0.000	0.031	0.000	0.000	0.165	83.215
KTDRSSGSPHSKAQNQQT	3482	52.737	0.000	0.000	0.000	0.995	0.085	123.421
KTINGSGSPHSKAQVRNT	3483	52.735	0.000	0.101	0.011	0.230	0.423	68.893
KTINGSGSPHSKAPSNQT	3484	52.680	1.494	4.762	0.003	0.330	0.208	87.951
KTINGSGSPHSKAQVGHT	3485	52.624	0.000	0.000	0.006	0.535	0.192	106.448
KNAIGSGSPHSKAQNQQT	3486	52.516	0.000	0.000	0.000	0.165	0.198	117.939
KAENGSGSPHSKAQNQQT	3487	52.487	0.000	0.157	0.029	0.000	0.242	120.256
KTINGSGSPHSKAQRDIT	3488	52.415	0.098	0.000	0.008	1.784	0.605	88.122
KTINGSGSPHSKAQMPNT	3489	52.408	0.084	0.036	0.025	0.057	0.359	66.040
KTVNGSGSPHSKSQNQQT	3490	52.395	0.033	0.077	0.013	0.105	0.175	58.000
KTIPAIGSPHSKAQNQQT	3582	52.346	0.000	0.009	0.000	0.034	0.134	51.949
KTINGSGSPHSKARGLQT	3491	52.275	0.000	0.000	0.036	1.235	1.425	169.881
KTELGSGSPHSKAQNQQT	3492	52.232	0.000	0.007	0.006	0.532	0.088	87.314
KAETGSGSPHSKAQNQQT	3493	52.219	0.000	0.047	0.581	0.009	0.188	132.940
KTINGSGSPHSKLQKQQT	3494	52.144	0.615	0.477	1.071	1.113	0.429	61.833
KTINGSGSPHSKAPSLQT	3495	52.137	0.041	1.614	0.002	0.902	0.222	70.363
KTINGSGSPHSKAQRDQT	3496	51.897	0.069	0.014	0.040	0.867	0.554	102.317
KTDVGSGSPHSKAQNQQT	3497	51.849	0.000	0.007	0.000	0.385	0.560	115.774
KTINGSGSPHSKNRDQQT	3498	51.830	0.000	0.008	0.000	0.480	0.138	100.300
KSINGSGSPHSKAPNLQT	3499	51.812	0.000	0.256	0.000	0.085	0.139	59.270
KTINGSGSPHSKAQAKGT	3500	51.727	0.048	0.016	0.000	0.271	0.525	104.917
KTVNGSGSPHSKAQDKQT	3501	51.580	0.428	0.000	0.069	0.041	0.063	69.225
KTINGGGSPHSKAQNPQA	3583	51.574	0.000	0.000	0.000	0.192	0.000	102.792
KTINGSGSPHSKAQSAHT	3502	51.569	0.068	0.070	0.000	0.589	0.249	79.498
KTINGNGSPHSKSQNQHT	3584	51.379	0.000	0.054	0.000	0.000	0.082	56.614
KTVPTSGSPHSKAQNQQT	3503	51.348	0.013	0.000	0.000	1.017	0.338	102.651
KTIDGSGSPHSKSQNHQT	3504	51.307	0.000	0.000	0.000	0.000	0.269	63.174
KTDVKSGSPHSKAQNQQT	3505	51.296	0.000	0.000	0.000	0.515	0.224	53.601
KAINRSGSPHSKAQDQQT	3506	51.262	0.000	0.000	0.000	0.000	0.036	54.631
KTINGSGSPHSKAQSTMT	3507	51.249	0.018	0.002	0.002	0.321	0.341	73.213
KTVNASGSPHSKAQNQLT	3508	51.249	0.000	0.000	0.000	0.000	0.268	99.559
KTINGSGSPHSKAQREMT	3509	51.076	0.000	24.900	143.49	1.564	0.476	70.961
KTVHGSGSPHSKAQSQQT	3510	51.057	0.000	0.000	0.000	0.143	0.146	54.185

KTINGGGSPHSKSQNRQT	3585	51.017	0.000	0.000	0.000	0.000	0.421	149.370
KTINGSGSPHSKAQYRAT	3511	51.008	0.000	0.158	0.000	0.690	0.120	50.650
KTINGGGSPHSKAQRQQT	3586	50.998	0.000	0.041	0.000	0.991	0.142	147.942
KTEPMSGSPHSKAQNQQT	3512	50.960	0.203	0.000	0.000	1.816	0.415	126.322
KTINGSGSPHSKNQWQQT	3513	50.800	0.000	0.044	0.047	0.111	0.324	65.506
KETAGSGSPHSKAQNQQT	3514	50.762	0.000	0.027	0.000	1.706	0.054	212.795
KTINGSGSPHSKAQRMNT	3515	50.686	0.000	108.747	0.019	0.943	0.264	97.975
KNNLGSGSPHSKAQNQQT	3516	50.670	0.000	0.019	0.000	0.406	0.121	102.408
KTINGSGSPHAKAQNHQT	3517	50.667	0.211	0.140	0.051	0.101	0.090	80.603
KTIIKNGSPHSKAQNQQT	3587	50.587	0.000	0.000	0.000	0.000	0.751	75.547
KTINGSGSPHSYHVNQQT	3588	50.486	0.000	0.056	0.059	0.528	0.275	179.489
KTINGSGSPHSKAGDSQT	3518	50.457	0.614	0.236	0.008	1.062	0.071	74.355
KTINGSGSPHSKLKSQQT	3519	50.368	0.000	0.296	0.000	1.796	1.096	95.240
KTINGSGSPHSKAQKIST	3520	50.285	0.000	0.000	0.088	0.108	0.302	51.115
KTEYNSGSPHSKAQNQQT	3521	50.256	0.000	0.000	0.000	0.000	0.009	62.679
KTINGSGSPHSKAPSMQT	3522	50.249	0.000	0.000	0.004	0.941	0.460	75.504
EAINGSGSPHSKAQNQQT	3523	50.243	0.629	0.094	0.000	0.057	1.519	117.305
KTINGSGSPHSKASPRQT	3524	50.227	0.088	0.005	0.068	1.761	0.530	67.241
KTINGSGSPHSKRMEQQT	3525	50.177	0.000	0.000	0.000	1.327	0.208	81.769
KTINGSGSPHSKAQYQNT	3526	50.099	0.000	0.008	0.000	0.017	0.119	71.846
KTERVSGSPHSKAQNQQT	3589	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KAEIGHDSPHKSGQNQQT	1754	63.249	0.000	0.000	0.000	0.060	0.024	27.173

[0479] **Table 21** provides the peptide sequence of 341 matured capsid variants, and the fold enrichment of these matured capsid variants relative to the AAV9 control that demonstrated a 75-fold or greater increase in expression in the brain of NHPs relative to the AAV9 control and had a fold-change in expression that was less than 2 relative to the AAV9 control in the liver and the DRG.

Table 21. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the brain of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTFNRSGSPHSKAQNQQI	3591	86.359	0.000	113.67	0.000	0.000	0.092	25.568
KTIIGSGSPHSKAQNRHT	3239	217.176	0.000	0.000	0.000	0.000	0.000	210.515
KTFPGSGSPHSKVQNQQT	3240	199.720	0.000	0.000	0.000	0.000	0.967	97.703
KTEKMSGSPHSKAQNQQT	3241	169.461	0.523	0.000	0.000	0.000	0.158	109.161
KAINGHDSPHKSGQIRQT	3606	108.510	0.000	23.908	0.000	0.132	0.261	8.862
KTINGHDSPHKIGQNQHA	3607	77.321	0.000	18.836	0.028	0.220	0.132	7.578
KEINGRGSPHSKAQNQQT	3527	134.390	0.239	0.000	0.000	0.000	0.232	52.311
KTVNRNGSPHSKAQNQQT	3528	133.016	0.000	0.416	0.000	0.000	0.000	85.361
KAINGYDSPHKSGQKQQT	3608	83.803	0.041	9.491	0.000	0.031	0.150	13.057
KTVNGSGSPHSKARDQQT	3242	124.789	0.123	0.039	0.312	0.569	0.454	132.137
KTESGHDSPHKSGQNQQT	3609	86.513	0.000	7.414	0.000	0.000	0.038	13.163
KTINGHDSPHKSGQSVQT	3610	75.748	0.010	6.808	0.000	0.165	0.058	9.321
KTFNGSGSPHSKAPNLQT	3243	121.436	0.000	0.167	0.000	0.000	0.015	168.920
KTEKTSGSPHSKAQNQQT	3244	120.337	0.000	0.355	0.000	0.000	0.119	101.467
TTINGHDSPHKSGQNQQT	3611	108.963	1.512	3.445	0.869	0.659	1.109	14.788
KTINGHESPHKSGRSQQT	3612	97.106	0.000	3.329	0.022	0.000	0.181	9.378
KTINGSGSPHSKAHVRQT	3245	119.798	0.000	0.000	0.262	0.694	1.039	165.590
KTVNGSGSPHSKAPNQHT	3246	117.207	0.000	0.109	0.000	0.000	0.074	51.008
KTEKISGSPHSKAQNQQT	3247	116.603	0.000	0.000	0.000	0.000	0.426	102.978
KTINGPGSPHSKAHNQQT	3529	115.742	0.146	0.000	0.235	0.000	0.513	52.508
KTINGHDSPHKSGQNKLE	3613	76.204	0.000	1.430	0.000	0.015	0.031	12.419
KTVNGSGSPHSKTQSQQT	3248	115.086	0.000	0.726	0.000	0.000	0.340	63.248

TTINGSGSPHSKAQNQQT	3249	114.856	1.340	14.856	0.827	1.281	0.957	72.058
KSINESGSPHSKAQNQQI	3250	113.833	0.000	0.000	0.000	0.000	0.000	67.649
KTINGHDSPHKTGQNQQK	3614	77.562	0.000	1.056	0.000	0.000	0.000	6.379
KTERTSGSPHSKAQNQQT	3251	112.957	0.000	0.009	0.000	1.128	0.207	117.374
KTINGSGSPHSKAQPAKT	3252	111.472	0.331	0.000	1.089	0.044	1.796	215.275
KTINGRGSPHKRGQNQQT	3837	120.889	0.100	0.814	0.434	0.458	0.614	13.988
KTINGSGSPHTKAQNPPT	3592	147.061	0.000	0.727	0.000	0.000	0.000	34.425
KTEKSSGSPHSKAQNQQT	3253	107.470	0.000	0.016	0.014	0.977	0.179	100.177
KAINGHDNPHKSGQNQQT	3615	88.906	0.297	0.721	0.482	0.222	0.130	9.702
KTSYGNGSPHSKAQNQQT	3530	105.937	0.000	0.000	0.000	0.000	0.114	105.894
KTINGQDSPHKSGQHQQA	3616	85.657	1.127	0.579	0.000	0.193	0.557	5.582
KTEKGSGSPHSKAQNQQT	3254	105.614	0.053	0.031	0.000	0.586	0.169	84.653
KTINGSGSPHSKSQTQQN	3255	104.474	0.000	0.131	0.000	0.084	0.038	54.021
KTERISGSPHSKAQNQQT	3256	103.692	0.000	0.000	0.000	0.062	0.370	89.637
KTERASGSPHSKAQNQQT	3257	103.669	0.000	0.000	0.000	0.127	0.070	115.550
KSINGHDSPHKSGQIQHT	3617	87.598	0.000	0.480	0.000	0.714	0.347	13.872
KELHGSGSPHSKAQNQQT	3258	102.680	0.000	0.000	0.000	1.634	0.592	96.554
KAINGSGSPHSKAQNLAT	3259	101.954	0.000	10.954	8.655	0.298	0.239	116.685
KTVNGSGSPHSKSQNQLT	3260	101.327	0.000	0.035	0.000	0.000	0.025	80.716
KAINGHDSPHKSGPRQQT	3618	145.142	0.000	0.408	0.000	0.000	0.000	8.259
KTVNGHDSPHKSGHTQQT	3619	82.246	0.000	0.378	1.142	0.000	0.123	6.160
KSINGHDSPHKSGQRQHT	3620	80.132	0.000	0.357	0.000	0.000	0.000	9.851
KTERNSGSPHSKAQNQQT	3261	99.892	0.000	0.000	0.000	0.000	0.107	87.392
KSLNGSGSPHTKAQNQQT	3593	81.515	0.197	0.333	0.000	0.000	0.085	45.140
KSVNGNGSPHSKAQNQQT	3531	99.385	0.000	1.329	0.000	0.359	0.079	51.016
KAINGHDSPHKSAQSQQT	3621	95.204	0.146	0.310	0.000	0.699	0.058	14.595
KSIYGHESPHKSGQNQQS	3622	90.947	0.817	0.310	0.000	0.000	0.243	8.064
KTFNGSGSPHSKAQGQQT	3262	99.253	0.000	0.208	0.000	0.128	0.099	81.459
KTVNGHDSPHKSLQNQQT	3623	112.925	0.000	0.301	0.059	0.000	0.322	16.726
KTINGSGSPHGWVQNQQT	3532	97.122	0.000	0.000	0.000	1.240	1.975	290.720
KTINGHGSPHSKAQNPQT	3838	83.478	0.000	0.288	0.219	0.000	0.260	11.001
KTSNGYDSPHKSGQKQQT	3624	77.001	0.032	0.286	0.000	0.000	0.016	8.813
KTVNGHDSPHKSGRNQET	3625	102.695	0.000	0.286	0.000	0.000	0.027	11.958
KTTNGHDSPHKSGQTQLT	3626	115.637	0.000	0.283	0.000	0.052	0.321	17.885
KAINGHDSPHKSEKNQQT	3627	77.103	0.000	0.274	0.000	0.000	0.000	26.868
KTERVSGSPHSKAQNQQT	3263	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KTINGSGSPHSKALNRQS	3264	96.843	0.136	0.532	0.000	0.042	0.178	55.945
KTERLSGSPHSKAQNQQT	3265	95.857	0.000	0.004	0.005	0.126	0.260	102.372
KIINGRDSPHKSGQDQQT	3628	78.773	0.000	0.254	0.000	0.000	0.156	16.132
KTDNGSGSPHSKAHNQQT	3266	95.164	0.000	0.000	0.000	0.000	0.027	55.313
KTFHGSGSPHSKTQNQQT	3267	94.714	0.000	0.210	0.120	0.000	0.000	51.119
KTISGHDSPHKTGHNQQT	3629	92.490	0.000	0.233	0.057	0.730	0.000	8.823
KTVNAHDSPHKSGQNQLT	3630	79.137	0.000	0.233	0.178	0.753	0.045	29.254
KTINGGGSPHSKAQTQQI	3533	92.345	0.000	0.000	0.000	0.000	0.023	54.199
KSINGYDSPHKSGQTQQT	3631	79.227	1.817	0.226	0.000	0.000	1.148	4.497
KTINGHESPHKSGQTQQI	3632	86.089	0.000	0.222	0.000	0.000	0.024	3.989
KTINGHDSPHKSGQSKQA	3633	101.460	0.000	0.222	0.000	0.185	0.114	7.510
KTSNGSGSPHSKAQNPPT	3268	91.528	0.000	0.000	0.000	0.000	0.039	51.541
ETINGSGSPHSKAQNLQT	3269	90.969	0.221	1.023	0.197	0.179	0.813	107.216
KTVHGNGSPHSKAQNQQT	3534	90.073	0.000	0.000	0.000	0.000	0.304	97.003
NTINGSGSPHSKAQNQQT	3270	90.017	1.712	1.261	1.171	0.923	0.540	55.179
KTINGGGSPHSKAQNQQC	3535	89.301	0.219	0.000	0.000	0.287	0.319	53.840
KTENMSGSPHSKAQNQQT	3271	89.247	0.000	0.000	0.000	0.000	0.260	130.568
KTENVSGSPHSKAQNQQT	3272	88.506	0.000	0.000	0.000	0.964	0.112	108.591
KTSSGSGSPHSKAQYQQT	3273	87.304	0.000	0.000	0.000	0.000	0.299	58.143
KTIDGGGSPHSKAQNKQT	3536	85.019	0.000	0.000	0.000	0.000	0.477	55.517
KTEKVSGSPHSKAQNQQT	3274	84.558	0.000	0.022	0.000	0.873	0.424	112.185
KAINGSGSPHSKAQDQET	3275	84.080	0.000	0.000	0.000	0.194	0.027	87.637

KTCNKSGSPHSKAQNQQT	3276	83.992	0.000	0.000	0.165	0.283	0.000	119.496
KTINGGGSPHSKAQNQLI	3537	83.881	0.000	0.000	0.000	0.046	0.387	78.383
KNINGGGSPHSKAQNQQT	3538	83.083	0.000	0.042	0.000	0.000	0.000	75.913
KTEHLSGSPHSKAQNQQT	3277	83.080	0.000	0.000	0.012	0.021	0.189	69.494
KAIIGHESPHKSGQNQQT	3634	88.563	0.000	0.150	0.000	0.062	0.145	8.530
KTINGHDSPHKTGQNQPP	3635	77.357	0.000	0.149	0.000	0.000	0.096	8.865
KAINGHDSPHKSGQSPQT	3636	75.734	0.095	0.148	0.000	0.000	0.238	14.195
KAEMGSGSPHSKAQNQQT	3278	83.049	0.000	0.020	0.000	0.768	0.112	135.019
KATNGSGSPHSKAQNHQT	3279	82.627	0.000	0.176	0.000	0.155	0.057	66.207
KTIKGNDSPHKSVQNQQT	3637	85.986	0.000	0.135	0.000	0.263	0.000	8.603
KAIKGSGSPHSKAQDQQT	3280	82.258	0.000	0.000	0.000	0.108	0.000	85.178
KTINGGGSPHSKSQNQLT	3539	82.231	0.000	0.070	0.000	0.000	0.498	126.986
KTEFGHDSPHKSGQNQQT	3638	77.245	0.000	0.124	0.000	0.561	0.063	16.337
KTINGHDSPHKSAQNYQT	3639	130.375	0.000	0.124	0.000	0.097	0.123	19.443
KTFNGSASPHSKALNQQT	3839	84.258	0.000	0.122	0.000	0.104	0.037	31.855
KTINGCGSPHASGQNQQT	3840	132.540	0.000	0.121	0.042	0.000	0.059	1.857
KTINAHDSPHKIGQNHQT	3640	106.832	0.000	0.121	0.000	0.000	0.231	5.074
KTVNGNGSPHSKAQNKQT	3540	81.481	0.000	0.000	0.000	0.000	0.122	69.455
KTINGHESPHKSAQNRQT	3641	95.531	0.000	0.113	0.000	0.130	0.082	4.815
KTINGSGSPHSKGHWQQT	3281	81.434	0.000	0.000	0.000	0.000	1.011	65.252
KTTNGHDSPHKSGQNQQG	3642	85.113	0.000	0.107	0.000	0.000	0.017	10.555
KTIKGQDSPHKIGQNQQT	3643	110.357	0.000	0.103	0.058	0.166	0.135	11.829
KTDKTSGSPHSKAQNQQT	3282	81.430	0.000	0.000	0.000	1.362	0.291	169.515
KTVNGHDSPHKSGQNHLT	3644	81.516	0.000	0.100	0.017	0.000	0.028	16.096
KTFKGSGSPHSKAPNQQT	3283	80.890	0.000	0.000	0.000	0.000	0.017	71.144
KSINGHDSPHKSGQYQHT	3645	88.195	0.000	0.099	0.000	0.000	0.149	14.485
KTINGNDSPHKSVQNHQT	3646	120.002	0.000	0.099	0.788	0.000	0.000	7.920
KTVNGSGSPHSKAQNQLI	3284	80.509	0.000	0.000	0.000	0.000	0.166	71.156
KTINGSGSPHSKRPEQQT	3285	80.418	0.000	0.013	0.000	0.149	0.361	50.319
KTINGSGSPHSKAQRTMT	3286	80.388	0.000	0.022	0.170	1.812	1.025	100.248
KTITGHDSPHKSGQNQWT	3647	81.658	0.000	0.090	0.000	0.936	0.000	7.744
KTNNGHDSPHKSVQNQHT	3648	115.172	0.000	0.083	0.000	0.000	0.062	7.934
KTEKASGSPHSKAQNQQT	3287	80.285	0.000	0.041	0.000	0.000	0.261	90.390
KTIDGHDSPHKSGQNQHA	3649	91.058	0.000	0.082	0.000	0.000	0.000	10.781
KSDQGSGSPHSKAQNQQT	3288	80.076	0.000	0.000	0.000	0.993	0.124	151.911
KTVNGHDSPHKSGQTRQT	3650	133.276	0.251	0.080	0.093	0.034	0.129	7.174
KTVNGHDSPHKSGQNLHT	3651	88.080	0.000	0.080	0.000	0.000	0.039	11.363
KAISGHDSPHKSGLNQQT	3652	78.846	0.000	0.079	0.000	0.000	0.015	11.045
KTEITSGSPHSKAQNQQT	3289	79.620	0.000	0.163	0.000	0.332	0.074	76.686
KTDKSSGSPHSKAQNQQT	3290	79.470	0.055	0.012	0.000	1.437	0.367	141.351
KAINGHDSPHKSAQNQET	3653	90.402	0.000	0.073	0.000	0.746	0.000	10.674
KTITGHDSPHKSGQHLQT	3654	137.945	0.000	0.072	0.000	0.000	0.000	4.187
KTIDGSGSPHSKAQNQQH	3291	79.090	0.000	0.000	0.000	0.136	0.049	57.914
KTVNGNGSPHSKAQNQHT	3541	78.849	0.000	0.000	0.000	0.000	0.045	54.086
KNTNGSGSPHSKAQNQQT	3292	78.445	0.000	0.000	0.000	0.571	0.177	89.719
KTINGHDSPHKSRLNQPT	3655	92.883	0.000	0.070	0.050	0.904	1.075	5.598
KTETHSGSPHSKAQNQQT	3293	77.974	0.000	0.067	0.000	0.000	0.512	57.287
KTVDGHDSPHKSGQKQQT	3656	78.802	0.000	0.069	0.000	0.157	0.342	7.200
KTINGQDSPHKSGQNQDT	3657	82.075	0.000	0.067	0.000	0.225	0.144	9.626
KTINGGGSPHSKALNQQN	3542	77.822	0.000	0.131	0.000	0.000	0.274	69.884
KTIEGHDSPHKSGRNQQT	3658	75.838	0.000	0.065	0.017	0.000	0.079	7.818
KTTNGHDSPHKSGQNLLT	3659	77.738	0.130	0.064	0.185	0.424	0.326	15.192
KTINGHDSPHKSGQLVIT	3660	76.781	0.089	0.064	0.000	0.338	0.475	11.323
KTVNGHDSPHKSRQSQQT	3661	76.458	0.000	0.063	0.000	0.000	0.021	8.136
KTINGSGSPHSKALHQHT	3294	77.502	0.000	0.052	0.041	0.000	0.188	68.196
KTINGHDSPHKSGRTQET	3662	81.599	0.000	0.062	0.000	0.000	0.137	7.270
KTINGHDSPHKSVQTHQT	3663	77.309	0.237	0.062	0.000	0.000	0.116	7.519
KTINGTGSPHSKAQNHQI	3543	77.089	0.171	0.000	0.000	0.000	0.166	54.281

KTINGSGSPHSKAQHRIT	3295	76.849	0.105	0.499	0.170	1.424	0.214	127.000
KTINGSGSPHSKAQYIHT	3296	76.170	0.000	0.014	0.033	1.523	0.168	59.649
KTSNGHDSPHKSGQNQPA	3664	75.834	0.000	0.056	0.000	0.000	0.000	8.501
KTEGKHDSPHKSGQNQQT	3665	98.384	0.000	0.056	0.000	0.000	0.000	10.345
KTENISGSPHSKAQNQQT	3297	76.072	0.000	0.000	0.000	0.115	0.132	83.118
KVINGHDSPHKSGQTQQT	3666	91.665	0.000	0.055	1.526	0.311	0.000	7.391
KTIIGGGSPHSKAHNQQT	3544	75.872	0.000	0.050	0.000	0.000	0.235	65.492
KTINGPDSPHKIGQNQQS	3667	85.726	0.000	0.055	0.171	0.000	0.063	10.055
KTINGSGSPHSKAQKFET	3298	75.788	0.000	0.000	0.028	0.108	0.093	65.588
KTSNESGSPHSKAQNHQT	3299	75.720	0.000	0.000	0.000	0.169	0.217	70.590
KTINGSGSPHSKAQFPST	3300	75.677	0.000	0.004	0.000	0.849	0.127	119.712
KTERPSGSPHSKAQNQQT	3301	75.669	0.000	0.029	0.000	0.000	0.156	73.894
KAVNGHDSPHKSVQNQQT	3668	81.051	0.448	0.051	0.000	0.665	0.091	11.288
KTINGNGSPHSKAQNPLT	3545	75.269	0.000	0.000	0.000	0.366	0.000	53.583
KSIKGNGSPHSKAQNQQT	3546	75.196	0.000	0.000	0.000	0.000	0.000	90.251
KTINGHDSPHKSRQDQHT	3669	75.595	0.000	0.049	0.118	0.030	0.045	8.540
KAINGPDSPHKSGQKQQT	3670	78.213	0.464	0.047	0.000	0.323	0.162	10.395
KTINGHDSPHKSRQSQHT	3671	88.544	0.499	0.046	0.000	0.059	0.032	8.324
KTIYGHDSPHKSVQNQLT	3672	92.381	0.000	0.043	0.000	0.103	0.016	12.323
KTVNGHDSPHKSGQNLLT	3673	83.969	0.114	0.040	0.023	0.000	0.035	18.894
KTESAHDSPHKSGQNQQT	3674	80.810	0.000	0.039	0.000	0.000	0.000	13.338
KTENKSGSPHSKAQNQQT	3594	103.854	0.000	0.037	0.000	0.000	0.119	31.182
KTTNGQDSPHKSGQNQQS	3675	92.419	0.000	0.037	0.043	0.000	0.079	7.592
KTDKGSGSPHSKAQNQQT	3595	94.572	0.000	0.037	0.000	0.951	0.367	47.888
KTIDGHDSPHKSGRNQQI	3676	80.240	0.000	0.037	0.000	0.040	0.144	10.363
KTINGYDSPHKSGQYQHT	3677	81.534	0.000	0.036	0.000	0.000	0.000	10.524
KTDNGHDSPHKSRQNQQT	3678	105.312	0.000	0.033	0.000	0.000	0.018	7.931
KTINGHDSPHKSWVRQQT	3679	125.537	0.000	0.033	0.000	0.291	0.174	11.687
KTINGHESPHKSGQNQHS	3680	92.248	0.000	0.032	0.012	0.090	0.088	9.720
KTVNGHDSPHKIGHNQQT	3681	120.985	0.000	0.029	0.000	0.000	0.009	10.167
KTCNGHDSPHKSGRNQQT	3682	94.616	0.000	0.025	0.000	0.000	0.128	12.496
KTINGNGSPHSKAQNHQA	3841	88.274	0.000	0.024	0.000	0.000	0.041	36.754
KNVVGHDSPHKSGQNQQT	3683	75.330	0.000	0.024	0.000	0.063	0.049	8.077
KTELWHDSPHKSGQNQQT	3684	85.323	0.057	0.020	0.000	0.000	0.243	9.915
KTELRHDSPHKSGQNQQT	3685	98.098	0.000	0.019	0.000	0.000	0.007	6.588
KTINGHDSPHKSNAWQQT	3686	84.825	0.000	0.016	0.000	0.000	0.132	15.788
KTDAGHDSPHKSGQNQQT	3687	88.924	0.000	0.013	0.000	1.076	0.070	18.107
KTEVGHDSPHKSGQNQQT	3688	112.457	0.000	0.011	0.000	0.000	0.138	13.125
KTESRHDSPHKSGQNQQT	3689	81.766	0.000	0.011	0.000	0.052	0.036	6.975
KSELGHDSPHKSGQNQQT	3690	107.059	0.000	0.005	0.000	0.000	0.055	13.285
KTINGHDSPHKSGQSVPT	3691	77.840	0.000	0.003	0.000	0.136	0.061	6.768
KTINGHESPHKSGQNIQP	3692	253.840	0.000	0.000	0.000	0.000	0.000	14.042
KTEMKHDSPHKSGQNQQT	3693	240.075	0.000	0.000	0.000	0.000	0.000	3.183
KTINGHDSPHKSVQNHLN	3694	196.758	0.000	0.000	0.000	0.000	0.000	14.557
KTINGHDSPHKIGLDQQT	3695	165.627	0.000	0.000	0.000	1.942	0.000	5.469
KTSNASGSPHSKAQHQQT	3596	165.206	0.000	0.000	0.000	0.000	0.082	40.558
KTINGHDSPHKRGPDQQS	3696	160.084	0.000	0.000	0.000	0.000	0.000	2.923
KTINGMGSPHSKTQNQQT	3842	158.728	0.000	0.000	0.000	0.000	0.638	47.809
KTIKGHDSPHKSGESQQT	3697	142.264	0.000	0.000	0.000	0.000	0.218	4.176
KTEGWHDSPHKSGQNQQT	3698	142.064	0.000	0.000	0.000	0.000	0.264	11.785
KTINGHDSPHKHGQNHQT	3699	141.405	0.191	0.000	0.000	0.000	0.000	10.214
KTEQLHDSPHKSGQNQQT	3700	138.345	0.000	0.000	0.000	0.000	0.000	12.606
KTVNGTGSPHSKAQNQLT	3843	137.639	0.000	0.000	0.000	0.000	0.277	48.950
KTIIGHDSPHKSGQYQHT	3701	131.825	0.000	0.000	0.000	0.000	0.211	5.762
KTSNGHDSPHKSVQNKQT	3702	130.640	0.000	0.000	0.000	0.172	0.039	11.850
KIVNGQVSPHKSGQNQQT	3703	129.649	0.000	0.000	0.000	0.000	0.031	16.942
KTVNGHDSPHKSGQRQLT	3704	129.641	0.000	0.000	0.000	0.000	0.487	20.145
KTVNGHDSPHKIGQNQLT	3705	128.582	0.000	0.000	0.499	0.027	0.199	20.957

KTINGHDSPHKSGQIIVT	3706	125.245	0.000	0.000	0.151	0.000	0.379	6.808
KTEKIHDSPHKSGQNQQT	3707	125.178	0.000	0.000	0.000	0.000	0.000	17.604
KTENAHDSPHKSGQNQQT	3708	124.477	0.000	0.000	0.000	0.000	0.062	15.805
KIGNGHESPHKSGQNQQT	3709	123.324	0.000	0.000	0.000	0.000	0.000	11.198
KEVMGHDSPHKSGQNQQT	3710	121.107	0.000	0.000	0.000	0.000	0.000	17.191
KTEVKHDSPHKSGQNQQT	3711	119.733	0.000	0.000	0.000	0.000	0.000	5.550
KTINGYDSPHKSGQKQST	3712	119.615	0.000	0.000	0.000	0.000	0.000	7.970
KTIHGNGSPHSKAQNQET	3844	117.388	0.000	0.000	0.000	0.000	0.000	38.874
KYQVGHDSPHKSGQNQQT	3713	112.797	0.000	0.000	0.000	0.000	0.542	9.335
KTEAMHDSPHKSGQNQQT	3714	111.765	0.000	0.000	0.000	0.000	0.000	16.142
KTIKGDDSPHKSVQNQQT	3715	109.397	0.000	0.000	0.000	0.000	0.000	19.125
KTINGHDSPHKSVQSHQT	3716	109.375	0.107	0.000	0.319	0.000	0.547	12.617
KTINGHDSPHKSGQFVVT	3717	108.725	0.000	0.000	0.000	0.124	0.406	10.179
KTVNGHDSPHKSRQNLQT	3718	107.496	0.205	0.000	0.000	1.934	0.062	8.616
KATNGHNSPHKSGQNQET	3719	106.806	0.000	0.000	0.000	0.000	0.000	10.566
KAINGHDSPHKSAQNQQI	3720	106.539	0.000	0.000	0.000	0.000	0.113	21.786
KTEHGHDSPHKSGQNQQT	3721	106.486	0.000	0.000	0.000	0.000	0.006	14.956
KTVENHDSPHKSGQNQQT	3722	106.468	0.000	0.000	0.000	0.000	0.156	9.246
KTIYGHDSPHKSGQSQPT	3723	106.431	0.000	0.000	0.000	0.155	0.137	6.562
KTISGHESPHKSGQNEQT	3724	105.740	0.000	0.000	0.000	0.378	1.384	9.156
KAIIGHDSPHKSAQNQQT	3725	105.292	0.000	0.000	0.000	0.000	0.553	16.793
KAIDGHDSPHKSGQNQLT	3726	104.701	0.331	0.000	0.000	0.201	0.638	16.109
KTIMGHDSPHKSVQNQQT	3727	104.683	0.000	0.000	0.000	0.000	0.000	8.029
KEVGGHDSPHKSGQNQQT	3728	103.896	0.000	0.000	0.000	0.000	0.000	16.899
KTINGHDSPHKSAQNLLT	3729	103.332	0.000	0.000	0.256	0.194	0.000	15.722
KTEFTHDSPHKSGQNQQT	3730	102.052	0.062	0.000	0.000	0.439	0.047	12.527
KTINASGSPHSKAINQQT	3597	101.122	0.233	0.000	0.000	0.000	0.145	47.196
KAINGNGSPHKRGQNQQT	3845	100.925	0.000	0.000	0.000	0.000	0.159	10.011
KSEMGHDSPHKSGQNQQT	3731	100.539	0.000	0.000	0.000	0.000	0.000	18.356
KAQQGHDSPHKSGQNQQT	3732	100.395	0.000	0.000	0.000	0.000	0.057	3.954
KTEVMHDSPHKSGQNQQT	3733	99.473	0.000	0.000	0.000	0.000	0.000	12.400
KAINGHDSPHKSGQSLQT	3734	99.310	0.058	0.000	1.439	0.254	0.056	17.323
KTINGSGSPHSKAPNQQH	3598	99.300	0.252	0.000	0.000	0.000	0.038	39.297
KCGEGHDSPHKSGQNQQT	3735	99.298	0.000	0.000	0.000	0.000	0.000	13.147
KTVNGHDSPHKSAQNHQT	3736	99.257	0.000	0.000	0.078	0.000	0.027	17.639
KTVNGHDSPHKSGQTQLT	3737	98.524	0.000	0.000	0.313	0.183	0.172	14.883
KTNNGHDSPHKSGRNRQT	3738	98.307	0.000	0.000	0.124	0.000	0.037	5.840
KTCNEHDSPHKSGQNQQT	3739	97.092	0.000	0.000	0.000	0.000	0.000	8.364
KTINGHDSPHKYGQNEQT	3740	96.960	0.000	0.000	0.000	0.000	0.000	4.613
KASNRHDSPHKSGHNQQT	3741	96.283	0.000	0.000	0.000	0.000	0.675	8.045
KTINGNGSPHSKAPNLQT	3846	95.963	0.000	0.000	0.000	0.000	0.247	36.341
KTETKHDSPHKSGQNQQT	3742	95.121	0.000	0.000	0.000	0.000	0.083	4.831
KSINGHDSPHKSQQNQQT	3743	94.479	0.000	0.000	0.000	0.000	1.696	9.633
KTIGGHDSPHKSGQNQQI	3744	94.420	0.000	0.000	0.000	0.000	0.333	19.324
KTDPQHDSPHKSGQNQQT	3745	93.931	0.000	0.000	0.000	0.906	0.019	11.749
KTINRHDSPHKIVQNQQT	3746	93.409	0.000	0.000	0.000	0.000	0.000	3.064
KTEQYHDSPHKSGQNQQT	3747	93.065	0.000	0.000	0.000	0.000	0.047	15.190
KTINGHDSPHKSVQSKQT	3748	92.445	0.000	0.000	0.078	0.000	0.047	4.263
KELVGHDSPHKSGQNQQT	3749	92.262	0.000	0.000	0.000	0.594	0.000	14.890
KTENRHDSPHKSGQNQQT	3750	91.675	0.000	0.000	0.000	0.000	0.000	13.282
KELMGHDSPHKSGQNQQT	3751	91.191	0.000	0.000	0.000	0.000	0.000	14.032
KTINGNDSPHKIGHNQQT	3752	91.183	0.000	0.000	0.117	0.000	0.270	11.095
KTIKGGGSPHSKAQDQQT	3847	91.172	0.000	0.000	0.000	0.064	0.085	49.580
KTEGHHDSPHKSGQNQQT	3753	89.922	0.000	0.000	0.000	0.000	0.000	23.929
KTEGYHDSPHKSGQNQQT	3754	89.891	0.000	0.000	0.000	0.000	0.000	15.116
KTVNGHDSPHKSGQTQQI	3755	89.801	0.000	0.000	0.657	0.000	0.542	11.543
KTINGQDSPHKSGQNPLT	3756	89.726	0.000	0.000	0.000	0.363	0.000	15.561
KTVNASGSPHSKAQNHQT	3599	89.467	0.091	0.000	0.000	0.045	0.252	39.024

KTINGHDSPHKSGRDQKT	3757	88.871	0.000	0.000	0.000	0.350	0.181	12.117
KTINGHDSPHKSVHNQQN	3758	88.715	0.089	0.000	0.081	0.000	0.143	10.787
KTINGHDSPHKSGQWKRT	3759	88.633	0.000	0.000	0.000	0.202	0.094	5.186
KTIDGSGSPHSKAENRQT	3600	87.993	0.092	0.000	0.000	0.139	0.054	40.629
KNEIGHDSPHKSGQNQQT	3760	87.758	0.000	0.000	0.000	0.000	0.055	14.110
KAINGHDSPHKSGQSQQI	3761	87.585	0.000	0.000	5.310	0.000	0.000	12.864
KIINGHDSPHKSRQAQQT	3762	86.966	0.000	0.000	0.000	0.000	0.000	9.193
KTPNGHDSPHKSGQNQQI	3763	86.683	0.000	0.000	0.000	0.000	0.109	21.278
KITNGHDSPHKSGQTQQT	3764	86.443	0.000	0.000	0.000	0.192	0.190	17.479
KTINGHDSPHKSVQNHQI	3765	86.395	0.000	0.000	0.000	0.000	0.000	9.148
KTINGHDSPHKSKQNQQA	3766	86.265	0.000	0.000	0.000	0.123	0.041	5.768
KTINGHDSPHKSAQNQLN	3767	86.153	0.000	0.000	0.000	0.050	0.019	15.587
KTDITHDSPHKSGQNQQT	3768	85.876	0.000	0.000	0.000	0.000	0.013	9.076
KTVNGHDSPHKSGQTQPT	3769	85.680	0.000	0.000	1.301	1.064	0.000	8.067
KTEKFHDSPHKSGQNQQT	3770	85.358	0.000	0.000	0.000	0.000	0.026	7.229
KTDQGHDSPHKSGQNQQT	3771	85.267	0.000	0.000	0.000	0.000	0.000	16.042
KTINGHDSPHKLWINQQT	3772	85.132	0.000	0.000	1.154	0.000	0.017	12.704
KGINGPDSPHKSGQNQQT	3773	85.080	0.000	0.000	0.084	0.000	0.054	13.750
KSEIGHDSPHKSGQNQQT	3774	84.789	0.000	0.000	0.000	0.000	0.013	15.955
KTINGHDSPHKSVQKQLT	3775	84.351	0.000	0.000	0.000	0.038	0.103	11.890
KTINGHPSPHWKGQNQQT	3848	84.153	0.000	0.000	0.000	0.000	0.058	3.280
KTVNGHDSPHKSGRNQLA	3776	83.858	0.000	0.000	0.000	0.000	0.132	21.252
KTNNVHDSPHKSGQNQQS	3777	83.697	0.000	0.000	0.000	0.176	0.000	7.117
KTIKGSGSPHSKVQDQQT	3601	83.077	0.000	0.000	0.034	0.000	0.107	21.001
KSEKGHDSPHKSGQNQQT	3778	82.982	0.000	0.000	0.000	0.000	0.105	16.662
KWSAGHDSPHKSGQNQQT	3779	82.949	0.000	0.000	0.000	0.000	0.211	12.499
KELAGHDSPHKSGQNQQT	3780	82.876	0.000	0.000	0.000	0.000	0.093	18.063
KTINGHDSPHKMGRNQQS	3781	82.787	0.000	0.000	0.000	0.000	0.000	6.467
KTDQAHDSPHKSGQNQQT	3782	82.402	0.000	0.000	0.141	0.000	0.000	13.397
KTETQHDSPHKSGQNQQT	3783	82.316	0.000	0.000	0.000	0.000	0.198	10.823
KTEMTHDSPHKSGQNQQT	3784	82.221	0.000	0.000	0.000	0.000	0.000	8.431
KTINGHDSPHKSGISIQT	3785	82.019	0.000	0.000	0.000	0.191	0.044	7.310
KTDAVHDSPHKSGQNQQT	3786	81.968	0.000	0.000	0.000	0.297	0.107	13.596
KTSNGHDSPHKSVQNLQT	3787	81.921	0.000	0.000	0.072	0.000	0.330	11.544
KTEKYHDSPHKSGQNQQT	3788	81.637	0.000	0.000	0.000	0.000	0.013	7.580
KQTQGHDSPHKSGQNQQT	3789	81.581	0.000	0.000	0.000	0.000	0.133	15.225
KTINGHDSPHKMAHNQQT	3790	81.329	0.000	0.000	0.000	0.000	0.094	15.949
KAINGSGSPHSKAQTQQA	3602	81.207	0.000	0.000	0.000	0.000	0.016	40.435
KTINGHDSPHKHGQNQQN	3791	81.065	0.000	0.000	0.000	0.000	0.000	4.110
KGADGHDSPHKSGQNQQT	3792	80.981	0.000	0.000	0.000	0.000	0.074	11.423
KVGEGHDSPHKSGQNQQT	3793	80.775	0.084	0.000	0.000	0.000	0.019	16.378
KANEGHDSPHKSGQNQQT	3794	80.470	0.000	0.000	0.000	0.000	0.000	12.818
KTDTMHDSPHKSGQNQQT	3795	80.364	0.000	0.000	0.000	0.000	0.000	13.166
KTEAKSGSPHSKAQNQQT	3603	80.088	0.192	0.000	0.000	0.000	0.613	47.130
KTINGHDSPHKSVQSQQS	3796	80.000	0.000	0.000	0.000	1.055	0.082	17.620
KTIPGSGSPHSKAQNLQT	3604	79.973	0.871	0.000	0.000	0.000	0.000	32.693
KTCIAHDSPHKSGQNQQT	3797	79.857	0.000	0.000	0.066	0.000	0.093	1.930
KTINGHDSPHKSGQTVCT	3798	79.730	0.000	0.000	0.000	0.050	0.030	7.873
KELRGHDSPHKSGQNQQT	3799	79.596	0.000	0.000	0.000	0.000	0.006	22.001
KCQIGHDSPHKSGQNQQT	3800	79.359	0.000	0.000	0.000	0.000	0.000	2.614
KGVMGHDSPHKSGQNQQT	3801	79.170	0.000	0.000	0.000	0.138	0.086	17.287
KACDGHDSPHKSGQNQQT	3802	78.648	0.000	0.000	0.000	0.000	0.128	17.767
KTINGQDSPHKSGQYQQI	3803	78.585	0.000	0.000	0.000	0.286	0.672	5.664
KTINGHDSPHKSGQQIMT	3804	78.534	0.000	0.000	0.000	0.000	0.058	7.067
KTINGHDSPHKSRQNEQS	3805	78.534	0.000	0.000	0.000	0.112	0.188	13.388
KASNGHDSPHKSGLNHQT	3806	78.451	0.000	0.000	0.000	0.000	0.000	17.975
KTVNGHDSPHKSGQSQPT	3807	78.309	0.000	0.000	0.000	0.000	0.231	10.627
KNELGHDSPHKSGQNQQT	3808	78.135	0.000	0.000	0.000	0.000	0.182	17.457

KTETFHDSPHKSGQNQQT	3809	78.070	0.000	0.000	0.000	0.782	0.007	4.693
KAAEGHDSPHKSGQNQQT	3810	77.793	0.000	0.000	0.000	0.000	0.060	13.552
KGQNGHDSPHKSGQNQQT	3811	77.770	0.000	0.000	0.000	0.107	0.056	13.618
KNEFGHDSPHKSGQNQQT	3812	77.740	0.000	0.000	0.000	0.000	0.029	16.318
KTSIGYDSPHKSGQNQQT	3813	77.730	0.000	0.000	0.000	0.057	0.178	4.831
KTDNGHDSPHKSGQNLQT	3814	77.565	0.504	0.000	0.000	0.000	0.000	16.184
KTEGQHDSPHKSGQNQQT	3815	77.423	0.000	0.000	0.000	0.000	0.748	20.310
KTITGHDSPHKSRQDQQT	3816	77.127	0.000	0.000	0.000	0.000	0.000	6.250
KAEHGHDSPHKSGQNQQT	3817	77.026	0.000	0.000	0.000	0.000	0.017	20.937
KTINGDDSPHKSGQKQLT	3818	76.968	0.000	0.000	0.000	0.163	0.014	15.820
KCDQGHDSPHKSGQNQQT	3819	76.887	0.000	0.000	0.000	0.193	0.013	27.317
KEILGHDSPHKSGQNQQT	3820	76.770	0.000	0.000	0.000	0.804	0.009	10.771
KTIHGSGSPHSKAQNQAT	3605	76.765	0.000	0.000	0.000	0.000	0.215	43.969
KTERNHDSPHKSGQNQQT	3821	76.751	0.000	0.000	0.000	0.000	0.000	14.979
KAINGDDSPHKSGHNQQT	3822	76.578	0.000	0.000	0.000	0.032	0.059	17.755
KTSNGHNSPHKSGQNQET	3823	76.515	0.000	0.000	0.000	0.000	0.000	4.764
KTINGHDSPHKSGQMIHT	3824	76.364	0.000	0.000	0.000	0.000	0.000	9.486
KNAIGHDSPHKSGQNQQT	3825	76.289	0.000	0.000	0.000	0.009	0.072	15.178
KTDKFHDSPHKSGQNQQT	3826	76.204	0.000	0.000	0.000	0.000	0.000	7.096
KTEGFHDSPHKSGQNQQT	3827	76.191	0.000	0.000	0.000	0.000	0.080	13.163
KVINGHDSPHKSGRNHQS	3828	75.961	0.000	0.000	0.000	0.000	0.000	13.568
KTITGHDSPHKSVQNRQT	3829	75.940	0.000	0.000	0.000	0.621	0.000	4.310
KTPDMHDSPHKSGQNQQT	3830	75.871	0.659	0.000	0.000	0.000	0.048	11.277
KTINGHDSPHKSGQKMNT	3831	75.820	0.000	0.000	0.000	0.000	0.167	6.373
KTELQHDSPHKSGQNQQT	3832	75.814	0.000	0.000	0.000	0.105	0.000	11.798
KTIHGHDSPHKSGQSQQN	3833	75.777	0.000	0.000	0.059	0.000	0.166	7.426
KTEIGHDSPHKSGQNQQT	3834	75.525	0.000	0.000	0.016	0.012	0.000	9.593
KTINGHDSPHKSGQYQHA	3835	75.308	0.000	0.000	0.000	0.000	0.017	17.081
KTELYHDSPHKSGQNQQT	3836	75.235	0.000	0.000	0.000	0.000	0.042	10.354

[0480] **Table 22** provides the sequences of 216 matured capsid variants having a CV of less than 1 for the liver RNA samples isolated and a 10-fold or greater increase in expression relative to AAV9 in the liver of NHPs. These matured variants showed preferential transduction of the liver over other tissues as shown by a low value for fold-enrichment relative to AAV9 in the other tissues investigated including the brain, DRG, heart and muscle. As such, **Table 22** provides TTM-001 and TTM-002 matured AAV capsid variants with liver-specific tropism. Across the peptides within the matured capsid variants in **Table 22,** approximately 175 of them comprised the sequence GSGSPH (SEQ ID NO: 4695) and further comprised additional modifications in the C-terminal region of the sequence.

Table 22. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the liver of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9					
		Liver RNA (NHP)	Liver DNA (NHP)	Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)
KTQRKSGSPHSKAQNQQT	4011	119.659	1.439	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQARKT	4681	96.557	3.644	0.000	0.000	0.000	0.000
KYIVGSGSPHSKAQNQQT	4682	94.721	4.480	0.000	0.000	0.000	0.000
KTINGSGSPHSMYMNQQT	4683	81.106	5.840	0.000	0.000	0.000	0.000
KTINGSGSPHSKAFYRQT	4684	77.541	3.577	0.000	0.000	0.000	0.000
KTINGSGSPHSKLKRQQT	4685	76.103	6.884	0.000	0.000	0.000	0.000
KTINGSGSPHSKRHRQQT	4686	73.225	4.648	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQKCIT	4687	69.547	1.887	0.000	0.000	0.000	0.000
KTINGSGSPHSKWRLQQT	4688	68.083	2.037	0.000	0.000	0.000	0.000

KTINGSGSPHSRCRNQQT	4689	64.416	5.150	0.000	0.000	0.000	0.000
KTINGSGSPHSFTCNQQT	4690	63.936	2.155	0.000	0.000	0.000	271.289
KTINGSGSPHSKFFIQQT	4691	63.255	6.916	0.000	0.000	0.000	0.000
KTINGSYSPHCLAQNQQT	4012	62.942	0.309	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQYSRT	4692	60.119	0.956	0.000	0.000	0.000	0.000
KTINGSGSPHIVWQNQQT	3849	58.021	6.056	0.000	0.000	0.000	0.000
KTINGSGSPHSKYFMQQT	3850	57.350	2.993	0.000	0.000	0.000	0.000
KTINGSGSPHSKARQRQT	3851	56.775	2.205	0.000	0.000	0.000	0.000
KTINGSGSPHSCHQNQQT	3852	56.242	8.562	0.000	0.000	0.000	0.000
KTINGSGSPHFPWQNQQT	3853	53.587	1.731	0.000	0.000	0.000	0.000
KTINGSGSPHSKIRRQQT	3854	53.528	1.388	0.000	0.000	0.000	0.000
KTINGSGSPHVYYQNQQT	3855	53.294	2.173	0.944	0.000	0.246	5.268
KTINGSGSPHSLYWNQQT	3856	53.262	0.000	0.000	0.000	0.000	0.000
KTINGSGSPHSKPKRQQT	3857	52.881	2.832	0.000	0.000	0.000	0.000
KPRWGSGSPHSKAQNQQT	3858	51.637	0.386	0.000	0.000	375.537	0.000
KTINGSGSPHSKAFSWQT	3859	51.304	1.805	0.000	0.000	0.000	0.000
KTINGSGSPHSRFWNQQT	3860	51.225	6.955	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQCLKT	3861	49.565	1.453	0.000	0.000	0.000	0.000
KTINGSGSPHSRMRNQQT	3862	48.902	2.816	0.000	0.000	0.000	0.000
KTINGSGSPHSVKKNQQT	3863	48.475	3.908	0.000	0.000	0.000	0.000
KTINGSGSPHSWAPNQQT	3864	47.897	1.789	0.000	0.000	0.000	0.000
KTINGSGSPHSLWKNQQT	3865	45.796	4.010	0.000	0.000	0.000	0.000
KTINGSGSPHSKARWQQT	3866	45.017	2.377	0.000	0.000	0.000	0.000
KTINGSGSPHSFRPNQQT	3867	44.801	9.191	0.000	0.000	0.000	0.000
KTINGSGSPHSKKVFQQT	3868	43.747	4.480	0.000	0.000	0.000	0.000
KTINGSLSPHFWAQNQQT	4013	43.190	2.041	0.000	0.000	0.000	0.000
KTINGSGSPHSYAFNQQT	3869	43.037	1.742	0.000	0.000	0.000	0.000
KTINHRISPHSKAQNQQT	4014	42.998	1.876	0.000	0.000	0.000	0.000
KTINGSGSPHSKACSRQT	3870	42.696	2.468	0.000	0.000	0.000	0.000
KTRRPSGSPHSKAQNQQT	4015	42.374	2.384	0.000	0.000	0.000	0.000
KYSAGSGSPHSKAQNQQT	3871	41.310	1.824	0.000	0.000	0.000	0.000
KTINGAYSPHRKAQNQQT	4016	40.969	1.283	0.000	0.000	0.000	0.000
KTINGSGSPHSKRLWQQT	3872	40.932	4.801	0.000	0.000	0.000	0.000
KTINGSGSPHSCSRNQQT	3873	40.372	4.293	0.000	0.000	0.000	0.000
KTINGSGSPHSRCPNQQT	3874	39.529	4.890	0.000	0.000	0.000	0.000
KTINGSGSPHSGACNQQT	3875	39.163	3.215	0.000	0.000	0.000	4733.916
KYYTGSGSPHSKAQNQQT	3876	38.777	1.199	0.000	0.000	0.000	0.000
KTINGSGSPHSKFRQQQT	3877	38.665	3.260	0.000	0.000	0.000	0.000
KTINGSGSPHSFPFNQQT	3878	38.584	4.693	0.000	0.000	0.000	0.000
KTINGSGSPHSFFGNQQT	3879	38.088	6.101	0.000	0.000	0.000	0.000
KTINGRRSPHGKAQNQQT	4017	37.728	3.259	0.000	0.000	0.000	0.000
KTINGSGSPHSMCQNQQT	3880	37.209	1.348	0.000	0.000	0.000	0.000
KTINGSGSPHSKLFWQQT	3881	37.022	4.178	0.000	0.000	0.000	0.000
KTINGSGSPHSKTRKQQT	3882	36.010	2.858	0.000	0.000	0.000	0.000
KTINGRTSPHRKAQNQQT	4018	35.792	5.682	0.000	0.000	0.000	0.000
KTINGSGSPHSGKRNQQT	3883	35.120	5.396	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQNFKR	3884	32.291	0.964	0.000	0.000	0.000	0.000
KTINGSGSPHFYRQNQQT	3885	31.724	9.342	0.000	0.000	0.000	0.000
KTINGSRSPHAWAQNQQT	4019	31.146	6.838	0.000	0.000	0.000	0.000
KTINGSGSPHCRVQNQQT	3886	31.043	1.203	0.000	0.000	0.000	0.000
KTINGSGSPHYGIQNQQT	3887	30.908	1.076	0.000	0.000	0.000	0.000
KTINKCLSPHSKAQNQQT	4020	30.667	5.097	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQRFKT	3888	30.363	0.139	0.000	0.000	0.000	0.000
KTINGSGSPHVNCQNQQT	3889	30.010	6.122	0.000	0.000	0.000	0.000
KTINGSGSPHSKPFRQQT	3890	29.842	8.700	0.000	0.000	0.000	0.000
KTINGSGSPHSLAWNQQT	3891	29.015	4.746	0.000	0.000	0.000	0.000
KTINGSGSPHSKRSYQQT	3892	28.973	2.116	0.000	0.000	0.000	0.000
KTINGSSSPHRCAQNQQT	4021	28.887	1.829	0.000	0.000	0.000	0.000

KTINGSGSPHWSYQNQQT	3893	28.607	3.751	0.000	0.000	0.000	0.000
KTINCRTSPHSKAQNQQT	4022	28.301	1.117	0.000	0.000	0.000	0.000
KTINGSGSPHRWLQNQQT	3894	28.147	6.882	0.000	0.000	0.000	0.000
KTIFDCGSPHSKAQNQQT	4023	27.844	1.602	0.000	0.000	0.000	0.000
KTINGSGSPHPSCQNQQT	3895	27.796	2.790	0.000	0.000	0.000	0.000
KTINGSGSPHSSWLNQQT	3896	27.318	3.271	0.000	0.000	0.000	0.000
KTINSPRSPHSKAQNQQT	4024	27.240	1.554	0.000	0.000	0.000	0.000
KPRFGSGSPHSKAQNQQT	3897	27.203	0.657	0.000	0.000	0.000	0.000
KWLTGSGSPHSKAQNQQT	3898	26.975	2.388	0.364	0.000	0.000	2578.486
KTINGSGSPHSKRRAQQT	3899	26.523	5.906	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQTCRT	3900	26.472	6.369	0.000	0.000	0.000	0.000
KTINGLDSPHRSRQNQQT	4025	26.403	0.321	0.000	0.000	0.000	0.000
KTINGSGSPHSKGCTQQT	3901	26.068	0.529	0.000	0.000	0.000	0.000
KTRTRSGSPHSKAQNQQT	4026	25.852	6.894	0.000	0.000	0.000	0.000
KTINGSGSPHVPWQNQQT	3902	25.294	3.435	0.000	0.000	0.000	0.000
KTINGSGSPHSKRYTQQT	3903	25.267	9.412	0.000	0.000	0.000	0.000
KTINGSISPHCPAQNQQT	4027	24.932	0.556	0.000	0.000	0.000	0.000
KTINGSGSPHSGCQNQQT	3904	24.818	1.981	0.000	0.000	0.000	0.000
KTINGSGSPHSFTPNQQT	3905	24.227	1.036	0.000	0.000	0.000	0.000
KTINGSGSPHSTTCNQQT	3906	23.771	3.315	0.000	0.000	0.000	0.000
KTINGSGSPHSKARMYQT	3907	23.424	0.313	0.000	0.000	0.000	0.000
KTINGLVSPHRKAQNQQT	4028	23.417	2.739	0.000	0.000	0.000	0.000
KTINGSGSPHPKRQNQQT	3908	23.055	2.355	0.000	0.000	0.000	0.000
KTINGSGSPHSKCFLQQT	3909	22.987	1.434	0.000	0.000	0.000	0.000
KTINGSGSPHWVPQNQQT	3910	22.907	3.219	0.000	0.000	0.000	0.000
KTINGSGSPHSFWSNQQT	3911	22.857	1.345	0.000	0.000	0.000	0.000
KRSYGSGSPHSKAQNQQT	3912	22.474	2.841	0.000	0.000	0.000	0.000
KYVFGSGSPHSKAQNQQT	3913	22.232	2.346	0.000	0.000	0.000	0.000
KTINGSGSPHSKFKNQQT	3914	21.951	1.074	0.000	0.000	0.000	0.000
KTINGSGSPHRIKQNQQT	3915	21.720	3.064	0.000	0.000	0.000	0.000
KTINGSGSPHSKAPRRQT	3916	21.645	3.940	0.000	0.000	0.000	0.000
KTINGSGSPHSFRYNQQT	3917	21.097	4.148	0.000	0.000	0.000	0.000
KTINGSGSPHSKMICQQT	3918	21.036	0.144	0.000	0.000	0.000	0.000
KTINGSGSPHLRWQNQQT	3919	21.014	9.649	0.000	0.000	0.000	0.000
KTINGSGSPHLPTQNQQT	3920	20.704	3.127	0.000	0.000	0.000	0.000
KTINGSGSPHSKWKSQQT	3921	20.390	1.239	0.000	0.000	4.904	0.163
KTINALRSPHSKAQNQQT	4029	20.053	1.655	0.000	0.000	0.000	0.000
KTINGSGSPHSYMRNQQT	3922	20.007	2.293	0.000	0.000	0.000	0.000
KTINGSGSPHSKAARRQT	3923	19.998	6.633	0.000	0.000	0.000	0.000
KTINGSGSPHLLCQNQQT	3924	19.796	3.484	0.673	0.000	0.000	1.309
KTINGSGSPHRCCQNQQT	3925	19.084	2.213	0.000	0.000	0.000	0.000
KTINGSGSPHLCVQNQQT	3926	19.030	1.428	0.000	0.000	0.000	0.000
KTINGSGSPHSKLTRQQT	3927	19.004	2.712	0.000	0.000	0.000	0.000
KTICGRGSPHSKAQNQQT	4030	18.923	2.171	0.000	0.000	0.000	0.000
KTTRKSGSPHSKAQNQQT	4031	18.849	2.617	0.000	0.000	0.000	0.000
KTINGSGSPHSKLCTQQT	3928	18.674	1.269	0.000	0.000	0.000	0.000
KKHLGSGSPHSKAQNQQT	3929	18.521	0.658	0.000	0.000	0.000	0.000
KTINGSGSPHSKIRGQQT	3930	18.150	1.584	0.000	0.000	0.000	0.000
KTMQRSGSPHSKAQNQQT	4032	18.020	3.159	0.000	0.000	0.000	0.000
KTINGSGSPHSYLVNQQT	3931	17.766	1.267	0.000	0.000	0.000	0.000
KTINGSGSPHQGCQNQQT	3932	17.676	1.037	0.000	0.000	0.000	0.000
KTINGSGSPHMAFQNQQT	3933	17.644	0.542	0.000	0.000	0.000	0.000
KTINGSGSPHSKACQFQT	3934	17.640	8.562	0.000	0.000	0.000	9.605
KTINGSGSPHSKWGLQQT	3935	17.543	2.639	0.000	0.000	0.000	0.000
KTINGSGSPHSKILRQQT	3936	17.419	2.546	0.000	0.000	0.000	0.000
KTINGSGSPHSFQINQQT	3937	17.418	0.269	0.308	0.000	1.568	0.000
KTINGSGSPHSKACISQT	3938	17.371	0.240	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQTHRT	3939	17.290	2.917	0.000	0.000	0.000	0.000

KTINGSGSPHSKALRCQT	3940	17.283	1.892	0.000	0.000	0.000	0.000
KTINGSGSPHSKAFYIQT	3941	17.172	0.239	0.000	0.000	0.000	0.000
KTINGSGSPHSKAHARQT	3942	17.075	1.800	0.000	0.000	0.000	0.000
KTINGSGSPHSLCLNQQT	3943	17.028	1.790	0.000	0.000	0.000	0.000
KTINGSGSPHSKAFVRQT	3944	16.935	1.985	0.000	0.000	0.000	0.000
KPPLGSGSPHSKAQNQQT	3945	16.897	0.805	0.000	0.000	0.000	0.000
KTINGSGSPHRPWQNQQT	3946	16.869	4.936	0.000	0.000	0.000	0.000
KPARGSGSPHSKAQNQQT	3947	16.793	1.391	0.000	0.000	0.000	0.000
KTINGSGSPHRPRQNQQT	3948	16.784	5.206	0.000	0.000	0.000	0.000
KTINGSGSPHSCPQNQQT	3949	16.701	1.776	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQFILT	3950	16.650	4.208	0.000	0.000	0.000	0.000
KTINGSSSPHWMAQNQQT	4033	16.635	2.390	0.000	0.000	0.000	0.000
KTRKRSGSPHSKAQNQQT	4034	16.603	2.075	0.000	0.000	0.000	0.000
KTINGSGSPHSVRYNQQT	3951	16.390	1.413	0.000	0.000	0.000	0.000
KSRRGSGSPHSKAQNQQT	3952	16.131	1.446	0.000	0.000	0.000	0.000
KTINGSGSPHSVRCNQQT	3953	15.860	3.912	0.000	0.000	0.000	0.000
KFFHGSGSPHSKAQNQQT	3954	15.412	0.897	0.000	0.000	0.000	0.000
KTINGSGSPHSKMPCQQT	3955	15.343	1.063	0.000	0.000	0.000	0.000
KTINGSGSPHSKKTSQQT	3956	15.244	1.344	0.000	0.000	0.000	0.000
KRYNGSGSPHSKAQNQQT	3957	15.160	0.806	0.000	0.000	0.000	0.000
KTINFTRSPHSKAQNQQT	4035	14.908	3.751	0.000	0.000	0.000	0.000
KTINGSGSPHSLPYNQQT	3958	14.792	2.048	0.000	0.000	0.000	0.000
KTINGSGSPHVYHQNQQT	3959	14.770	1.733	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQSRKT	3960	14.589	2.715	0.000	0.000	0.000	0.000
KTINGSGSPHSYTRNQQT	3961	14.535	1.986	0.000	0.000	0.000	0.000
KTINNLRSPHSKAQNQQT	4036	14.514	1.354	0.000	0.000	0.000	0.000
KTINGRPSPHGKAQNQQT	4037	14.442	0.705	0.000	0.000	0.000	0.000
KTINWSRSPHSKAQNQQT	4038	14.399	5.624	0.000	0.000	0.000	0.000
KTINGSGSPHLVYQNQQT	3962	14.196	1.045	0.000	0.000	0.000	0.000
KTINGTRSPHKKAQNQQT	4039	14.173	1.152	0.700	0.225	0.052	4.082
KTINGSGSPHSKALRWQT	3963	14.118	5.252	0.000	0.000	0.000	0.000
KTINGSGSPHYRYQNQQT	3964	14.107	1.027	0.000	0.000	0.000	0.000
KTINGSGSPHSWLKNQQT	3965	13.995	0.603	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQMQIT	3966	13.990	0.371	0.000	0.000	0.000	0.000
KTINGSVSPHCTAQNQQT	4040	13.502	2.955	0.000	0.000	0.000	0.000
KTINGSGSPHCPAQNQQT	3967	13.359	1.409	0.000	0.000	0.000	0.000
KTINGSGSPHSMCTNQQT	3968	13.114	0.392	0.000	0.000	0.000	0.000
KTINGSGSPHSPPDNQQT	3969	12.973	0.033	0.000	0.000	0.000	0.000
KTINGSGSPHSKRNYQQT	3970	12.781	5.528	0.000	0.000	0.000	0.000
KTTRCSGSPHSKAQNQQT	4041	12.639	8.168	0.000	0.000	0.000	0.000
KTKLCSGSPHSKAQNQQT	4042	12.570	2.139	0.000	0.000	0.000	0.000
KTINLGCSPHSKAQNQQT	4043	12.564	0.654	0.000	0.000	0.000	0.000
KTINGSGSPHRWTQNQQT	3971	12.490	0.844	0.000	0.000	0.000	0.000
KTISGHDSPHISGQYQQT	4044	12.395	0.420	0.000	0.000	0.074	1214.588
KTINGSGSPHSKACRLQT	3972	12.297	6.537	0.000	0.000	0.000	0.000
KTINGSGSPHPRKQNQQT	3973	12.249	3.248	0.000	0.000	0.000	0.000
KTINGSGSPHSKCSVQQT	3974	12.246	1.465	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQYVRT	3975	12.239	3.275	0.000	0.000	0.000	0.000
KTINGSGSPHSKARISQT	3976	12.142	1.565	0.000	0.000	0.000	0.000
KTINGRRSPHMKAQNQQT	4045	12.136	3.510	0.000	0.000	0.000	0.000
KTINGPWSPHRKAQNQQT	4046	12.103	0.434	0.000	0.000	0.000	0.000
KTINGSGSPHPFVQNQQT	3977	12.091	1.286	0.000	0.000	0.000	0.000
KTINGSGSPHSKLPKQQT	3978	11.856	0.274	0.000	0.000	0.000	0.000
KTINSCFSPHSKAQNQQT	4047	11.847	1.016	0.000	0.000	0.000	0.000
KTINGSGSPHSKSEQQQT	3979	11.785	1.769	0.000	0.000	0.000	0.000
KTINGSGSPHWVAQNQQT	3980	11.703	3.634	0.000	0.000	0.000	0.000
KTINGSGSPHSLYQNQQT	3981	11.590	1.503	0.000	0.000	0.000	0.000
KTINGSGSPHSKVRMQQT	3982	11.572	1.835	0.000	0.000	0.000	0.000

KTINYTRSPHSKAQNQQT	3983	11.514	0.431	0.000	0.000	0.000	0.000
KTIKRYGSPHSKAQNQQT	4048	11.461	2.022	0.000	0.000	0.000	0.000
KTINGSGSPHCALQNQQT	4693	11.404	3.867	0.000	0.000	0.000	0.000
KTINGSGSPHSSCTNQQT	3984	11.382	3.363	0.000	0.000	0.000	0.000
KTINGSGSPHSKNSRQQT	3985	11.280	1.093	0.000	0.000	0.000	0.000
KTINGSGSPHSKRKRQQT	3986	11.215	3.027	0.000	0.000	0.000	0.000
KTINGSGSPHLCTQNQQT	3987	11.176	2.489	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQSAKT	3988	11.162	4.200	0.000	0.000	0.000	0.000
KTINGSGSPHSTCLNQQT	3989	11.132	4.762	0.000	0.000	0.000	0.000
KTINGSGSPHSYARNQQT	3990	11.131	0.996	0.000	0.000	0.000	0.000
KTINGSGSPHSKQRPQQT	3991	11.130	2.347	0.000	0.000	0.000	0.000
KTINGSGSPHSKRVVQQT	3992	11.094	1.639	0.000	0.000	0.000	0.000
KRFSGSGSPHSKAQNQQT	3993	11.024	1.358	0.000	0.000	0.000	0.000
KTINGSGSPHKSGQNPQT	3994	11.014	11.790	0.000	0.000	0.000	0.000
KTINRYSSPHSKAQNQQT	4049	10.926	1.544	0.000	0.000	0.000	0.000
KTTGRSGSPHSKAQNQQT	4050	10.863	0.126	0.000	0.000	0.000	0.000
KTINGSGSPHSKALRHQT	3995	10.774	4.532	0.000	0.000	0.000	0.000
KTINGSGSPHSYYSNQQT	3996	10.680	2.856	0.000	0.000	0.000	0.000
KTINGSGSPHSLTCNQQT	3997	10.658	2.214	0.490	0.000	0.163	1.398
KTINGSGSPHSCQSNQQT	3998	10.631	1.468	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQSIKT	3999	10.544	1.355	0.000	0.000	0.000	0.000
KYSMGSGSPHSKAQNQQT	4000	10.478	1.587	0.000	0.000	0.000	0.000
KTINGSGSPHSKAKGWQT	4001	10.450	1.827	0.000	0.000	0.000	0.000
KTIVGSGSPHSKPQNQQT	4002	10.381	0.894	0.000	0.000	0.000	0.000
KTINGSGSPHFPFQNQQT	4003	10.322	3.715	0.000	0.000	0.000	0.000
KPFLGSGSPHSKAQNQQT	4004	10.318	1.328	0.000	0.000	0.000	0.000
KTINGSGSPHSKCTSQQT	4005	10.311	5.821	0.493	0.232	1.413	2.353
KTINRQFSPHSKAQNQQT	4051	10.275	4.480	0.000	0.000	0.000	0.000
KTINGSGSPHSVFENQQT	4006	10.218	0.224	0.000	0.000	0.000	0.000
KTINGSGSPHSKAKKVQT	4007	10.102	3.974	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQRCST	4008	10.084	0.762	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQFCLT	4009	10.065	3.371	0.000	0.000	0.000	0.000
KTINGSGSPHGRYQNQQT	4010	10.028	0.778	0.000	0.000	0.000	0.000

[0481] **Table 23** provides the peptide sequences of 43 matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the heart samples isolated, and that also demonstrated a 4-fold or greater fold-increase in expression in the heart relative to the AAV9 control. A number of the matured variants shown in **Table 23** also demonstrated increased expression in other tissues isolated from the NHPs, including the brain, muscle, and/or liver, and are therefore pan-tropic.

Table 23. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the heart of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Heart (NHP)	Brain (NHP)	DRG (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTITGHDSPHSKAQNQQT	4052	34.375	230.437	4.338	1.378	19.165	5.672	0.000
KTINGSGSPHKSGQYQQT	4053	33.208	851.414	8.704	17.754	17.342	9.915	12.911
KTINGSGSPHKSGQDQQT	4054	31.166	218.057	34.358	33.372	27.081	8.836	24.849
KTINGSGSPHKSGQIQQT	4055	27.293	201.467	48.033	12.706	17.874	13.192	10.912
KTINGSGSPHKSGRNQQT	4056	27.283	313.826	8.723	36.593	15.252	12.352	21.595
KTINGSGSPHKSGKNQQT	4057	25.992	230.621	6.343	97.671	15.369	7.226	31.282
KTIYGHDSPHSKAQNQQT	4058	25.673	269.879	3.694	8.391	11.895	6.197	0.000
KTINGSGSPHKSGQNQQS	4059	24.783	244.030	16.675	26.058	18.059	9.809	29.751
KTINGSGSPHKSGQNLQT	4060	24.464	392.519	15.629	0.371	29.977	18.332	30.446
KAINGHDSPHSKAQNQQT	4061	22.460	640.466	7.358	9.986	9.358	8.490	0.000

KTVNGHDSPHSKAQNQQT	4062	21.066	614.034	3.392	30.908	21.560	11.933	121.235
KTIKGHDSPHSKAQNQQT	4063	20.803	213.564	24.646	12.361	15.379	6.551	13.319
KSINGHDSPHSKAQNQQT	4064	20.698	246.819	7.592	28.235	11.773	6.888	280.630
KTINGSGSPHKSGQTQQT	4065	19.925	466.459	55.454	15.485	15.473	6.446	15.179
KTINGSGSPHKSGHNQQT	4066	19.548	287.922	12.159	20.851	17.821	10.084	21.011
KTFNGHDSPHSKAQNQQT	4067	19.301	239.922	9.109	17.215	12.193	6.413	30.747
KTINGSGSPHKSGLNQQT	4068	19.136	319.093	3.083	4.096	14.009	7.446	9.340
KTINGHDSPHSKALNQQT	4069	18.542	605.641	13.375	1.902	12.621	7.054	51.283
KTINGSGSPHKSGQNQLT	4070	18.454	317.452	33.967	28.952	18.533	8.992	36.272
KTLNGHDSPHSKAQNQQT	4071	18.236	195.734	19.341	9.266	25.732	13.333	0.000
KTINGSGSPHKSGQNQHT	4072	14.269	313.837	7.125	39.273	29.714	7.797	25.119
KTIDGHDSPHSKAQNQQT	4073	13.836	242.100	1.731	12.555	17.223	7.439	0.000
KTNNGHDSPHSKAQNQQT	4074	12.872	134.488	0.504	3.877	17.044	5.982	22.358
KTINGSGSPHKSGQKQQT	4075	12.357	323.373	10.936	1172.3	12.604	7.970	48.699
KTINGSGSPHKSGQNRQT	4076	11.563	145.363	36.865	3.855	11.403	7.667	16.860
KTINGSGSPHKSGQNQQN	4077	11.507	156.385	582.38	8.559	9.273	7.668	18.138
KTINGSGSPHKSGQNQQA	4078	11.313	135.164	12.425	12.699	9.714	6.077	17.265
KTINGHDSPHSKAHNQQT	4079	10.024	236.106	19.495	5.258	2.406	3.316	45.691
KTINGHDSPHSKAQNQQT	4080	8.954	186.839	9.457	5.507	5.929	3.651	31.453
KTINGSGSPHKSGQNQQP	4081	8.744	261.947	43.435	10.217	6.468	4.265	19.828
KTINGHDSPHCKAQNQQT	4082	8.417	15.165	0.887	2.368	3.328	0.771	148.172
KTINGHDSPHSKAQNQQS	4083	5.678	603.027	7.280	0.670	4.301	4.307	65.271
KTINGSGSPHKSGQNQQT	4084	5.586	115.994	28.397	4.326	5.307	3.569	24.908
KTINGHDSPDKSGQNQQT	4085	5.569	30.854	4.934	1.112	0.671	0.781	14.499
KPINGHDSPHKSGQNHQS	4086	5.203	36.266	0.000	0.258	4.478	0.521	28.786
KTSNGSGSPHKSGQNQQT	4087	4.746	197.282	4.177	4.466	3.972	7.425	75.623
KTVNGSGSPHKSGQNQQT	4088	4.610	200.076	2.739	2.873	2.725	3.478	43.548
KTINGHDSTHKSGHNQQT	4089	4.369	27.630	2.883	1.302	0.421	0.176	12.973
KTINGHDSPHSKAQNQQN	4090	4.271	319.610	1.163	5.173	3.406	4.995	50.220
KTIYGSGSPHKSGQNQQT	4091	4.140	110.329	2.603	2.545	4.488	4.110	29.293
KTINGLDSQHKSGQNQQT	4092	4.055	12.958	3.240	3.205	0.645	0.296	5.608

[0482] **Table 24** provides the peptide sequences of 14 matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the muscle samples isolated (e.g., quadriceps), and that also demonstrated a 4-fold or greater fold-increase in expression in the muscle relative to the AAV9 control. A number of the matured variants shown in **Table 24** also demonstrated increased expression in other tissues isolated from the NHPs, including the brain, heart, and/or liver, and are therefore pan-tropic.

Table 24. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the muscle (e.g., quadriceps) of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Muscle (NHP)	Brain (NHP)	DRG (NHP)	Heart (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTINGSGSPHKSGRNQQT	4056	36.593	313.826	8.723	27.283	15.252	12.352	21.595
KTIIGHDSPHSKAQNQQT	4095	27.271	341.528	5.423	26.154	18.305	6.293	0.000
KTIYGHDSPHSKAQNQQT	4058	8.391	269.879	3.694	25.673	11.895	6.197	0.000
KTINGSGSPHKSGQNQQS	4059	26.058	244.030	16.675	24.783	18.059	9.809	29.751
KTVNGHDSPHSKAQNQQT	4062	30.908	614.034	3.392	21.066	21.560	11.933	121.235
KTIKGHDSPHSKAQNQQT	4063	12.361	213.564	24.646	20.803	15.379	6.551	13.319
KSINGHDSPHSKAQNQQT	4064	28.235	246.819	7.592	20.698	11.773	6.888	280.630
KTINGSGSPHKSGHNQQT	4066	20.851	287.922	12.159	19.548	17.821	10.084	21.011

KTFNGHDSPHSKAQNQQT	4067	17.215	239.922	9.109	19.301	12.193	6.413	30.747
KTSNGHDSPHSKAQNQQT	4096	18.580	507.189	7.777	17.770	21.537	8.789	70.219
KTINGHDSPHSKAQNQQT	4080	5.507	186.839	9.457	8.954	5.929	3.651	31.453
KTINGSGSPHKSGQNQQT	4084	4.326	115.994	28.397	5.586	5.307	3.569	24.908
KTINGHDSPHSKAQNQQN	4090	5.173	319.610	1.163	4.271	3.406	4.995	50.220
KTINGSGSPHSKAQNRRR	4097	4.237	8.348	0.291	0.636	1.597	5.396	158.853

[0483] Additional variants were identified following generation and screening in NHPs that had the following properties. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4253, 4281, 4290-4295, 4304, 4305, 4320, 4328-4335, 4337-4340, 4353, 4355, 4369, 4387, 4421, 4424-4428, 4430, 4432, 4433, 4435, 4436-4449, 4452, 4455, 4476, 4483, or 4484 had a raw virus count 10 or greater, a CV of less than 1 for the brain samples isolated from the NHPs, demonstrated a 50-fold or greater increase in expression in the brain of mice and NHPs relative to AAV9, and demonstrated 2-fold or less expression in the liver and DRG of NHPs relative to AAV9. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4098-4105, 4254-4280, 4282-4289, 4296-4303, 4306-4327, 4336, 4341-4352, 4354, 4356-4420, 4422, 4423, 4425, 4429, 4431, 4434, 4444, 4450, 4451, 4453, 4454, 4456-4475, 4477-4482, or 4485 had a CV of less than 1 in across the brain samples isolated from the NHPs and demonstrated a 100-fold or greater increase in expression in the brain of NHPs relative to AAV9. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4102 and 4106-4252 had normalized virus counts of greater than or equal to 0.01, a CV of less than 1 across the liver RNA samples isolated from the NHPs, and demonstrated a 20-fold or greater increase in expression in the liver of NHPs relative to AAV9. TM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NO: 4105 had a raw virus count 9.9 or greater, a CV of less than 1 across the muscle samples isolated from the NHPs, and 5-fold or greater increase in expression in the muscle of the NHPs relative to AAV9. TM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NO: 4105 also had a raw virus count 9.9 or greater, a CV of less than 1 across the samples isolated from the heart of the NHPs, and 5-fold or greater increase in expression in the heart of the NHPs relative to AAV9.

[0484] These data demonstrate that following two maturation approaches, matured TTM-001 and TTM-002 capsid variants (AAV9 capsid variants) with loop IV modifications were generated with significantly enhanced CNS tropism over wild-type AAV9 controls in both NHPs and mice, while also exhibiting de-targeting in peripheral tissues (e.g., the liver and DRG). These resulting matured variants therefore demonstrated cross-species CNS tropism in both NHPs and mice. Matured TTM-001 and TTM-002 capsid variants with liver-specific tropism were also generated with at least 10 times the expression compared to wild-type AAV9 in the liver of NHPs. Several matured variants were also generated with increased expression in the heart and skeletal muscle (e.g., quadriceps) relative to wild-type AAV9 in NHPs.

Example 5. Evaluation of TTM-001 and TTM-002 AAV capsid variants in Diverse Primate Species

[0485] This Example evaluates the tropism and cross-species compatibility of the TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variants in two diverse primate species, marmosets (*Callithrix jacchus*) and African green monkeys (*Chlorocebus sabaeus*), as compared to their tropism in cynomolgus macaques (*Macaca fascicularis*) provided in Example 1. The cross-species compatibility and tropism of an AAV9 capsid variant comprising the amino acid sequence of SPHKYG (SEQ ID NO: 966) was also investigated in this example. The amino acid and DNA sequences of TTM-001 and TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0486] To investigate tropism in African green monkeys, AAV particles comprising the TTM-001 capsid variant, the TTM-002 capsid variant, an AAV9 capsid variant comprising SEQ ID NO: 966, or an AAV9 control under the control of a synapsin promoter, were intravenously injected into NHPs (n=2, 3-12 years of age) at a dose of 2E13 vg/kg. After 14-days in life, the brains and tissues (liver, DRG, quadriceps, and heart) of the NHPs were collected and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the AAV9 wild-type control.

[0487] To investigate tropism in marmoset monkeys, AAV particles comprising the TTM-001 capsid variant, the TTM-002 capsid variant, an AAV9 capsid variant comprising SEQ ID NO: 966, or an AAV9 control, were intravenously injected into NHPs (n=2, >10 months of age) at a dose of 2E13 vg/kg (8.75E12 vg/mL). After 28-days in life, the brains and tissues (liver quadriceps, and heart) of the NHPs were collected and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the AAV9 wild-type control.

[0488] As provided in **Table 25** (African green monkeys) and **Table 26** (marmosets), both the TTM-001 and TTM-002 capsid variants demonstrated increased CNS tropism in diverse primate species. The TTM-001 capsid variant demonstrated a 73.6-fold increase in expression relative to AAV9 in the brain of cynomolgus macaques (**Table 14**, Example 1), a 43.5-fold increase in expression relative to AAV9 in the brain of African green monkeys, and a 703.3-fold increase in expression relative to AAV9 in the brain of marmosets. The TTM-002 capsid variant demonstrated a 62.6-fold increase in expression relative to AAV9 in the brain of cynomolgus macaques (**Table 14**), a 13.8-fold increase in expression relative to AAV9 in the brain of African green monkeys, and a 366.6-fold increase in expression relative to AAV9 in the brain of marmosets. Both TTM-001 and TTM-002 led to a significant increase in expression relative to AAV9 in the heart of both African green monkeys and marmosets (**Table 25** and **Table 26**). The AAV9 capsid variant comprising SEQ ID NO: 966 also demonstrated in increase in expression relative to AAV9 in the brain and heart of both African green monkeys and marmosets. Furthermore, TTM-001, TTM-002, and the AAV9 capsid variant comprising SEQ ID NO: 966, also all led to increased expression in the brain of both BALB/c

and C57Bl/6 mice (**Table 16**, Example 1), demonstrating an average fold change in expression relative to AAV9 across both species of mice of 63.1, 66.8, and 126.97, respectively.

Table 25. NGS-fold enrichment of TTM-001 (comprises SEQ ID NO: 941), TTM-002 (comprises SEQ ID NO: 2), and an AAV9 capsid variant comprising SEQ ID NO: 966 in African green monkeys

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9					
		Brain	DRG	Heart	Liver DNA	Liver RNA	Muscle
SPHSKA	941	43.525	1.010	184.789	0.242	1.547	1.715
HDSPHK	2	13.779	0.678	35.991	0.084	0.087	0.144
SPHKYG	966	9.805	0.071	44.865	0.085	0.136	0.234

Table 26. NGS-fold enrichment of TTM-001 (comprises SEQ ID NO: 941), TTM-002 (comprises SEQ ID NO: 2), and an AAV9 capsid variant comprising SEQ ID NO: 966 in marmosets

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9				
		Brain	Heart	Liver DNA	Liver RNA	Muscle
SPHSKA	941	703.610	48.979	0.268	0.779	0.425
HDSPHK	2	366.625	18.572	0.075	0.276	0.229
SPHKYG	966	150.209	17.232	0.045	0.014	0.146

[0489] Taken together, these data demonstrate that the AAV9 capsid variants of TTM-001 and TTM-002 demonstrated increased CNS tropism relative to the AAV9 control in the CNS across three diverse primate species and two species of mice, providing evidence of strong cross-species capacity. The AAV9 capsid variant comprising the amino acid sequence of SEQ ID NO: 966 also demonstrated strong CNS expression relative to the AAV9 control in two species of NHPs and two species of mice, also showing strong cross-species capacity.

Example 6. Advanced maturation of TTM-002 capsid variant in mice

[0490] This Example describes additional maturation of the TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variant in mice. In order to mature the TTM-002 capsid variant, sets of three contiguous amino acids were randomized across the mutagenesis region in TTM-002 sequence, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 982. Unlike the maturation performed in in Example 3, where the SPH motif that was observed in the AAV capsid variants that demonstrated the greatest fold-enrichment in the NHP brain relative wild-type AAV9 was not disrupted, in the maturation approach used in this Example, the SPH motif was not held constant to further explore the role of this motif in the capsid variant. The matured TTM-002 capsid variants that resulted from the maturation approach were pooled together for subsequent testing and characterization in mice.

[0491] The library of matured AAV capsid variants generated from the TTM-002 matured AAV capsid variant were intravenously injected into the tail vein of three CD-1 Outbred mice (Charles River; 6-8 weeks of age) at a dose of 1.0 x 10^{12} VG/dose. After about 28 days in life, the brains of the mice were isolated, and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the corresponding TTM-002 non-matured control, and the peptides comprised within the variants were identified. Variants were filtered by those with a raw virus count in the sample above 10 and a coefficient of variance (CV) that was greater than 1 (identifies the peptides/variants reliably detected in the majority of the samples isolated from the three mice).

[0492] Following the advanced maturation screen and filtering of the variants, 1302 variants demonstrated an increase in expression relative to the non-matured TTM-002 capsid variant in the brain of the outbred mice. Of the 1302 variants with improved tropism relative to the non-matured TTM-002, 1283 comprised the SPH motif in the same position as the non-matured TTM-002 capsid variant (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 982). Mutations in the region of the SPH motif present in the non-matured TTM-002 capsid variant only consistently appear in those variants with a fold change of 0.2 or 0.1 or lower relative to the non-matured TTM-002 control in the brain of the mice. This indicates that the SPH motif may be important to the increased brain tropism that observed for the TTM-002 capsid variant. In instances when the SPH motif was disrupted, the fold change of the matured variants of TTM-002 decreased considerably in relation to the non-matured TTM-002 variant which comprised the SPH motif.

Example 7. Tropism of TTM-002 AAV capsid variant

[0493] This Example further investigates the tropism and CNS cells transduced by the TTM-002 capsid variant (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2), as outlined in Table 3 above. The amino acid and DNA sequences of TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0494] AAV particles were generated with the TTM-002 capsid variant encapsulating a GFP transgene (AAV_TTM-002.GFP) or a payload driven by a heterologous CBA constitutive promoter (AAV_TTM-002.Payload).

[0495] Two tandem single cell RNA sequencing runs (scRNA-Seq) of mouse cells derived from the midbrain area were performed. In the first run, cells were pooled from two mice at day 28 post treatment with AAV_TTM-002.Payload particles. In the second run we treated with AAV_TTM-002.GFP particles, in the same manner but without xenografts. Orthotopic xenografts of MDA-MB-361-Luc#1 high passage cells grown as tumorspheres (in tumorsphere media; Sigma # C-28070) were injected (250,000 cells/2µL/mouse) intracranially into 2-month old female SCID CB17 (Mutation: Icr-Prkdcscid/IcrIcoCrl) congenic immunodeficient mice (Charles River Laboratories). The injections

were 2.5mm (lateral), -1mm (posterior) with respect to bregma, lowered -3mm ventral and raised +.5 mm dorsal to a final -2.5mm ventral position. Two days later, dilutions of the AAV_TTM-002.Payload particles (run 1), or in the case without xenografts, dilutions of AAV_TTM-002.GFP particles (run 2) were prepared. IV injections of 100µL (2.5e11 VG/animal) of the AAV_TTM-002.payload particles or AAV_TTM-002.GFP particles were administered through the tail veins of mice (n=5 mice per groups). At 7 days post-injection, mice from run 1 were imaged in an AmiHTX (Spectral Imager) for bioluminescence of the human tumor cells due to expression of luciferase in response to intraperitoneal luciferin injections.

[0496] At 28 days post-injection with the AAV_TTM-002.payload particles or AAV_TTM-002.GFP particles, two mice from each run were necropsied, brain samples were isolated, and the midbrain was dissected and isolated. The midbrain samples were then exposed to a cold protease inhibitor (Creative Biomart #NATE-0633) and were dissociated at 6 degrees centigrade. For the samples collected from the mice of run 1 (AAV_TTM-002.Payload particles), myelin depletion was performed (Miltenyi, #130-096-731), cells were filtered through a 40µM mesh to filter out neurons) and loaded on a 10X chromium G chip. scRNA-Seq was performed (10X Genomics) and samples were sequenced on a NextGen500 Sequencing machine (Illumina). For the samples collected from run 2 (AAV_TTM-002.GFP particles and no xenografts), the cells were not myelin depleted or filtered through 40µM mesh to include neurons. The cells isolated after run 2 were FACS sorted for GFP+/7AAD- (live GFP+ cells). The resultant cells were loaded on a 10X chromium G chip and the scRNA-Seq was run and processed (10X Genomics).

[0497] For run 1, the scRNA-Seq data was filtered to include cells with only greater than 1000 genes per cell and less than 5000, and less than 20 percent mitochondrial gene expression. For run 2, the scRNA-Seq data was filtered to include cells with only greater than 200 genes per cell and less than 5000, and less than 20 percent mitochondrial gene expression. The data were normalized, scaled, and integrated into one combined dataset. Clusters were generated with a resolution of 0.3 and each cluster identity was determined using a panel of cell type specific genes (e.g., as described in Brown *et al.*, 2021. "Deep Parallel Characterization of AAV Tropism and AAV-Mediated Transcriptional Changes via Single-Cell RNA Sequencing". *Front. Immunol.* 12:730825; the contents of which are hereby incorporated by reference in its entirety). The percentage of GFP sorted cells per cluster was calculated as was the percentage of payload expressing genes per cluster as parallel measures of TTM-002 transduction.

[0498] For payload expressing cells, endothelial cells had the highest proportion of payload positive cells, followed by astrocytes (**Table 27**). For GFP+ sorted cells, endothelial cells had the highest proportion of GFP positive cells, and astrocytes were the third highest cell type when sorting by proportion of cells expressing GFP (**Table 27**). These data indicate TTM-002 transduction exhibits an endothelial and astrocytic tropism. Furthermore, the astrocytic cluster had the second highest level of expression of Olig2 (oligodendrocytes demonstrated the greatest Olig2 expression). IHC staining

was performed on brain samples isolated from AAV_TTM-002.GFP infected mice and demonstrated that GFP co-localized with some but not all Olig2+ cells. No co-staining was observed with mylein basic protein (MBP), a marker of oligodendrocytes. Co-staining with GFP was also not observed in NeuN positive cells (neurons), GFAP positive cells (astrocytes), and Iba1 positive cells (microglia). GFP staining was observed throughout the sagittal section of the mouse brain, which was demonstrative of increased staining in the midbrain. The GFP expressing cells observed did not have a bipolar morphology like oligodendrocyte progenitor (OPC) cells and therefore, together with the scRNA-Seq data, these results indicated that at day 28 post AAV treatment, Olig2+ astrocytes in the midbrain are being transduced by AAV particles comprising a TTM-002 capsid, in a cell type specific tropism.

Table 27. Quantification of payload positive cells and GFP positive cells

Cluster Identity	% Payload Cells/Cluster	Cluster Identity	% GFP Cells/Cluster
Endothelial-2	6.58	Endothelial-2	6.58
Astrocyte	4.50	Endothelial-1	3.45
Pericytes	4.23	Vascular and leptomeningeal Cells (VLM)	2.38
Mature Oligos	3.85	Astrocyte	2.37
Endothelial-1	3.09	Vascular smooth muscle cells (VSC)	1.03
Committed Oligos	1.90	Pericytes	0.77
Vascular smooth muscle cells (VSC)	1.72	Microglia	0.00
Microglia	0.40	Committed Oligos	0.00
Macrophages	0.00	Macrophages	0.00
Vascular and leptomeningeal cells (VLM)	0.00	Oligodendrocytes	0.00
Oligodendrocytes	0.00	Committed Oligos-2	0.00
Committed Oligos-2	0.00	Mature Oligos	0.00

Example 8. Individual Capsid Characterization of TTM-001, TTM-002, TTM-003, TTM-006, and TTM-027 in NHPs

[0499] This example describes the transduction level, tropism, ability to cross the blood brain barrier, and overall spatial distribution in the central nervous system (CNS) and peripheral tissues of the AAV capsid variants TTM-002 (SEQ ID NO: 982 (amino acid) and SEQ ID NO: 984 (DNA), comprising SEQ ID NO: 2), TTM-001 (SEQ ID NO: 981 (amino acid) and SEQ ID NO: 983 (DNA), comprising SEQ ID NO: 941); TTM-003 (SEQ ID NO: 36 (amino acid) and SEQ ID NO: 12 (DNA), comprising SEQ ID NO: 3589), TTM-006 (SEQ ID NO: 39 (amino acid) and SEQ ID NO: 15 (DNA), comprising SEQ ID NO: 3241), and/or TTM-027 (SEQ ID NO: 4 (amino acid) and SEQ ID NO: 5 (DNA), comprising SEQ ID NO: 3272), relative to AAV9 following intravenous administration in African green monkeys (*Chlorocebus sabaeus*), marmosets (*Callithrix jacchus*), and/or cynomolgus macaques (*Macaca fascicularis*).

A. Evaluation of TTM-002 in African Green Monkeys (Chlorocebus sabaeus)

[0500] AAV particles were generated with the TTM-002 capsid variant or the AAV9 capsid control which comprised a self-complementary viral genome encoding an histone H2b protein with an HA tag driven by a ubiquitous CBA promoter. The AAV particles comprising the TTM-002 capsid variant or the AAV9 capsid control were administered to the NHPs (n=2) intravenously at a dose of 1e12 VG/kg or 1e13 VG/kg. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-qPCR and viral DNA (biodistribution) by ddPCR.

[0501] As shown in Table 28, the TTM-002 capsid variant resulted in increased brain biodistribution in all brain regions investigated as compared to AAV9 at both doses tested. The TTM-002 capsid variant also led to increased transgene expression in the brain relative to AAV9 at both doses tested (Table 29). In the spinal cord, the TTM-002 capsid variant distributed to the cervical spinal cord and the spinal cord ventral horn at a higher level relative to AAV9 (Table 28) and it mediated higher transgene expression than AAV9 in both the full spinal cord and the ventral horn (Table 29). When administered at a dose of 1e13 VG/kg, TTM-002 delivered 1-2 viral genomes (VGs) per cell on average across multiple brain areas, outperforming AAV9 by 4- to 24-fold, and was capable of expressing 16- to 186-fold more transgene RNA (Table 28 and Table 29). The TTM-002 capsid variant exhibited lower biodistribution (Table 28) and transgene expression (Table 29) in the DRG relative to AAV9, indicating that TTM-002 capsid variant was detargeted in the DRG relative to AAV9. Similar expression and distribution were observed by immunohistochemistry performed on these CNS tissues. High-throughput analysis of immunohistochemistry stainings indicated that TTM-002 was capable of targeting upwards of 50% of cells in the brain (**FIG. 5A**), including both astrocytes and neurons (**FIG. 5B**). In contrast with the tropism in mice as provided in Example 9, TTM-002 demonstrated a bias towards Sox9(+) astrocytes over neurons, labeled with either NeuN or SMI311.

[0502] Distribution and transgene expression was also measured in the peripheral tissues of the liver, heart, and quadriceps. In the liver, TTM-002 capsid variant exhibited lower biodistribution (Table 28) and transgene expression (Table 29) relative to AAV9, indicating that TTM-002 capsid variant was detargeted in the liver relative to AAV9. In the heart, the TTM-002 capsid variant exhibited comparable levels of biodistribution relative to AAV9 (Table 28), but increased transgene expression relative to AAV9 (Table 29). In the quadriceps, TTM-002 capsid variant exhibited lower biodistribution (Table 28) and lower transgene expression (Table 29), relative to AAV9. Similar expression and distribution were observed by immunohistochemistry performed on these peripheral tissues.

Table 28: Quantification of viral genome copies per diploid genome (biodistribution) by ddPCR following intravenous administration of AAV particles comprising a TTM-002 capsid

Tissue	1e12 VG/kg	1e13 VG/kg

	AAV9 (VG copies/ diploid genome)	**TTM-002** (VG copies/ diploid genome)	**TTM-002 relative to AAV9**	**AAV9** (VG copies/ diploid genome)	**TTM-002** (VG copies/ diploid genome)	**TTM-002 relative to AAV9**
Putamen	0.03	0.37	12.3	0.26	2.4	9.2
Caudate	0.02	0.58	29	0.14	2.1	14.7
Thalamus	0.06	0.21	3.5	0.25	1.0	4
Hippocampus	0.03	0.29	9.7	0.16	1.56	9.8
Substantia Nigra	0.05	0.34	6.8	0.37	1.38	3.7
Motor Cortex	0.03	0.56	19	0.27	2.4	8.9
Frontal Cortex	0.04	0.67	17	0.20	3.6	18
Temporal Cortex	0.03	0.31	10	0.11	2.67	24
Cerebral Cortex	0.008	0.08	10	0.03	0.16	5.3
Dentate Nucleus	0.06	0.10	1.7	0.32	3.21	10
Cervical Spinal Cord	0.03	0.12	4	0.19	0.91	4.8
Thoracic Spinal Cord	0.04	0.03	0.75	0.36	0.38	1.1
Lumbar Spinal Cord	0.04	0.03	0.75	0.29	0.37	1.3
C5 Ventral Horn	0.04	0.25	6.3	0.29	2.2	7.6
L5 Ventral Horn	0.06	0.28	4.7	0.31	1.9	6.1
Cervical DRG	0.07	0.01	-7	0.81	0.36	-2.3
Thoracic DRG	0.06	0.01	-6	1.31	0.43	-3
Lumbar DRG	0.07	0.01	-7	1.31	0.57	-2.3
Liver	9.5	1.2	-7.9	127	7.7	-16.5
Heart	0.6	0.7	1.2	5.4	5.4	1
Quadriceps	0.2	0.06	-3.3	1.7	0.6	-2.8

Table 29: Quantification of transgene mRNA by RT-qPCR following intravenous administration of AAV particles comprising a TTM-002 capsid

Tissue	**1e12 VG/kg**			**1e13 VG/kg**		
	AAV9 (transgene mRNA fold over housekeeping gene) (2^{-dCT})	**TTM-002** (transgene mRNA fold over housekeeping gene) (2^{-dCT})	**TTM-002 relative to AAV9**	**AAV9** (transgene mRNA fold over housekeeping gene) (2^{-dCT})	**TTM-002** (transgene mRNA fold over housekeeping gene) (2^{-dCT})	**TTM-002 relative to AAV9**
Putamen	0.02	0.3	15	0.09	4.22	47
Caudate	0.02	0.8	40	0.11	4.29	39
Thalamus	0.04	0.4	10	0.4	5.8	14.5
Hippocampus	0.02	0.4	20	0.1	4.3	43
Substantia Nigra	0.1	1.2	12	0.3	11.6	39
Motor Cortex	0.08	5.00	63	0.36	21.8	61
Frontal Cortex	0.04	3.1	78	0.3	27.7	92
Temporal Cortex	0.02	0.8	40	0.1	26.9	27
Cerebral Cortex	0.04	1.1	28	0.2	17.4	87

Dentate Nucleus	0.3	0.9	3	1.8	42.0	23
Cervical Spinal Cord	0.2	2.0	10	0.8	20.2	25
Thoracic Spinal Cord	0.13	0.25	1.9	0.7	4.8	6.9
Lumbar Spinal Cord	0.4	0.5	1.3	2.2	9.2	4.2
C5 Ventral Horn	0.2	1.4	7	1.7	33	19
L5 Ventral Horn	1.1	3.4	3.1	12.4	102	8.2
Cervical DRG	3.6	1.2	-3	63.1	15.9	-4
Thoracic DRG	1.8	1.3	-1.4	43.9	15.7	-2.8
Lumbar DRG	1.9	1.0	-1.9	34.9	27.6	-1.3
Liver	0.88	0.25	-3.5	2.2	0.97	-2.3
Heart	8.7	42	4.8	110	363	3.3
Quadriceps	9.7	1.1	-8.3	59	21	-2.8

[0503] Taken together, these data demonstrate that TTM-002 is an enhanced CNS tropic capsid in NHPs (African green monkeys) that can infect non-neuronal cells. TTM-002 was also detargeted in the DRG and liver relative to AAV9, but showed increased transgene expression in the heart relative to AAV9. Additionally, the TTM-002 capsid variant was able to successfully penetrate the blood brain barrier following intravenous injection.

B. Evaluation of TTM-001 and TTM-002 in Marmosets (Callithrix jacchus)

[0504] AAV particles were generated with the TTM-002 capsid variant, the TTM-001 capsid variant, or the AAV9 capsid control, each of which comprised a self-complementary viral genome encoding a histone H2b protein with an MYC tag (TTM-002 capsid variant), His tag (TTM-001 capsid variant), or HA tag (AAV9 control capsid) driven by a ubiquitous CAG promoter. The AAV particles comprising the TTM-002 capsid variant, the TTM-001 capsid variant, or the AAV9 capsid control were administered to the marmosets (*Callithrix jacchus*) (n=3) intravenously in a single solution, at the doses indicated in Table 53. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-qPCR, protein expression by IHC, and viral DNA (biodistribution) by ddPCR. Data were then normalized to the dose of each viral vector in the dosing solution.

Table 53. Titer of the AAV particles comprising the various capsids in solution dosed in marmosets

Capsid Variant	Actual Titer Dosed	Ratio of Capsid Variant to AAV9
TTM-001	1.44×10^{11} vg/mL	0.34
AAV9	4.00×10^{11} vg/mL	1.0
TTM-002	4.17×10^{11} vg/mL	1.0

[0505] As shown in Table 54, both the TTM-001 and TTM-002 capsid variants demonstrated increased biodistribution in the caudate and motor cortex in the brain of the marmosets relative to the AAV9 control. The TTM-001 and TTM-002 capsid variants also led to increased transgene expression (Table 55) in the caudate and motor cortex in the brain of the marmosets. In fact, biodistribution and transgene expression were increased over 100-400 fold for both TTM-001 and TTM-002 in the brain relative to AAV9. TTM-002 delivered upwards of 280-fold more viral genomes and expressed 500-fold higher transgene RNA levels than AAV9 (Tables 54 and 55). Similar expression and distribution was observed by immunohistochemistry. More specifically, staining for TTM-001 and TTM-002 was detected in the mid-brain, caudate, putamen, thalamus, and cerebellum, and this staining was increased for both capsid variants in each of these brain tissues relative to AAV9. Staining for TTM-001 and TTM-002 was also observed in the molecular and granule layer of the cerebellum.

[0506] Biodistribution and transgene expression were also measured in the peripheral tissues of the liver, heart, and quadriceps. In the liver, the TTM-002 capsid variant exhibited lower biodistribution (Table 54) and transgene expression (Table 55) relative to AAV9, indicating that the TTM-002 capsid variant was detargeted in the liver relative to AAV9 in marmosets. The TTM-001 capsid variant demonstrated comparable biodistribution and transgene expression in the liver (Table 54 and Table 55) as well as comparable transgene expression in the heart and muscle (Table 55) relative to AAV9. Both TTM-001 and TTM-002 led to decreased biodistribution (Table 54) relative to AAV9 in the heart and muscle, and TTM-002 also resulted in lower transgene expression in the heart and muscle relative to AAV9 (Table 55).

Table 54. Quantification of viral genome copies per diploid genome (biodistribution) by ddPCR following intravenous administration of AAV particles comprising a TTM-001 capsid or a TTM-002 capsid normalized to the actual titer of the viral vector in the dosing solution (vg/dg = viral genome copies/ diploid genome)

	Tissue									
	Caudate		Motor Cortex		Heart		Muscle		Liver	
Capsid	vg/dg	vg/dg relative to AAV9	vg/dg	vg/dg relative to AAV9	vg/dg	vg/dg relative to AAV9	vg/dg	vg/dg relative to AAV9	vg/dg	vg/dg relative to AAV9
TTM-001	1.67	142.70	2.69	124.06	0.28	0.53	0.08	0.39	14.86	0.99
TTM-002	3.55	294.36	5.80	264.86	0.33	0.69	0.08	0.32	6.92	0.49
AAV9	0.01	1.00	0.02	1.00	0.48	1.00	0.23	1.00	13.79	1.00

Table 55. Quantification of transgene mRNA by RT-qPCR following intravenous administration of AAV particles comprising a TTM-001 capsid or a TTM-002 capsid normalized to the actual titer of the viral vector in the dosing solution (mRNA = transgene mRNA fold over housekeeping gene; rel. to AAV9= transgene mRNA fold over housekeeping gene relative to AAV9)

Capsid	Tissue									
	Caudate		Motor Cortex		Heart		Muscle		Liver	
	mRNA	rel. to AAV9	mRNA	rel. to AAV9	mRNA	rel. to AAV9	mRNA	rel. to AAV9	mRNA	rel. to AAV9

TTM-001	17.56	594.71	27.80	586.23	16.05	1.40	0.26	1.19	3.23	1.93
TTM-002	14.21	479.39	19.73	410.40	2.78	0.27	0.06	0.46	0.62	0.36
AAV9	0.03	1.00	0.05	1.00	12.67	1.00	0.15	1.00	1.85	1.00

These data in marmosets for TTM-002 were similar to those observed in African green monkeys, further demonstrating cross-species compatibility of the TTM-002 capsid variant. Taken together, these data demonstrate that TTM-001 and TTM-002 are enhanced CNS tropic capsids in marmosets. TTM-002 was also detargeted in the liver, heart, and muscle relative to AAV9 in marmosets, where TTM-001 demonstrated comparable biodistribution and/or transgene expression in the liver, heart, and muscle compared to AAV9. Additionally, the TTM-001 and TTM-002 capsid variants were able to successfully penetrate the blood brain barrier following intravenous injection.

C. Evaluation of TTM-001, TTM-002, TTM-003, TTM-006, and TTM-027 in Cynomolgus Macaques (Macaca fascicularis)

[0507] AAV particles were generated with the TTM-002 capsid variant, the TTM-001 capsid variant, the TTM-003 capsid variant, the TTM-006 capsid variant, the TTM-027 capsid variant, or the AAV9 capsid control which comprised a self-complementary viral genome encoding a histone H2b protein driven by a ubiquitous CAG promoter. The AAV particles comprising the TTM-002 capsid variant, the TTM-001 capsid variant, the TTM-027 capsid variant or the AAV9 capsid control were administered to a first group of male cynomolgus macaques (*Macaca fascicularis*; 4-6 kg body weight; over 2 years old) intravenously in a single solution, at a total dose per group of 2e13 VG/kg or a dose per capsid of 4e12 VG/kg. The AAV particles comprising the TTM-003 capsid variant or the TTM-006 capsid variant were administered to a second group of male cynomolgus macaques (*Macaca fascicularis*; 4-6 kg body weight; over 2 years old) intravenously in a single solution, at a total dose per group of 2e13 VG/kg or a dose per capsid of 4e12 VG/kg. The in-life period was 28 days for both groups, and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-qPCR; protein expression by IHC/chromogenic staining (e.g., DAB staining for percent of DAB+ cells indicating the percent of cells transduced); percent positive cells (e.g., neurons, motor neurons, and astrocytes) in brain and spinal cord regions by immunofluorescence microscopy; and viral DNA (biodistribution) by ddPCR.

[0508] As shown in Table 56, TTM-001, TTM-002, TTM-003, TTM-006, and TTM-027 demonstrated increased CNS transduction and/or biodistribution in several regions of the brain (greater than 30% of cells transduced observed in several regions for multiple capsid variants) and spinal cord of the cynomolgus macaques after intravenous administration at a relatively low dose of 4e12 vg/kg. More specifically, TTM-003 was capable of transducing up to 40% of cells in the caudate, putamen, and cortex; TTM-027 was capable of transducing up to 30% of cells in the caudate,

putamen, and cortex; and both showed improved delivery to the spinal cord relative to AAV9 and TTM-002, at a dose of 4e12 vg/kg.

[0509] Cell-typing was also performed in the putamen, substantia nigra, and temporal cortex of the brain to measure the percent of neurons (NeuN+ cells) and astrocytes (Sox9+ cells) that were transduced by the AAV particles comprising the TTM-003 and TTM-027 capsid variants or the AAV9 controls (Table 57). TTM-003 was capable of transducing up to 47.8% of neurons and 79.5% of astrocytes in the putamen; 25.3% of neurons and 87.5% of astrocytes in the temporal cortex; and 33.7% of neurons and 18.6% of astrocytes in the substantia nigra (Table 57). TTM-027 was capable of transducing up to 27% of neurons and 41.8% of astrocytes in the putamen; 12.3% of neurons and 51.4% of astrocytes in the temporal cortex; and 21.1% of neurons and 12.2% of astrocytes in the substantia nigra (Table 57). Co-localization of TTM-027 and TTM-003 with motor neurons (ChAT+ cells) was also observed in the spinal cord by immunofluorescence microscopy (Table 57). Across the lumbar, cervical, and thoracic spinal cord, TTM-003 was capable of transducing 78.5% of motor neurons and TTM-027 was capable of transducing 53.5% of motor neurons (Table 57).

[0510] In the peripheral tissues, all of the TTM-001, TTM-002, TTM-003, TTM-006, and TTM-027 capsid variants tested exhibited robust liver de-targeting relative to AAV9 (Table 58).

Table 56. Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR, transgene mRNA by RT-qPCR (mRNA = transgene mRNA fold over housekeeping gene), and percent of DAB+ cells in tissues of the CNS of cynomolgus macaques

	Putamen		
Capsid	**vg/dg**	**mRNA**	**%DAB+ Cells**
AAV9	0.1	0.03	2
TTM-001	0.2	0.05	5
TTM-002	0.4	0.2	13
TTM-027	1.2	0.83	29
TTM-006	0.7	0.19	15
TTM-003	1.1	1.69	39
	Caudate		
Capsid	**vg/dg**	**mRNA**	**%DAB+ Cells**
AAV9	0.04	0.02	2
TTM-001	0.16	0.03	5
TTM-002	0.42	0.15	14
TTM-027	1.09	0.67	23
TTM-006	0.74	0.64	27
TTM-003	1.09	2.99	41
	Motor Cortex		
Capsid	**vg/dg**	**mRNA**	**%DAB+ Cells**
AAV9	0.1	0.02	1
TTM-001	0.3	0.02	4
TTM-002	0.7	0.07	9
TTM-027	1.5	1.38	22
TTM-006	0.8	1.36	14
TTM-003	1.2	7.43	40
	Cervical (C3) Spinal Cord		
Capsid	**vg/dg (ventral horn)**	**mRNA (ventral horn)**	**%DAB+ Cells (grey matter)**

AAV9	0.1	0.4	2
TTM-001	0.1	0.1	2
TTM-002	0.3	0.5	8
TTM-027	0.6	1.9	8
TTM-006	0.9	3.1	15
TTM-003	1.0	10.7	16
	Cervical Dorsal Root Ganglion		
Capsid	**vg/dg**	**mRNA**	**%DAB+ Cells**
AAV9	0.10	3.9	1
TTM-001	0.04	0.3	2
TTM-002	0.04	1.0	2
TTM-027	0.05	1.6	1
TTM-006	0.18	7.4	2
TTM-003	0.12	21.2	1

Table 57. Quantification of neurons (%NeuN positive cells), motor neurons (%chAT positive cell) and/or astrocytes (% Sox9 cells) transduced with the TTM-003 and TTM-027 capsid variants in the putamen, temporal cortex, substantia nigra, and spinal cord

	Putamen	
Capsid	% NeuN Positive Cells	% Sox9 Positive Cells
AAV9 (control 1)	0.2	2.7
AAV9 (control 2)	0.5	6.5
TTM-003	47.8	79.5
TTM-027	27.0	41.8
	Temporal Cortex	
Capsid	% NeuN Positive Cells	% Sox9 Positive Cells
AAV9 (control 1)	0.1	2.7
AAV9 (control 2)	0.1	4.9
TTM-003	25.3	87.5
TTM-027	12.3	51.4
	Substantia Nigra	
Capsid	% NeuN Positive Cells	% Sox9 Positive Cells
AAV9 (control 1)	2.7	2.8
AAV9 (control 2)	1.6	7.0
TTM-003	33.7	18.6
TTM-027	21.1	12.2
	Lumbar, Cervical, and Thoracic Spinal Cord	
Capsid	% ChAT Positive Cells	
AAV9 (control 1)	14.9	
AAV9 (control 2)	23.8	
TTM-003	78.5	
TTM-027	53.5	

Table 58. Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR, transgene mRNA by RT-qPCR (mRNA = transgene mRNA fold over housekeeping gene), and percent of DAB+ cells in the peripheral tissues of cynomolgus macaques

	Liver		
Capsid	**vg/dg**	**mRNA**	**%DAB+ Cells**
AAV9	147	8.9	93
TTM-001	15	0.2	20
TTM-002	13	0.4	32
TTM-027	2	0.2	7
TTM-006	9	0.4	24
TTM-003	5	0.4	24
Capsid	**Heart**		

	vg/dg	mRNA	%DAB+ Cells
AAV9	2.2	25.8	27
TTM-001	0.4	3.5	10
TTM-002	1.0	8.0	20
TTM-027	0.6	3.4	9
TTM-006	0.7	9.0	20
TTM-003	0.9	23.6	16
	Muscle (Vastus Lateralis)		
Capsid	**vg/dg**	**mRNA**	
AAV9	0.58	1.38	
TTM-001	0.09	0.04	
TTM-002	0.24	0.08	
TTM-027	0.21	0.05	
TTM-006	0.86	9.84	
TTM-003	1.01	10.85	
	Muscle (Gastrocnemius)		
Capsid	**vg/dg**	**mRNA**	
AAV9	0.56	2.13	
TTM-001	0.08	0.05	
TTM-002	0.22	0.13	
TTM-027	0.18	0.05	
TTM-006	0.51	1.04	
TTM-003	0.58	1.57	

[0511] Taken together, these data demonstrate that TTM-001, TTM-002, TTM-003, TTM-006, and TTM-027 are enhanced CNS tropic capsids in cynomolgus macaques that were capable of crossing the blood brain barrier following intravenous injection, even at a low dose of 4e12 vg/kg. TTM-003 and TTM-027 were also capable of transducing both neurons and astrocytes in several brain tissues as well as motor neurons in the spinal cord. All capsids variants also demonstrated robust liver de-targeting relative to AAV9.

D. Individual Evaluation of TTM-003 in Cynomolgus Macaques (Macaca fascicularis)

[0512] AAV particles were generated with the TTM-003 capsid variant which comprised a self-complementary viral genome encoding a histone H2b protein with an HA tag driven by a ubiquitous CAG promoter. The AAV particles comprising the TTM-003 capsid variant were administered to cynomolgus macaques (*Macaca fascicularis*) (n=3 male monkeys; 4-12 years of age) intravenously at a dose of 3e13 VG/kg. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-ddPCR, viral DNA (biodistribution) by ddPCR, and immunohistochemistry (IHC)/chromogenic quantification of percent positive cells in various tissues (cellular tropism).

[0513] As shown in Table 59, substantial and widespread transduction of TTM-003 was observed in the brain and spinal cord in NHPs following intravenous comprising the TTM-003 capsid variant. When administered at a dose of 3e13 VG/kg, TTM-003 was capable of transducing multiple cell types in the brain and spinal cord, including neurons and astrocytes, as quantified in Table 60. Distribution and transgene expression was also measured in the peripheral tissues of liver, heart, and muscle as provided in Table 60.

[0514] Taken together, these data demonstrate that TTM-003 is a CNS-tropic capsid in NHPs (cynomolgus macaques) that can infect both neuronal and non-neuronal cells. Additionally, the TTM-003 capsid variant was able to successfully penetrate the blood brain barrier following intravenous injection.

Table 59: Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR; transgene mRNA expression by RT-ddPCR (mRNA = transgene mRNA expression relative to a housekeeping gene (mTBP)); and the percentage of cells transduced with the TTM-003 capsid variant measured by co-localized staining of HA (payload tag) and DAB, NeuN (neurons), or Sox9 (astrocytes) in the brain and spinal cord of NHPs (each value represents the average from 3 NHPs)

Tissue	vg/dg	mRNA	% HA and DAB Positive Cells	% HA and NeuN Positive Neurons	% HA and Sox9 Positive Astrocytes
Frontal Cortex	7.5	1.4	40	8.3	86.2
Motor Cortex	6.5	7.4	60	13.7	88.4
Temporal Cortex	4.5	0.9	47	13.4	95.1
Entorhinal Cortex	-	-	34	5.9	87.8
Hippocampus	3.3	1.5	34	11.2	79.2
Thalamus	7.6	3.1	46	40.8	91.8
Caudate	7	2.5	55	-	-
Putamen	5.3	1.8	52	30.8	88
Substantia Nigra	3.1	1.5	19	13.1	45.5
Lateral Geniculate Nucleus (LGN)	-	-	74	-	-
Dentate Nucleus	2.1	1.9	38	-	-
Cerebellar Cortex	1.4	2.9	-	-	-
Spinal Cord - Cervical	4.3	8.2	20	-	78.4
Spinal Cord - Thoracic	-	-	28	-	85.9
Spinal Cord -Lumbar	-	-	24	-	83.8
DRG - Cervical	2.1	5.1	62	-	-
DRG - Thoracic	6.2	0.9	71	-	-
DRG - Lumbar	2.6	4.8	65	-	-

Table 60: Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR; transgene mRNA expression by RT-ddPCR (mRNA = transgene mRNA relative to a housekeeping gene (mTBP)); and percentage of cells transduced with the TTM-003 capsid variant measured by co-localized HA (payload tag) and DAB staining in the peripheral tissues of NHPs (each value represents the average of three individual NHPs)

Tissue	vg/dg	mRNA	% HA and DAB Cells
Liver	52.2	0.4	48
Heart	5.3	67	40
Vastus Lateralis	1.4	0.7	43
Gastrocnemius	1.6	10.6	39

E. Evaluation of TTM-027 in Cynomolgus Macaques (Macaca fascicularis)

[0515] AAV particles were generated with the TTM-027 capsid variant or the AAV9 capsid control which comprised a self-complementary viral genome encoding a histone H2b protein driven by a ubiquitous CAG promoter. The AAV particles comprising the TTM-027 capsid variant or the AAV9 capsid control were administered to a group of male cynomolgus macaques (*Macaca fascicularis*; 8-9

kg body weight; 4-10 years old; n=3) intravenously in a single solution, at a total dose per group of 2e13 VG/kg or a dose per capsid of 4e12 VG/kg. The in-life period was 28 days, and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-ddPCR; protein expression by IHC/chromogenic staining and quantification of percent positive cells; and viral DNA (biodistribution) by ddPCR.

[0516] As shown in **Table 61**, TTM-027 demonstrated increased CNS transduction in several brain regions and the spinal cord of the cynomolgus macaques after intravenous administration at a relatively low dose of 4e12 vg/kg.

Table 61. Quantification of percent DAB+ cells; viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR; and transgene mRNA expression by RT-ddPCR (mRNA = transgene mRNA expression relative to a housekeeping gene (mTBP)) in tissues of the CNS of cynomolgus macaques

	%DAB Positive Cells		
Tissue	**AAV9**	**TTM-027**	**%DAB positive cells relative to AAV9**
Caudate	2	46	23
Putamen	2	45	22.5
Thalamus	2	36	18
Substantia Nigra	2	15	7.5
Hippocampus	1	32	32
Entorhinal Cortex	2	30	15
Temporal Cortex	1	41	41
Primary Motor Cortex	4	47	11.75
Dentate Nucleus	8	37	4.63
Lateral Geniculate Nucleus (LGN)	8	55	6.88
Cervical Spinal Cord	10	22	2.2
Thoracic Spinal Cord	14	20	1.43
Lumbar Spinal Cord	13	21	1.62
Cervical DRG	57	59	1.04
Thoracic DRG	50	49	0.98
Lumbar DRG	51	58	1.14
	vg/dg		
Tissue	**AAV9**	**TTM-027**	**vg/dg relative to AAV9**
Caudate	0.1	2.9	29.00
Putamen	0.1	2.3	23.00
Primary Motor Cortex	0.2	2.4	12.00
Cervical Spinal Cord	0.4	3.0	7.50
Cervical DRG	1.4	0.1	0.07
	mRNA		
Tissue	**AAV9**	**TTM-027**	**mRNA relative to AAV9**
Caudate	0.046	2.5	54.35
Putamen	0.1	1.0	10.00
Cervical DRG	3.5	0.3	0.09

[0517] The percentage of DAB positive cells, biodistribution, and mRNA expression were also quantified in the peripheral tissues of the liver, heart, and muscle, which is provided in Table 62. The TTM-027 capsid variant exhibited robust liver de-targeting relative to AAV9 (Table 62).

Table 62. Quantification of percent DAB+ cells; viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR; and transgene mRNA expression by RT-ddPCR (mRNA = transgene mRNA expression relative to a housekeeping gene (mTBP)) in the peripheral tissues of cynomolgus macaques

	%DAB Positive Cells		
Tissue	**AAV9**	**TTM-027**	**%DAB positive cells relative to AAV9**
Liver	65	11	0.17
Heart	19	15	0.79
Gastrocnemius Muscle	9	16	1.78
Vastus Lateralis	21	13	0.62
	vg/dg		
Tissue	**AAV9**	**TTM-027**	**vg/dg relative to AAV9**
Liver	113.9	1.0	0.01
Heart	2.2	0.1	0.05
Gastrocnemius Muscle	1.07	0.04	0.04
Vastus Lateralis	1.7	0.1	0.06
	mRNA		
Tissue	**AAV9**	**TTM-027**	**mRNA relative to AAV9**
Liver	19.6	2.1	0.11
Heart	33.0	1.1	0.03
Gastrocnemius Muscle	6.29	0.51	0.08
Vastus Lateralis	0.51	0.02	0.04

[0518] Taken together, these data demonstrate that TTM-027 is an enhanced CNS tropic capsid in cynomolgus macaques that was capable of crossing the blood brain barrier following intravenous injection, even at a low dose of 4e12 vg/kg, which is consistent with what was observed in Example 8C above.

F. Individual Evaluation of TTM-027 in Cynomolgus Macaques (Macaca fascicularis)

[0519] AAV particles were generated with the TTM-027 capsid variant which each comprised a self-complementary viral genome encoding a histone H2b protein with an HA tag driven by a ubiquitous CAG promoter. The AAV particles comprising the TTM-027 capsid variant were administered to cynomolgus macaques (*Macaca fascicularis*) (n=3 male monkeys; 7.4-11 years of age) intravenously at a dose of 3e13 VG/kg. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-qPCR, viral DNA (biodistribution) by ddPCR, and immunohistochemistry (IHC)/chromogenic and immunofluorescent quantification of percent positive cells in various tissues (cellular tropism).

[0520] As shown in Table 63, substantial and widespread transduction of TTM-027 was observed in the brain and spinal cord of NHPs following intravenous administration of the AAV particles comprising the TTM-027 capsid variant. More specifically, TTM-027 demonstrated superior viral genome biodistribution in a variety of CNS tissues and regions, broader expression in the CNS as shown by both transgene mRNA expression and IHC (Table 63 and Table 64), as well as a highly neurotropic and astrocytic tropism in the brain and the spinal cord (Table 64 and Table 65). TTM-027 when administered intravenously at a dose of 3e13 vg/kg was capable of transducing up to 21-65% of neurons (HA and NeuN positive cells) and 87-97% of astrocytes (HA and Sox9 positive cells) in

multiple brain regions; up to 96% of Purkinje Neurons in the cerebellum; up to 84-94% of motor neurons (HA and ChAT positive cells) in the spinal cord; and up to 93-97% of astrocytes (HA and Sox9 positive cells) in the spinal cord (Table 64). TTM-027 was also able to transduce 97.9% of the dopaminergic neurons in the substantia nigra, as indicated by cells that were positive for both tyrosine hydroxylase (TH) and HA (payload tag). The TTM-027 capsid variant was well tolerated in the NHPs.

Table 63: Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR; transgene mRNA expression by RT-qPCR (mRNA = transgene mRNA expression relative to a housekeeping gene (mTBP)); and the percentage of cells transduced with the TTM-027 capsid variant measured by co-localized staining of HA (payload tag) and DAB in the brain and spinal cord of NHPs (each value represents the average from 3 NHPs; for regions of the DRG, sensory neuron data are shown)

Tissue	vg/dg	mRNA	% HA and DAB Positive Cells
Frontal Cortex	6.1	6.1	53.8
Motor Cortex	7.3	3.1	68.1
Temporal Cortex	1.7	3.8	51.8
Hippocampus	5.4	1.8	34.7
Thalamus	8.7	5.1	50.3
Caudate	7.6	5.7	57.5
Putamen	6.0	1.8	59.1
Substantia Nigra	2.6	5.4	37.9
Dentate Nucleus	2.7	17.7	55.2
Cervical Spinal Cord	5.3	5.9	25.0
Lumbar Spinal Cord	4.4	11.4	21.3
Cervical DRG	1.8	4.1	45.5
Thoracic DRG	6.9	3.1	41.0
Lumbar DRG	2.5	3.7	41.6
Tissue	% DAB Positive Cells		
Entorhinal Cortex	41.0		
Lateral geniculate nucleus (LGN)	74.5		
Thoracic Spinal Cord	23.6		
Purkinje Neurons	95.7		
Pontine Nuclei	52.7		
Inferior Olivary Nuclei	42.6		

Table 64: Quantification of the percentage of cells transduced with the TTM-027 capsid variant measured by co-localized staining of HA (payload tag) and either NeuN (neurons) or Sox9 (astrocytes) in the brain of NHPs (each value represents the average from 3 NHPs)

Tissue	% HA and NeuN Positive Neurons	% HA and Sox9 Positive Astrocytes
Caudate	58	99
Entorhinal Cortex	25	97
Frontal Cortex	42	99
Hippocampus	21	87
Motor Cortex	43	98
Putamen	58	95
Substantia Nigra	51	89
Temporal Cortex	31	97
Thalamus	66	97

Table 65: Quantification of the percentage of cells transduced with the TTM-027 capsid variant measured by co-localized staining of HA (payload tag) and either ChAT (motor neurons) or

Sox9 (astrocytes) in the gray matter of the spinal cord of NHPs (each value represents the average from 3 NHPs)

Tissue	% HA and ChAT Positive Neurons	% HA and Sox9 Positive Astrocytes
Cervical Spinal Cord (C2)	84	96
Thoracic Spinal Cord (T8)	86	97
Lumbar Spinal Cord (L2)	94	92

[0521] The biodistribution and mRNA expression following intravenous administration of AAV particle comprising the TTM-027 capsid variant at a dose of 3e13 vg/kg was also measured in the peripheral tissues of the liver, heart, and muscle (vastus lateralis and gastrocnemius) as provided in Table 66). TTM-027 showed very low biodistribution and mRNA expression in the liver in NHPs (Table 66), and demonstrated substantially reduced liver tropism.

Table 66: Quantification of viral genome copies per diploid genome (vg/dg) (biodistribution) by ddPCR, and transgene mRNA expression relative to a housekeeping gene (mTBP) by RT-ddPCR in the peripheral tissues of NHPs (each value represents the average from 3 NHPs)

Tissue	vg/dg	Transgene mRNA expression relative to a housekeeping gene (mTBP)	% DAB Positive Cells
Liver	13.9	0.5	56.1
Heart	2.7	8.0	38.2
Vastus Lateralis	1.5	2.2	18.3
Gastrocnemius	2.2	9.6	38.9

[0522] Taken together, the individual characterization of the TTM-027 capsid variant further demonstrates and confirms that the TTM-027 is an enhanced CNS tropic capsid in cynomolgus macaques, capable of crossing the blood brain barrier following intravenous injection, consistent with what was observed in Examples 8C and 8E above.

Example 9. Dose Response Evaluation of the TTM-002 and TTM-027 AAV capsid variants

[0523] This Example investigates transduction of the TTM-002 (SEQ ID NO: 982 (amino acid) and SEQ ID NO: 984 (DNA), comprising SEQ ID NO: 2) and TTM-027 (SEQ ID NO: 4 (amino acid) and SEQ ID NO: 5 (DNA), comprising SEQ ID NO: 3272) capsid variants following intravenous administration at increasing doses in mice.

[0524] AAV particles were generated with the TTM-002 capsid variant or the TTM-027 capsid variant which comprised a single stranded viral genome encoding a histone protein with an HA tag (H3F3-HA) and a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) driven by a ubiquitous CBA promoter. The AAV particles comprising the TTM-002 capsid variant or the TTM-027 AAV capsid variant were administered to mice (n=3 mice per dosing group; Balb/c; 6-8 weeks of age) via tail vein injection at increasing doses of 1e12 vg/kg, 3.2e12 vg/kg, 1e13 vg/kg, 3.2e13 vg/kg, or 1e14 vg/kg. The dose of 3.2e12 vg/kg was approximately equivalent to the dose used per capsid in the cynomolgus macaques (*Macaca fascicularis*) in Example 8C above. The in-life

period was 28 days and CNS tissues were collected for measuring transgene mRNA (expression) by qPCR and the percent of HA positive cells in the brain.

[0525] As shown in Table 67 and **FIG. 4A**, a dose dependent increase in transduction of both the TTM-002 and TTM-027 capsid variants was observed in the mouse cortex following intravenous administration of the AAV particles at the increasing doses. The percent of cells transduced in the mouse cortex with TTM-027 was higher at all doses compared to TTM-002. At the highest dose tested, 1e14 vg/kg, TTM-027 transduced 65% of cells in the cortex, whereas TTM-002 transduced 38% of cells, with TTM-002 demonstrating an even distribution between neurons and astrocytes, identified by NeuN and Sox9 markers, respectively (Table 68). It was also observed that an increase in dose from 3.2e12 to 3.2e13 vg/kg resulted in a greater than 3 fold increase in percent positive cells. Consistent with the percentage of TTM-002 or TTM-027 positive cells, a dose dependent increase in transgene mRNA expression was also observed in the mouse brain following intravenous administration of the TTM-002 and TTM-027 capsid variants at the increasing doses (**FIG. 4B** and Table 67).

[0526] Measurements in Table 67 are by co-localization of chromogenic HA staining and hematoxylin(each value is the average of three individual measurements within each cortex taken from three mice). Measurements in Table 68 are in the mouse cortex by fluorescence microscopy and co-staining with HA and cell-type specific markers (each value is the average of three individual measurements within each cortex taken from three mice).

[0527] Taken together, these data demonstrate a dose-dependent response across a 2-log dose range in mouse (1e12 to 1e14 vg/kg), without reaching saturation at the maximal dose (Table 67 and Table 68).

Table 67. Quantification of cells positive for the TTM-002 or TTM-027 capsid variant per mm2 (HA positive cells/mm2) or percentage of cells transduced with the TTM-002 or TTM-027 capsid variants (% HA positive cells) in the mouse cortex , as well as quantification by qPCR of transgene mRNA expression relative to a housekeeping gene (mTBP) in the mouse brain, following intravenous administration

Capsid Variant	Dosage (vg/kg)	HA Positive Cells/mm^2	% HA Positive Cells	Transgene mRNA expression relative to housekeeping gene
TTM-002	1e14	679.147	37.668	9.3349
	3.2e13	414.043	26.279	3.7168
	1e13	277.497	19.078	2.8445
	3.2e12	151.841	8.450	0.9074
	1e12	61.018	3.616	0.1681
Vehicle	0	0.185	0.011	0.0003
TTM-027	1e14	1019.777	65.451	19.9655
	3.2e13	835.525	46.076	14.0024
	1e13	585.873	31.717	6.7856
	3.2e12	301.636	14.169	0.9269
	1e12	78.350	4.427	0.6379

Table 68. Quantification of total cells (HA positive cells/mm2), neurons (NeuN positive cells that are also HA positive/mm2), and astrocytes (Sox9 positive cells that are also HA positive/mm2) positive for the TTM-002 capsid variant per mm2 or percentage of total cells (%HA positive cells), neurons (% NeuN positive cells that are also HA positive), and astrocytes (% Sox9 positive cells that are also HA positive) transduced with the TTM-002 capsid variant

Capsid Variant	Dosage (vg/kg)	HA Positive Cells/mm^2	% HA Positive Cells	NeuN Positive Cells that are also HA positive/mm^2	% NeuN Positive Cells that are also HA positive	Sox9 Positive Cells that are also HA positive/mm^2	% Sox9 Positive Cells that are also HA positive
TTM-002	1e14	495.9	28.6	154.7	13.5	26.2	12.8
	3.2e13	344.0	18.8	126.8	9.2	19.8	14.6
	1e13	270.7	15.6	73.2	5.5	12.0	8.0
	3.2e12	176.9	8.2	59.2	3.6	8.5	4.4
	1e12	57.9	3.5	7.3	0.6	4.4	2.3
Vehicle	0	0	0	0	0	0	0

Example 10: Individual Characterization of TTM-002 and TTM-001 Capsid Variants in Mice

[0528] The goal of these experiments was to determine the transduction level, tropism, ability to cross the blood brain barrier, and overall spatial distribution in the brain, heart, and liver of the TTM-001 and TTM-002 capsids and variants thereof relative to AAV9 following intravenous injection in mice. TTM-001 (SEQ ID NO: 981), TTM-002 (SEQ ID NO: 982), and variants of the TTM-002 and TTM-001 capsids comprising local modifications in loop IV were investigated including TTM-003 (SEQ ID NO: 36), TTM-006 (SEQ ID NO: 39), TTM-018 (SEQ ID NO: 51), and TTM-019 (SEQ ID NO: 52). The amino acid sequences for these capsid variants are provided, e.g., in Table 4.

[0529] AAV particles were generated with each of these capsid variants encapsulating a fluorescent reporter construct, ZsGreen-HA, driven by a CAG promoter. Each capsid variant and AAV9 control were tested by intravenously administering by tail vein injection, the AAV particle formulation at 1e13 VG/kg to three BALB/c mice. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA expression.

[0530] The brains isolated from mice injected with the AAV particles encapsulated in the TTM-002 capsid, the TTM-001 capsid, or variants of the TTM-001 or TTM-002 capsid comprising local modifications were assayed to calculate ZsGreen expression and/or transgene DNA. Data were provided as fold over the AAV9 control (Table 69). All of the variants of the TTM-001 and TTM-002 capsids as well as TTM-001 and TTM-002 demonstrated increased CNS tropism and expression in the brain relative to AAV9 (Table 69; **FIGs. 6A-6B**). More specifically, TTM-001 and TTM-002 showed a broad distribution throughout the entire brain and spinal cord, outperforming the AAV9 control by approximately 30- and 40-fold, respectively, in terms of viral DNA biodistribution and transgene RNA expression (**FIGs. 6A-6B**; Table 69). The variants of the TTM-001 and TTM-002 capsids as well as TTM-001 and TTM-002 also demonstrated reduced mRNA and DNA expression in

the liver by qPCR relative to the AAV9 control, with TTM-002 showing 14-fold lower gene expression than the AAV9 control (Table 69; **FIGs. 6C-6D**). Similar results were observed by immunohistochemistry (IHC) staining of the brain (including the cortex, thalamus, and cerebellum), spinal cord (grey matter), and liver for transduction by AAV particles comprising the AAV capsid variants investigated. Transduction of the heart, skeletal muscle, and kidney did not show major differences between AAV9 and TTM-002.

Table 69. ZsGreen Expression and Transgene DNA and/or RNA expression for variants of the TTM-001 and TTM-002 capsids relative to AAV9 in mice

Capsid Variant	Brain		Liver	
	ZsGreen Expression fold change relative to AAV9	Transgene DNA fold change relative to AAV9	Transgene RNA fold change relative to AAV9	Transgene DNA fold change relative to AAV9
AAV9	1.0	1.0	1.000	1.000
TTM-001	32.3	31.9	0.337	0.348
TTM-002	40.9	37.0	0.072	0.034
TTM-006	16.1	36.9	0.036	0.013
TTM-018	22.8	27.0	0.231	0.223
TTM-019	14.6	14.4	0.117	0.112
TTM-003	17.3	14.6	0.015	0.026

Example 11: *In vivo* Evaluation of TTM-002 AAV Capsid Variant Comprising an HA-tagged Nucleotide Sequence Encoding GBA in Cynomolgus Monkeys

[0531] This Example investigates the distribution and efficacy of an AAV comprising a TTM-002 AAV capsid variant (SEQ ID NO: 982) and a codon-optimized nucleotide sequence (SEQ ID NO: 1773) encoding a GBA and an HA-tag (TTM-002.GBA_VG17-HA). Mauritius male cynomolgus monkeys (Macaca fascicularis; 3-6 years of age; 3-8 kg in weight; n= 3 per group) were administered TTM-002.GBA_VG17-HA at 3e12 vg/kg or 1e13 vg/kg by intravenous administration. Monkeys were also administered a vehicle control (modified PBS) or 1e13 vg/kg of an AAV9 capsid comprising the same payload construct was used as control (AAV9.GBA_VG17-HA) for comparison. Biodistribution of GBA1-HA protein was assessed following a 28-day treatment period. Primary readouts included biochemical analysis of viral genomes and mRNA, immunohistochemical analysis of HA levels, and histopathology readouts in the brain, spinal cord, liver, kidney, and heart tissues. Secondary readouts included biochemical analysis of GCase activity, LC/MS-MS analysis of GBA1 levels, and cage-side observations including weekly body weight.

[0532] Histopathology analysis revealed no signs of toxicity in the kidneys, hearts, brains, and spinal cords of the treated monkeys at both AAV dosages.

[0533] TTM-002.GBA_VG17-HA led to increased viral genome biodistribution in all CNS tissues (**FIG. 1**; Table 46A-H) and reduced liver transduction as compared to AAV9.GBA_VG17-HA.

Table 46A: Viral genome biodistribution in the putamen

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.00	0.00	
	0.01		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.17	0.23	1.00
	0.44		
	0.07		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.83	1.68	7.47
	1.92		
	2.30		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.39	0.46	
	0.48		
	0.51		

Table 46B: Viral genome biodistribution in the motor cortex

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.01	0.01	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.14	0.31	1.00
	0.60		
	0.19		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	3.19	2.36	7.65
	1.53		
	2.37		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.57	1.00	
	0.94		
	1.50		

Table 46C: Viral genome biodistribution in the frontal cortex

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.14	0.25	1.00
	0.42		
	0.18		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	1.14	1.54	6.27
	1.19		
	2.46		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.51	0.86	
	0.87		
	1.22		

Table 46D: Viral genome biodistribution in the substantia nigra

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.22	0.28	1.00
	0.43		
	0.17		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	1.20	1.07	3.88
	0.67		
	1.34		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.37	0.43	
	0.34		
	0.57		

Table 46E: Viral genome biodistribution in the C3 Ventral Horn

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.04	0.03	
	0.02		
	0.03		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.37	0.45	1.00
	0.74		
	0.24		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	1.37	1.33	2.98
	1.26		
	1.37		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.77	1.03	
	1.27		
	1.05		

Table 46F: Viral genome biodistribution in the DRG

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.01	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.81	0.72	1.00
	0.98		
	0.38		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	2.04	0.55	0.76
	0.65		
	0.48		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.28	0.23	
	0.11		
	0.32		

Table 46G: Viral genome biodistribution in the liver

Treatment	Animal Average	Group Average	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.01		
AAV9.GBA_VG17-HA 1e13 vg/kg	195.49	140.22	1.00
	111.71		
	113.48		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	54.48	36.68	0.26
	28.26		
	27.31		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	21.65	16.12	
	9.07		
	17.66		

Table 46H: Viral genome biodistribution in the heart

Treatment	Animal Ave	Group Ave	Fold over AAV9
Vehicle	0.00	0.04	
	0.00		
	0.12		
AAV9.GBA_VG17-HA 1e13 vg/kg	2.78	2.38	1.00
	2.84		
	1.51		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	2.45	1.66	0.70
	1.46		
	1.08		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.65	0.73	
	0.77		
	0.78		

[0534] TTM-002.GBA_VG17-HA led to increased human GBA1 mRNA expression over the expression of the TBP housekeeping gene in the dentate nucleus, putamen, substantia nigra, motor and frontal cortex, and spinal cord (Tables 47A-E). Compared to animals treated with AAV9.GBA_VG17-HA, comparable levels of human GBA1 mRNA expression were observed in the DRG, liver, or heart of animals treated with TTM-002.GBA_VG17-HA (Tables 47F-H).

Table 47A: GBA1 mRNA expression relative to TBP in the frontal cortex

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		

AAV9.GBA_VG17-HA 1e13 vg/kg	0.05	0.04	
	0.06		
	0.01		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.34	0.65	16.65
	0.91		
	0.68		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.05	0.38	9.71
	0.52		
	0.55		

Table 47B: GBA1 mRNA expression relative to TBP in the motor cortex

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.02	
	0.00		
	0.07		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.02	0.03	
	0.05		
	0.01		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.28	0.43	16.60
	0.31		
	0.70		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.08	0.59	22.95
	0.70		
	1.00		

Table 47C: GBA1 mRNA expression relative to TBP in the putamen

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.04	0.05	
	0.11		
	0.01		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.26	1.26	23.51
	2.12		
	1.41		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.07	0.16	3.02

Table 47D: GBA1 mRNA expression relative to TBP in the substantia nigra

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.08	0.14	
	0.32		
	0.03		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.42	0.84	5.85
	0.39		
	1.72		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.14	0.25	1.77

Table 47E: GBA1 mRNA expression relative to TBP in the spinal cord

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.17	1.40	
	3.74		
	0.29		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	1.22	2.86	2.04
	3.85		
	3.50		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	2.03	3.03	2.17

Table 47F: GBA1 mRNA expression relative to TBP in the DRG

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	53.23	26.01	
	13.21		
	11.60		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	22.68	22.89	0.88
	29.26		
	16.75		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	6.00	7.58	0.29

Table 47G: GBA1 mRNA expression relative to TBP in the heart

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.04	
	0.00		
	0.12		
AAV9.GBA_VG17-HA 1e13 vg/kg	64.58	48.99	
	88.47		
	42.77		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	38.29	37.93	0.77
	61.89		
	13.62		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	11.47	8.16	0.17

Table 47H: GBA1 mRNA expression relative to TBP in the liver

Treatment	FC animal	Group Ave FC Glox4 rel TBP	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	6.71	5.39	
	2.26		
	7.20		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	2.88	2.37	0.44
	1.64		
	2.57		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	6.60	3.28	0.61

[0535] As compared to AAV9.GBA_VG17-HA, TTM-002.GBA_VG17-HA led to increased human GBA1 mRNA in the dentate nucleus, cervical spinal cord, frontal cortex, motor cortex, putamen, and substantia nigra (**FIG. 2**; Tables 48A-E). Compared to animals treated with AAV9.GBA_VG17-HA, comparable levels of human GBA1 mRNA expression were observed in the DRG, liver, or heart of animals treated with TTM-002.GBA_VG17-HA relative to endogenous cynomolgus GBA1 (Tables 48F-H).

Table 48A: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the frontal cortex

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9

Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.03	0.02	
	0.03		
	0.01		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.14	0.22	9.74
	0.34		
	0.19		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.02	0.15	6.64
	0.21		
	0.23		

Table 48B: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the motor cortex

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.02	0.01	
	0.02		
	0.01		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.20	0.29	22.31
	0.23		
	0.43		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.05	0.25	19.08
	0.34		
	0.35		

Table 48C: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the putamen

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.02	0.02	
	0.05		
	0.00		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.10	0.47	19.52
	0.83		
	0.47		
TTM-002.GBA_VG17-HA low dose	0.02	0.05	2.11

3e12 vg/kg			

Table 48D: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the substantia nigra

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.06	0.10	
	0.22		
	0.02		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.24	0.53	5.23
	0.26		
	1.07		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.09	0.16	1.61

Table 48E: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the spinal cord

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	0.09	0.58	
	1.50		
	0.15		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	0.44	1.01	1.73
	1.40		
	1.17		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	0.56	0.80	1.37

Table 48F: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the DRG

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	BLQ	BLQ	
	BLQ		
	BLQ		
AAV9.GBA_VG17-HA 1e13 vg/kg	33.15	14.51	
	5.88		
	4.49		

TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	7.17	7.66	0.53
	10.38		
	5.43		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	2.40	2.16	0.15

Table 48G: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the heart

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	0.00	0.04	
	0.00		
	0.12		
AAV9.GBA_VG17-HA 1e13 vg/kg	39.25	45.82	
	65.29		
	32.92		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	27.67	26.87	0.59
	45.23		
	7.71		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	7.48	5.07	0.11

Table 48H: Human GBA1 mRNA expression relative to endogenous cynomolgus GBA1 mRNA in the liver

Treatment	FC rel cyGBA individ	FC rel cyGBA Group	Fold over AAV9
Vehicle	0.00	0.00	
	0.00		
	0.00		
AAV9.GBA_VG17-HA 1e13 vg/kg	5.11	3.66	
	1.17		
	4.70		
TTM-002.GBA_VG17-HA high dose 1e13 vg/kg	1.77	1.43	0.39
	1.17		
	1.35		
TTM-002.GBA_VG17-HA low dose 3e12 vg/kg	3.84	2.10	0.57

[0536] Immunohistochemical analysis showed that TTM-002.GBA_VG17-HA led to greater GBA1-HA levels in the brain as compared to AAV9 (Table 49).

Table 49: HA chromogenic IHC quantitative image analysis following TTM002.GBA_VG17-HA or AAV9.GBA_VG17-HA treatment

Treatment	% HA + total cells per region

	Frontal Cortex	Motor Cortex	Putamen	Substantia Nigra
Vehicle	0.2	0	0.5	0.2
AAV9.GBA_VG17-HA 1E13 vg/kg	0.5	0.1	0.6	1.3
TTM002.GBA_VG17-HA 1E13 vg/kg	1.6	0.8	11.3	2.5
TTM002.GBA_VG17-HA 3E12 vg/kg	0.9	0.5	2.4	0.4

[0537] Co-staining analysis showed that HA protein expression was detected in both neurons and astrocytes of the putamen and substantia nigra of subjects treated with TTM002.GBA_VG17-HA but not in subjects treated with AAV9.GBA_VG17-HA or vehicle (Table 50).

Table 50: Astrocyte co-staining analysis following TTM002.GBA_VG17-HA or AAV9.GBA_VG17-HA treatment

Animal ID	Treatment	Putamen		Substantia Nigra	
		Neurons	Astrocytes	Neurons	Astrocytes
1	Vehicle	-	-	-	-
2	AAV9.GBA_VG17-HA 1E13 vg/kg	+	-	+	-
3	TTM002.GBA_VG17-HA 1E13 vg/kg	TBD	TBD	+	+
4	TTM002.GBA_VG17-HA 1E13 vg/kg	+	+	+	+
5	TTM002.GBA_VG17-HA 1E13 vg/kg	+	+	TBD	TBD

Example 12: In vivo Promoter Selection Studies

[0538] ITR-to-ITR sequences comprising promoters were packaged into AAV6 capsids and delivered by intrastriatal injection to Sprague Dawley rats at a dose of $1x10^{10}$ VG. Tissue samples were collected at 3 weeks or 10 weeks and frataxin protein levels quantified. Frataxin constructs comprising truncated CBA and CMV promoters were packed into an AAV9 variant capsid (VOY201) and administered by intravenous delivery to Sprague Dawley rats at a dose of either $6.3x10^{12}$ or $2x10^{13}$ VG/kg. After 28 or 90 days, tissue samples were collected and processed for quantification of frataxin expression (ng/mg). The sequence for the VOY201 capsid is disclosed in, e.g., PCT/US2019/053681, the contents of which are incorporated herein in their entirety.

[0539] Promoters CMV-D7 (SEQ ID NO: 1750) and CBA-D8 (SEQ ID NO: 1742) demonstrated the target moderate frataxin expression as compared to the other constructs and were therefore selected for further study.

[0540] To test the durability and persistence of frataxin expression driven by the CMV-D7 (SEQ ID NO: 1750) and CBA-D8 (SEQ ID NO: 1742) promoters, a time course study was conducted. Viral genomes comprising a CMV-D7 (SEQ ID NO: 1750) or a CBA-D8 (SEQ ID NO: 1742 promoter with a frataxin payload sequence were packaged into another AAV9-variant (VOY101) capsid to generate AAV particles. These AAV particles were administered by intravenous delivery via the tail vein to male Sprague Dawley rats at one of two doses ($6.3x10^{12}$ or $2x10^{13}$). At 28, 90, or 180 days after administration, tissue samples were collected (heart, liver, cerebellum, thoracic and lumbar DRG) and processed for quantification of vector genome per diploid cell and frataxin expression levels based on an Anti-Frataxin SimpleStep ELISA. Data are shown below in Tables 51 and 52, **FIGs. 3A, 3B, 3C and 3D.**

Table 51. Frataxin expression (ng/mg)

Tissue	CMV-D7						CBA-D8					
	6.3e12			2.3e13			6.3e12			2.3e13		
	28d	90d	180d	28d	90d	180d	28d	90d	180d	28d	90d	180d
Heart	14.9	168.7	98.5	37.4	254.9	234.7	20.4	112.1	164.6	77.5	713.8	304.8
Cerebellum	1.0	1.9	4.3	5.8	13.6	23.6	0.9	2.2	3.1	6.9	11.5	21.4
Lumbar DRG	75.2	144.7	64.7	249.0	250	152.1	45.0	98.3	53.2	121.3	212.8	95.9

Table 52. Vector genome/diploid cell (VG/dc)

Tissue	CMV-D7						CBA-D8					
	6.3e12			2.3e13			6.3e12			2.3e13		
	28d	90d	180d	28d	90d	180d	28d	90d	180d	28d	90d	180d
Heart	1.8	2.1	1.8	3.3	8.11	7.2	1.1	2.2	1.8	3.6	9.6	6.1
Liver	0.7	0.6	0.6	4.2	2.4	2.9	0.7	0.5	0.5	3.2	1.4	0.9
Cerebellum	0.0	0.0	0.00	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
Thoracic DRG	0.1	0.1	0.1	0.5	0.4	0.1	0.1	0.1	0.1	0.5	0.4	0.3
	CBA (no miR-122)						CMV					
	6.3e12			2.3e13			6.3e12			2.3e13		
	28d	90d	180d	28d	90d	180d	28d	90d	180d	28d	90d	180 d
Heart	4.3	7.0	7.0	-	-	-	-	-	-	4.8	-	-
Liver	0.8	0.4	0.6	-	-	-	-	-	-	5.7	-	-
Cerebellum	0.1	0.0	0.0	-	-	-	-	-	-	0.1	-	-
Thoracic DRG	0.5	0.4	0.1	-	-	-	-	-	-	2.2	-	-

[0541] In tissue collected from the heart ventricle, driving frataxin expression using the CMV-D7 (SEQ ID NO: 1750) promoter enhanced frataxin expression 0.2-2.5x, while driving frataxin expression using the CBA-D8 (SEQ ID NO: 1742) promoter enhanced frataxin expression 0.3-7.8x. (**FIG. 3A**).

[0542] In tissue collected from the cerebellum, driving frataxin expression using the CMV-D7 (SEQ ID NO: 1750) promoter enhanced frataxin expression 0.01-0.31x, while driving frataxin

expression using the CBA-D8 (SEQ ID NO: 1742) promoter enhanced frataxin expression 0.01-0.28x. (**FIG. 3B**) .

[0543] In tissue collected from the lumbar DRG, driving frataxin expression using the CMV-D7 (SEQ ID NO: 1750) promoter enhanced frataxin expression 1.6-6.2x, while driving frataxin expression using the CBA-D8 (SEQ ID NO: 1742) promoter enhanced frataxin expression 1.1-5.2x. (**FIG. 3C**) .

[0544] Immunohistochemical analysis was performed on 30μm tissue samples collected 28 days after AAV particle administration. An anti-hFXN antibody (1/50,000) was used. Frataxin expression driven by the CMV-D7 (SEQ ID NO: 1750) and CBA-D8 (SEQ ID NO: 1742) promoters was detected in the dentate nucleus of treated rats.

[0545] Each of CMV-D7 (SEQ ID NO: 1750), CBA-D8 (SEQ ID NO: 1742) and CBA (SEQ ID NO: 1734) promoters showed similar distribution and expression patterns in the DRG and brain. In the heart, CMV-D7 and CBA-D8 promoters generated FXN expression approximately 50-260-fold lower than CBA-driven frataxin expression.

[0546] The CMV-D7 (SEQ ID NO: 1750) and CBA-D8 (SEQ ID NO: 1742) promoters both drove frataxin expression in the cerebellum, heart and DRG at 180 days after administration of the AAV particles. At this time point, expression in the cerebellum was approximately 3-fold greater than that achieved using a reference CBA promoter, indicating that the CMV-D7 and CBA-D8 promoters are active in target cells of the cerebellum.

IX. Equivalents and Scope

[0547] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the Detailed Description provided herein. The scope of the present disclosure is not intended to be limited to the above Detailed Description, but rather is as set forth in the appended claims.

[0548] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0549] In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the disclosure (*e.g.*, any, composition, therapeutic or active ingredient; any method of production;

any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0550] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the disclosure in its broader aspects.

[0551] While the present disclosure has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the disclosure.

[0552] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

CLAIMS

What is claimed is:

1. An adeno-associated virus (AAV) particle comprising:

a) an AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3], wherein:

(i) optionally [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G;

(ii) [N2] comprises the amino acid sequence of SPH: and

(iii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid;

and

b) a viral genome comprising a frataxin (FXN)-encoding sequence.

2. The AAV particle of claim 1, wherein the amino acid sequence [N1]-[N2]-[N3] is in hypervariable loop IV of the AAV capsid variant.

3. The AAV particle of claim 1 or claim 2, wherein the AAV capsid variant is an AAV9 capsid variant.

4. The AAV particle of any one of claims 1-3, wherein [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G.

5. The AAV particle of any one of claims 1-4, wherein [N2]-[N3] comprises the amino acid sequence of SPHSKA (SEQ ID NO: 941).

6. An adeno-associated virus (AAV) particle comprising a viral genome comprising a frataxin (FXN)-encoding sequence and an AAV9 capsid variant comprising the amino acid sequence of SPHSKA (SEQ ID NO: 941).

7. The AAV particle of claim 6, wherein the amino acid sequence of SPHSKA (SEQ ID NO: 941) is in hypervariable loop IV of the AAV9 capsid variant.

8. The AAV particle of claim 6 or claim 7, wherein the amino acid sequence of SPHSKA (SEQ ID NO: 941) is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 4 or SEQ ID NO: 36.

9. The AAV particle of any one of claims 6-8, wherein the AAV9 capsid variant further comprises one, two, or all of: an N at an amino acid position corresponding to position 452, an E at an amino

acid position corresponding to position 451, and/or a V at an amino acid position corresponding to position 453 of SEQ ID NO: 4.

10. The AAV particle of claim any one of claims 6-9, wherein the AAV9 capsid variant comprises the amino acid sequence of KTENVSGSPHSKAQNQQT (SEQ ID NO: 3272).

11. The AAV particle of any one of claims 6-10, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 90% identity to SEQ ID NO: 4;

(ii) a VP2 protein comprising an amino acid sequence having at least 90% identity to positions 138-742 of SEQ ID NO: 4; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 4.

12. The AAV particle of any one of claims 6-11, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 4;

(ii) a VP2 protein comprising an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 4; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 4.

13. The AAV particle of any one of claims 6-12, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 99% identity to SEQ ID NO: 4;

(ii) a VP2 protein comprising an amino acid sequence having at least 99% identity to positions 138-742 of SEQ ID NO: 4; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 4.

14. The AAV particle of any one of claims 6-13, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4; and/or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

15. The AAV particle of any one of claims 6-13, wherein the AAV9 capsid variant comprises:

(i) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 4;

(ii) an E at an amino acid position corresponding to position 451 and a V at an amino acid position corresponding to position 453 of SEQ ID NO: 4; and

(iii) no other modifications relative to wild type AAV9.

16. The AAV particle of any one of claims 6-8, wherein the AAV9 capsid variant further comprises one, two, or all of: an E at an amino acid position corresponding to position 451, an R at an amino acid position corresponding to position 452, and/or a V at an amino acid position corresponding to position 453 of SEQ ID NO: 36.

17. The AAV particle of any one of claims 6-8 and 16, wherein the AAV9 capsid variant comprises the amino acid sequence of KTERVSGSPHSKAQNQQT (SEQ ID NO: 3589).

18. The AAV particle of any one of claims 6-8, 16, and 17, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 90% identity to SEQ ID NO: 36;

(ii) a VP2 protein comprising an amino acid sequence having at least 90% identity to positions 138-742 SEQ ID NO: 36; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 36.

19. The AAV particle of any one of claims 6-8 and 16-18, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 36;

(ii) a VP2 protein comprising an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 36; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 36.

20. The AAV particle of any one of claims 6-8 and 16-19, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising an amino acid sequence having at least 99% identity to SEQ ID NO: 36;

(ii) a VP2 protein comprising an amino acid sequence having at least 99% identity to positions 138-742 of SEQ ID NO: 36; and/or

(iii) a VP3 protein comprising an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 36.

21. The AAV particle of any one of claims 6-8 and 16-20, wherein the AAV9 capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 36; and/or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

22. The AAV particle of any one of claims 6-8 and 16-20, wherein the AAV9 capsid variant comprises:

(i) the amino acid sequence SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to an amino acid position corresponding to position 455 of SEQ ID NO: 36;

(ii) an E at an amino acid position corresponding to position 451, an R at an amino acid position corresponding to position 452, and a V at an amino acid position corresponding to position 453 of SEQ ID NO: 36; and

(iii) no other modifications relative to wild type AAV9.

23. The AAV particle of any one of claims 1-4, wherein [N1]-[N2]-[N3] is present immediately subsequent to a position corresponding to the amino acid position 452 of SEQ ID NO: 982; and

wherein the AAV capsid variant comprises an amino acid sequence at least 90% identical, e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical, to the amino acid sequence of SEQ ID NO: 982, e.g., to positions 203-742 of SEQ ID NO: 982.

24. The AAV particle of claim 23, wherein [N1] comprises GHD.

25. The AAV particle of claim 23 or claim 24, wherein [N1] comprises the amino acid G at a position corresponding to position 453, the amino acid H at position 454, and the amino acid D at position 455 of SEQ ID NO: 138 or SEQ ID NO: 982.

26. The AAV particle of any one of claims 23-25, wherein [N3] comprises KSG.

27. The AAV particle of any one of claims 23-26, wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to SEQ ID NO: 982;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 138-742 SEQ ID NO: 982; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity to positions 203-742 of SEQ ID NO: 982.

28. The AAV particle of any one of claims 23-27, wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to SEQ ID NO: 982;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to positions 138-742 SEQ ID NO: 982; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 95% identity to positions 203-742 of SEQ ID NO: 982.

29. The AAV particle of any one of claims 23-28, wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to SEQ ID NO: 982;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to positions 138-742 SEQ ID NO: 982; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 99% identity to positions 203-742 of SEQ ID NO: 982.

30. The AAV particle of any one of claims 23-29, wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982.

31. The AAV particle of any one of claims 1-30, wherein the FXN protein encoded by the FXN-encoding sequence is not a cynomolgus FXN protein.

32. The AAV particle of any one of claims 1-31, wherein the FXN-encoding sequence encodes a human FXN protein.

33. The AAV particle of any one of claims 1-32, wherein the FXN-encoding sequence comprises SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824.

34. The AAV particle of any one of claims 1-33, wherein the FXN-encoding sequence comprises SEQ ID NO: 1824.

35. The AAV particle of any one of claims 1-34, wherein the viral genome further comprises a promoter operably linked to the FXN-encoding sequence.

36. The AAV particle of claim 35, wherein the promoter comprises a human elongation factor 1α-subunit (EF1α) promoter, a cytomegalovirus (CMV) immediate-early enhancer and/or promoter, a chicken β-actin (CBA) promoter, a CAG promoter, a β glucuronidase (GUSB) promoter, a ubiquitin C (UBC) promoter, a neuron-specific enolase (NSE) promoter, a platelet-derived growth factor (PDGF) promoter, a platelet-derived growth factor B-chain (PDGF-β) promoter, a intercellular adhesion molecule 2 (ICAM-2) promoter, a synapsin (Syn) promoter, a methyl-CpG binding protein 2 (MeCP2) promoter, a Ca2+/calmodulin-dependent protein kinase II (CaMKII) promoter, a metabotropic glutamate receptor 2 (mGluR2) promoter, a neurofilament light chain (NFL) or neurofilament heavy chain (NFH) promoter, a β-globin minigene nβ2 promoter, a preproenkephalin (PPE) promoter, a enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) promoter, a glial fibrillary acidic protein (GFAP) promoter, a myelin basic protein (MBP) promoter, a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512), or a functional fragment or truncation of any of the foregoing.

37. The AAV particle of claim 35 or claim 36, wherein the promoter is a CMV promoter or CBA promoter, or a functional fragment or truncation thereof.

38. The AAV particle of any one of claims 35-37, wherein the promoter is a truncated CBA promoter.

39. The AAV particle of claim 38, wherein the truncated CBA promoter is 50-400 nucleotides in length, e.g., 100-332 nucleotides in length.

40. The AAV particle of any one of claims 35-39, wherein the promoter comprises or consists of the nucleotide sequence of any one of SEQ ID NOs: 1738, 1740, and 1742 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to any one of SEQ ID NOs: 1738, 1740, and 1742.

41. The AAV particle of claim 37, wherein the promoter is a truncated CMV promoter.

42. The AAV particle of claim 41, wherein the truncated CMV promoter is 109 nucleotides in length.

43. The AAV particle of claim 41 or claim 42, wherein the promoter comprises or consists of the nucleotide sequence of SEQ ID NO: 1750 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1750.

44. The AAV particle of any one of claims 1-43, wherein the viral genome further comprises a miRNA (miR) binding site that modulates expression of the encoded FXN protein in a cell or tissue of the liver.

45. The AAV particle of claim 44, wherein the viral genome comprises 3 copies of the miR binding site.

46. The AAV particle of claim 45, wherein the 3 copies of the miR binding site are identical.

47. The AAV particle of claim 45 or claim 46, wherein the 3 copies of the miR binding site are continuous.

48. The AAV particle of any one of claims 44-47, wherein the miR binding site is a miR122 binding site.

49. The AAV particle of any one of claims 44-48, wherein:

the miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1827 or a sequence having one, two, three, or at most four substitutions relative to SEQ ID NO: 1827; or

the 3 copies of continuous miR122 binding sites (miR122 binding site series) comprises the nucleotide sequence of SEQ ID NO: 1826 or a sequence having one, two, three, four, five, six, seven, eight, nine, or at most ten substitutions relative to SEQ ID NO: 1826.

50. The AAV particle of any one of claims 1-49, wherein the viral genome further comprises at least one inverted terminal repeat (ITR) region.

51. The AAV particle of claim 50, wherein the at least one ITR region comprises an AAV2 ITR.

52. The AAV particle of claim 50 or claim 51, wherein the viral genome comprises a 5' ITR region and a 3' ITR region.

53. The AAV particle of claim 52, wherein the 5' ITR region and the 3' ITR region is each an AAV2 ITR.

54. The AAV particle of claim 53, wherein:

the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

the 3' ITR region comprises the nucleotide sequence of SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

55. The AAV particle of any one of claims 1-54, wherein the viral genome further comprises an intron/exon region comprising an intron region and/or an exon region,

wherein the intron/exon region comprises:

an immediate-early 1 (ie1) intron region and/or a human beta-globin (hBglobin) intron region; and/or

an ie1 exon region and/or an hBglobin exon region.

56. The AAV particle of claim 55, wherein the intron region comprises:

an ie1 intron 1 comprising of the nucleotide sequence of SEQ ID NO: 1819 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

a hBglobin intron 2 comprising the nucleotide sequence of SEQ ID NO: 1820 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

57. The AAV particle of claim 55 or claim 56, wherein the exon region comprises:

an ie1 exon region comprising the nucleotide sequence of SEQ ID NO: 1817 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

an hBglobin exon region comprising the nucleotide sequence of SEQ ID NO: 1821 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

58. The AAV particle of any one of claims 1-57, wherein the viral genome further comprises a polyadenylation (polyA) region.

59. The AAV particle of claim 58, wherein the polyA region comprises a human growth hormone (hGH) polyA region, optionally wherein the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

60. The AAV particle of any one of claims 1-32, wherein the viral genome comprises:

(i) a 5' inverted terminal repeat (ITR) region;

(ii) a promoter;

(iii) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824; and

(iv) a 3' ITR region.

61. The AAV particle of any one of claims 1-32, wherein the viral genome comprises:

(i) a 5' inverted terminal repeat (ITR) region;

(ii) a promoter;

(iii) an intron and/or exon region;

(iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(v) at least one miR122 binding site; and

(vi) a 3' ITR region.

62. The AAV particle of any one of claims 1-32, wherein the viral genome comprises:

(i) a 5' inverted terminal repeat (ITR) region;

(ii) a promoter;

(iii) an intron and/or exon region;

(iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(v) at least one miR122 binding site;

(vi) a polyadenylation (polyA) region; and

(vii) a 3' ITR region.

63. The AAV particle of any one of claims 1-32, wherein the viral genome comprises:

(i) a 5' inverted terminal repeat (ITR) region;

(ii) a promoter;

(iii) an intron and/or exon region;

(iv) the FXN-encoding sequence, wherein the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a nucleotide sequence that is at least 80% identical (e.g., at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 1824;

(v) at least one miR122 binding site;

(vi) a polyadenylation (polyA) region;

(vii) a filler sequence; and

(viii) a 3' ITR region.

64. The AAV particle of claim 62 or claim 63, wherein:

(i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1742 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

(vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

65. The AAV particle of claim 64, wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1841 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto, optionally wherein the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

66. The AAV particle of claim 62 or claim 63, wherein:

(i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1750 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

(vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

67. The AAV particle of claim 66, wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1840 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto, optionally wherein the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

68. The AAV particle of claim 62 or claim 63, wherein:

(i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1738 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

(vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

69. The AAV particle of claim 68, wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1838 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at

least 97%, at least 98%, or at least 99% identical) thereto, optionally wherein the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

70. The AAV particle of claim 62 or claim 63, wherein:

(i) the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 1811 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(ii) the promoter consists of the nucleotide sequence of SEQ ID NO: 1740 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iii) the intron/exon region comprises the nucleotide sequence of SEQ ID NO: 1816 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(iv) the FXN-encoding sequence comprises the nucleotide sequence of SEQ ID NO: 1824 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(v) the at least one miR122 binding site comprises a miR122 binding site series comprising SEQ ID NO: 1826 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto;

(vi) the polyA region comprises the nucleotide sequence of SEQ ID NO: 1828 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and/or

(vii) the 3' ITR region comprises SEQ ID NO: 1812 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto.

71. The AAV particle of claim 70, wherein the viral genome further comprises a filler sequence comprising the nucleotide sequence of SEQ ID NO: 1839 or a sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto, optionally wherein the filler sequence is positioned 3' to the polyA region and 5' to the 3' ITR.

72. The AAV particle of any one of claims 1-32, wherein the viral genome comprises:

(a) the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at

least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1797;

(b) the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1801;

(c) the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1808; or

(d) the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1809.

73. The AAV particle of any one of claims 9-15, wherein the viral genome comprises:

(a) the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1797;

(b) the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1801;

(c) the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1808; or

(d) the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1809.

74. The AAV particle of any one of claims 16-22, wherein the viral genome comprises:

(a) the nucleotide sequence of SEQ ID NO: 1797 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at

least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1797;

(b) the nucleotide sequence of SEQ ID NO: 1801 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1801;

(c) the nucleotide sequence of SEQ ID NO: 1808 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1808; or

(d) the nucleotide sequence of SEQ ID NO: 1809 or a nucleotide sequence that is at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to the nucleotide sequence of SEQ ID NO: 1809.

75. An adeno-associated virus (AAV) particle comprising a viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 and an AAV capsid variant comprising:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4; and/or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

76. An adeno-associated virus (AAV) particle comprising a viral genome comprising the nucleotide sequence of SEQ ID NO: 1797 and an AAV capsid variant comprising:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 36; and/or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

77. The AAV particle of any one of claims 1-76, wherein the viral genome is single-stranded.

78. A cell comprising the AAV particle of any one of claims 1-77, optionally wherein the cell is a mammalian cell (e.g., an HEK293 cell), an insect cell (e.g., an Sf9 cell), or a bacterial cell.

79. A method of making an AAV particle of any one of claims 1-77, wherein the method comprises:

(i) providing a cell comprising the viral genome comprising a frataxin (FXN)-encoding sequence and a nucleic acid encoding the AAV capsid variant; and

(ii) incubating the cell under conditions suitable to encapsulate the viral genome in the AAV capsid variant;

thereby making the AAV particle.

80. The method of claim 79, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and

wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 4;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 4; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 4 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 4.

81. The method of claim 80, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 4, the amino acid sequence of positions 138-742 of SEQ ID NO: 4, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 4.

82. The method of claim 79, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and

wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 36;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 36; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 36 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 36.

83. The method of claim 82, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 36, the amino acid sequence of positions 138-742 of SEQ ID NO: 36, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 36.

84. The method of claim 79, wherein the viral genome comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 90% identical (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) thereto; and

wherein the AAV capsid variant comprises:

(i) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to SEQ ID NO: 982;

(ii) a VP2 protein comprising the amino acid sequence of positions 138-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 138-742 SEQ ID NO: 982; or

(iii) a VP3 protein comprising the amino acid sequence of positions 203-742 of SEQ ID NO: 982 or an amino acid sequence having at least 90% identity (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity) to positions 203-742 of SEQ ID NO: 982.

85. The method of claim 84, wherein the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982, the amino acid sequence of positions 138-742 of SEQ ID NO: 982, and/or the amino acid sequence of positions 203-742 of SEQ ID NO: 982.

86. The method of any one of claims 79-85, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the cell.

87. The method of any one of claims 79-86, wherein the cell comprises a second nucleic acid molecule encoding the AAV capsid variant.

88. The method of claim 87, further comprising, prior to step (i), introducing the second nucleic acid molecule into the cell.

89. The method of any one of claims 79-88, wherein the cell comprises a mammalian cell (e.g., an HEK293 cell), an insect cell (e.g., an Sf9 cell), or a bacterial cell.

90. A pharmaceutical composition comprising the AAV particle of any one of claims 1-77 and a pharmaceutically acceptable excipient.

91. A pharmaceutical composition comprising the AAV particle of any one of claims 5-22 and a pharmaceutically acceptable excipient.

92. A pharmaceutical composition comprising the AAV particle of any one of claims 9-15, 61, 64, 67, 70, and 75, and a pharmaceutically acceptable excipient.

93. A pharmaceutical composition comprising the AAV particle of any one of claims 16-22, 62, 65, 68, 71, and 76, and a pharmaceutically acceptable excipient.

94. A method of delivering a frataxin (FXN) protein to a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 1-77, thereby delivering the FXN protein.

95. The method of claim 94, wherein the subject has, has been diagnosed with having, or is at risk of having a disorder associated with FXN deficiency.

96. The method of claim 95, wherein the disorder associated with FXN deficiency is Friedreich's Ataxia (FA).

97. A method of treating a disorder associated with frataxin (FXN) deficiency in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 1-77, thereby treating the disorder.

98. A method of treating a disorder associated with frataxin (FXN) deficiency in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 5-22, thereby treating the disorder.

99. A method of treating a disorder associated with frataxin (FXN) deficiency in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 92 or the AAV particle of any one of claims 9-15, 61, 64, 67, 70, and 75, thereby treating the disorder.

100. A method of treating a disorder associated with frataxin (FXN) deficiency in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 93 or the AAV particle of any one of claims 16-22, 62, 65, 68, 71, and 76, thereby treating the disorder.

101. The method of any one of claims 97-100, wherein the subject has, has been diagnosed with having, or is at risk of having a disorder associated with FXN deficiency.

102. The method of any one of claims 97-101, wherein the disorder is Friedreich's Ataxia (FA).

103. The method of any one of claims 97-102, wherein the administration results in an increase in the subject's FXN protein level as compared to baseline.

104. The method of any one of claims 97-103, wherein the treatment results in amelioration of at least one symptom of Friedreich's Ataxia (FA).

105. The method of claim 104, wherein the at least one symptom of FA comprises impaired sensory functions, impaired motor function (e.g., ataxia and/or involuntary movements), fatigue, chronic pain, seizures, impaired speech, sleep disturbances, metabolic disorders (e.g., diabetes), and/or increased spasticity.

106. The method of any one of claims 100-105, wherein the treatment stabilizes, slows the progression of, or improves the subject's FA as determined by the modified Friedreich Ataxia Rating Scale (mFARS), the Scale for the Assessment and Rating of Ataxia (SARA), and/or the International Cooperative Ataxia Rating Scale (ICARS).

107. The method of claim 106, wherein the treatment slows the subject's progression of FA as measured by mFARS, SARA, and/or ICARS relative to an individual with the disorder associated

with FXN deficiency who has not been administered the pharmaceutical composition or the AAV particle.

108. The method of any one of claims 97-107, wherein the subject is a human.

109. The method of any one of claims 97-108, wherein the AAV particle or the pharmaceutical composition is delivered to a cell or tissue of the CNS, optionally wherein the AAV particle or the pharmaceutical composition is delivered via intravenous administration.

110. The method of any one of claims 97-109, further comprising evaluating, e.g., measuring, the level of FXN expression, e.g., FXN gene, FXN mRNA, and/or FXN protein expression, in the subject, e.g., in a cell, tissue, or fluid, of the subject.

111. The method of claim 110, wherein the level of FXN protein expression is measured by an enzyme-linked immunosorbent assay (ELISA), a Western blot, an immunohistochemistry assay, or a frataxin biofluid assay.

112. The method of claim 110 or claim 111, wherein the cell or tissue is a cell or tissue of the central nervous system (CNS).

113. The method of claim 110 or claim 111, wherein the cell or tissue is a peripheral cell or tissue.

114. The method of any one of claims 97-113, wherein the administration results in an increase in:

(i) the level of FXN protein or FXN gene expression in a cell, tissue, (e.g., a cell or tissue of the CNS, e.g., the cortex, striatum, thalamus, cerebellum, and/or brainstem), and/or fluid (e.g., CSF and/or serum), of the subject; and/or

(ii) the level of viral genomes (VG) per cell in a CNS tissue (e.g., the cortex, striatum, thalamus, cerebellum, brainstem, and/or spinal cord) of the subject, optionally wherein the VG level is increased by greater than 50 VGs per cell, as compared to a peripheral tissue.

115. The method of any one of claims 97-114, further comprising administering to the subject at least one additional therapeutic agent and/or therapy.

116. The method of claim 115, wherein the at least one additional therapeutic agent and/or therapy comprises an agent and/or therapy for treating the disorder associated with FXN deficiency (e.g., Friedreich's Ataxia).

117. The method of claim 115 or claim 116, wherein the at least one additional therapeutic agent and/or therapy comprises omaveloxolone or idebenone.

118. The method of any one of claims 97-117, further comprising administering an immunosuppressant to the subject.

119. The method of claim 118, wherein the immunosuppressant comprises a corticosteroid (e.g., prednisone, prednisolone, methylprednisolone, and/or dexamethasone), rapamycin, mycophenolate mofetil, tacrolimus, rituximab, and/or eculizumab hydroxychloroquine.

120. The pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 1-77 for use in a method of treating a disorder according to any one of claims 100-119.

121. The pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 1-77 for use in the treatment of a disorder associated with FXN deficiency in a subject, optionally wherein the disorder is Friedreich's Ataxia.

122. The pharmaceutical composition or the AAV particle for use of claim 121, wherein the subject has, has been diagnosed with having, or is at risk of having Friedreich's Ataxia.

123. Use of an effective amount of the pharmaceutical composition of any one of claims 90-93 or the AAV particle of any one of claims 1-77 in the manufacture of a medicament for the treatment of a disorder associated with FXN deficiency in a subject, optionally wherein the disorder is Friedreich's Ataxia.

124. The use of claim 123, wherein the subject has, has been diagnosed with having, or is at risk of having Friedreich's Ataxia.

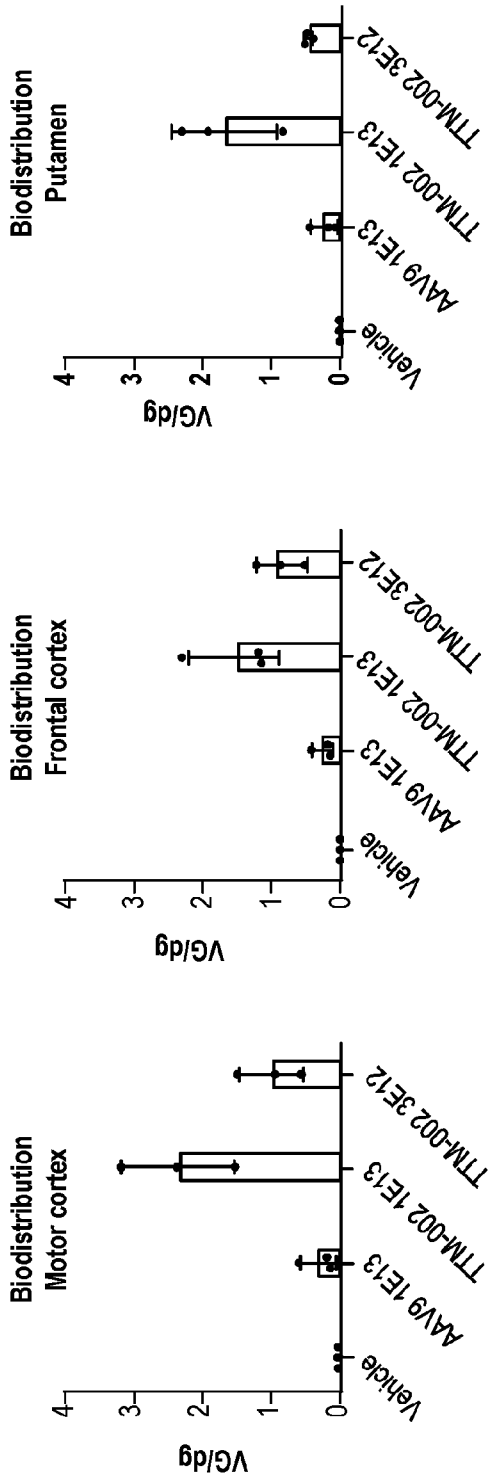
Biodistribution
Motor cortex
VG/dg
0
1
2
3
4
Vehicle
AAV9 1E13
TTM-002 1E13
TTM-002 3E12
Biodistribution
Frontal cortex
VG/dg
0
1
2
3
4
Vehicle
AAV9 1E13
TTM-002 1E13
TTM-002 3E12
Biodistribution
Putamen
VG/dg
0
1
2
3
4
Vehicle
AAV9 1E13
TTM-002 1E13
TTM-002 3E12

FIG. 1

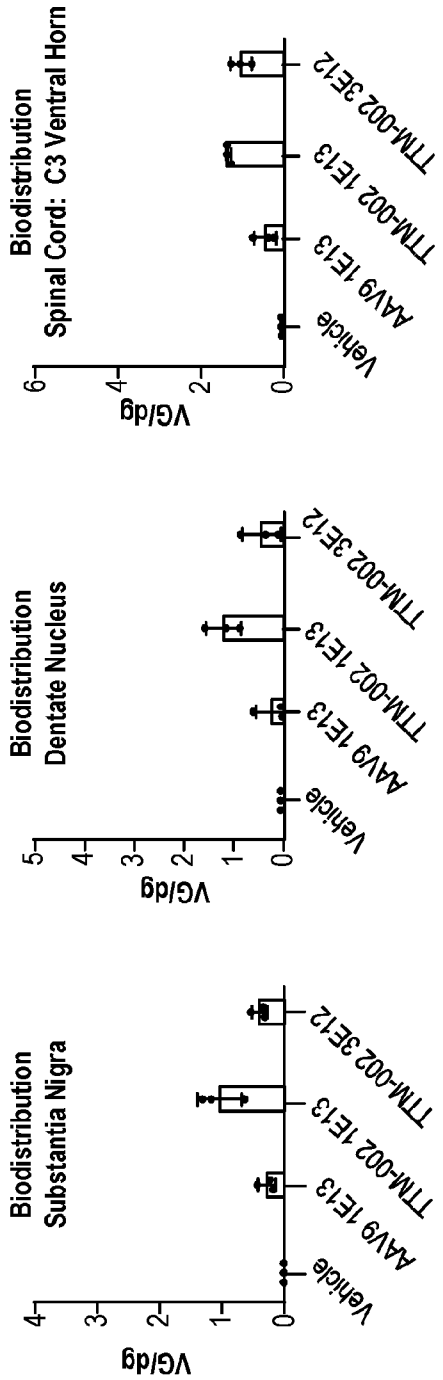

FIG. 1 (continued)

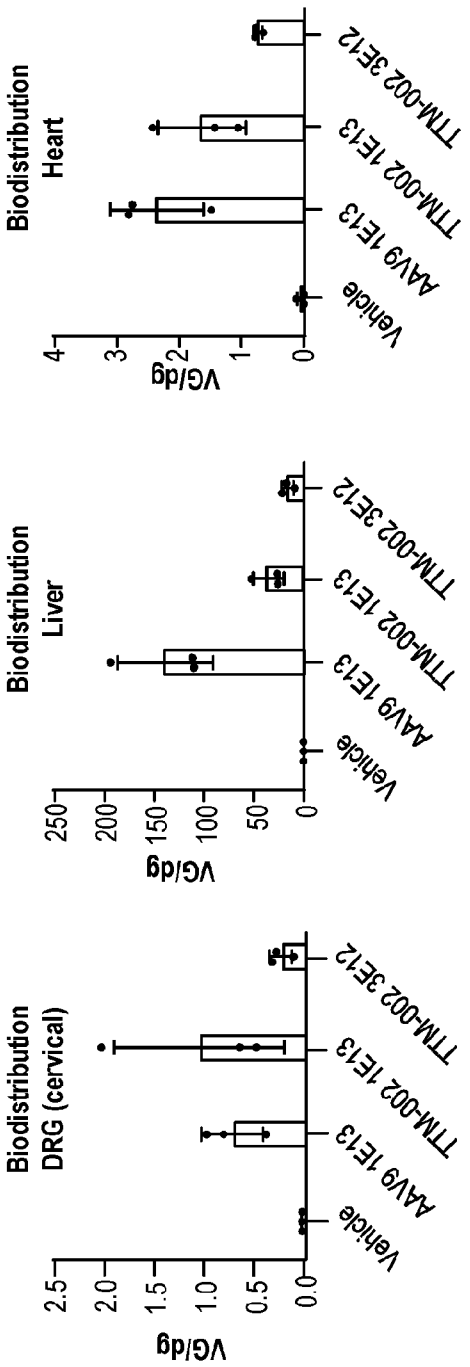

FIG. 1 (continued)

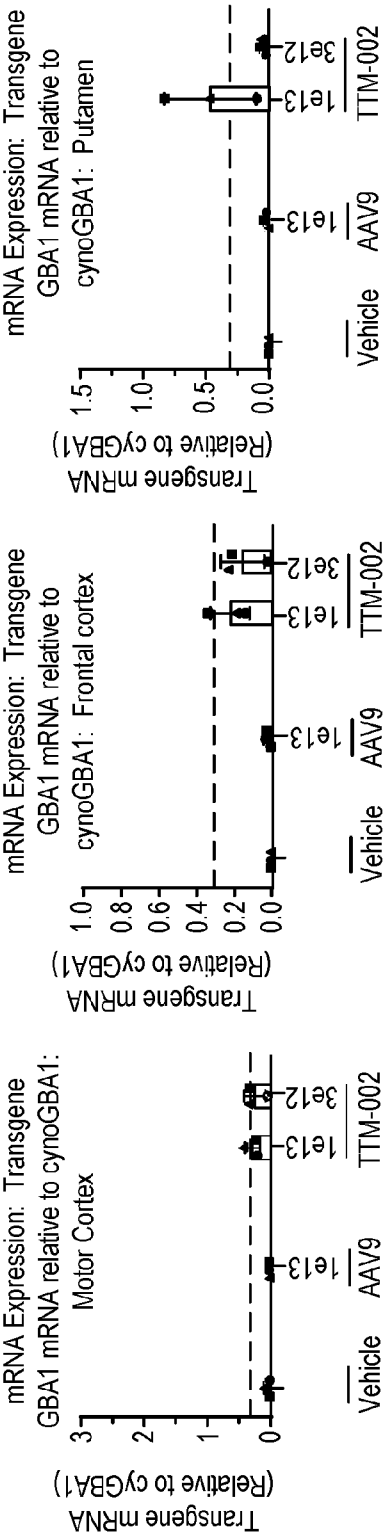
mRNA Expression: Transgene GBA1 mRNA relative to cynoGBA1: Motor Cortex
Transgene mRNA (Relative to cyGBA1)
0
1
2
3
Vehicle
AAV9
1e13
1e13
3e12
TTM-002
mRNA Expression: Transgene GBA1 mRNA relative to cynoGBA1: Frontal cortex
Transgene mRNA (Relative to cyGBA1)
0.0
0.2
0.4
0.6
0.8
1.0
Vehicle
AAV9
1e13
1e13
3e12
TTM-002
mRNA Expression: Transgene GBA1 mRNA relative to cynoGBA1: Putamen
Transgene mRNA (Relative to cyGBA1)
0.0
0.5
1.0
1.5
Vehicle
AAV9
1e13
1e13
3e12
TTM-002

FIG. 2

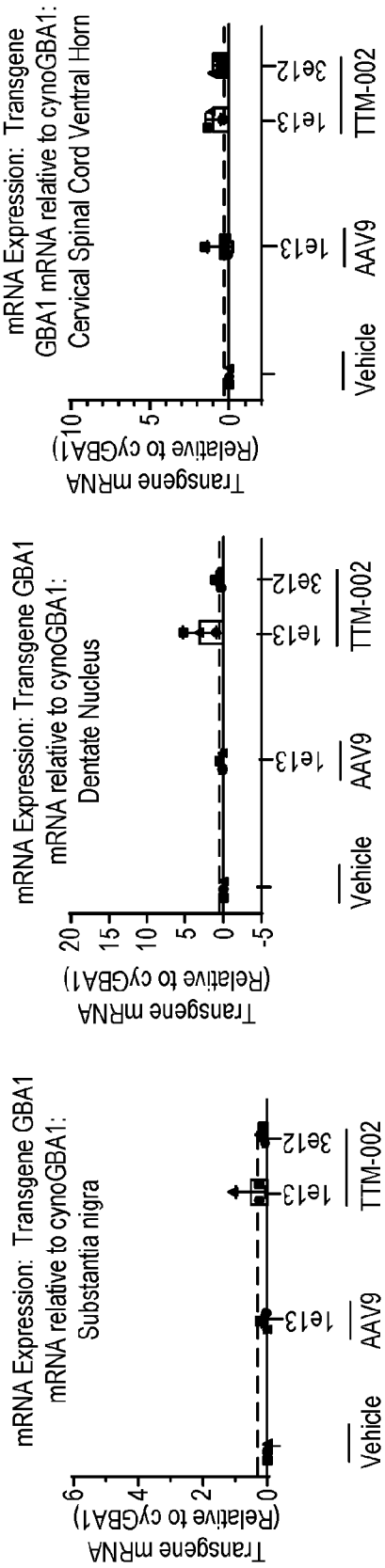

FIG. 2 (continued)

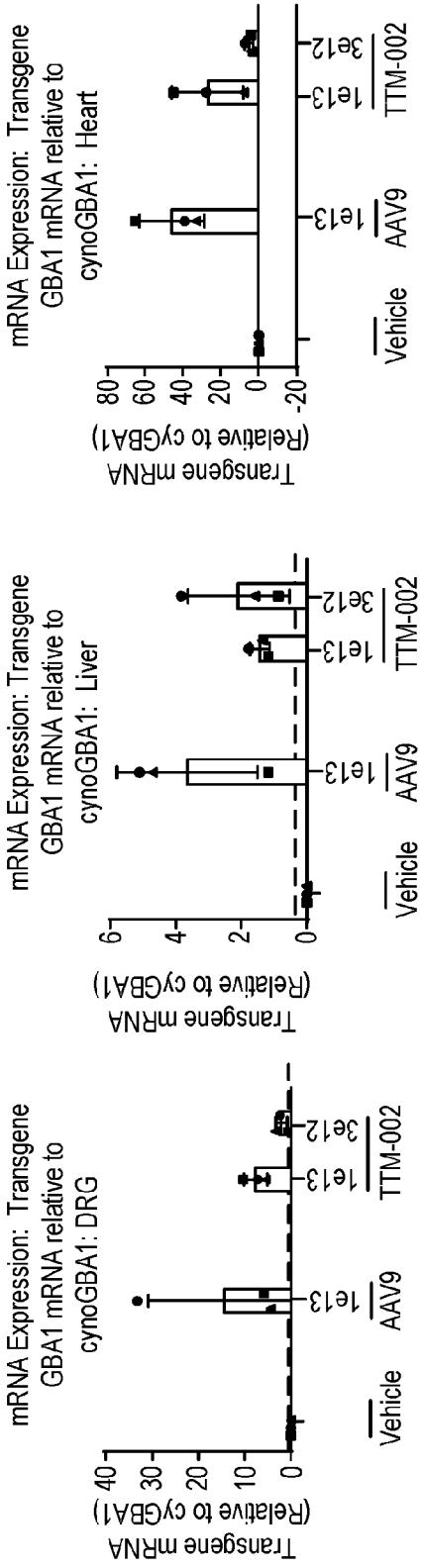

FIG. 2 (continued)

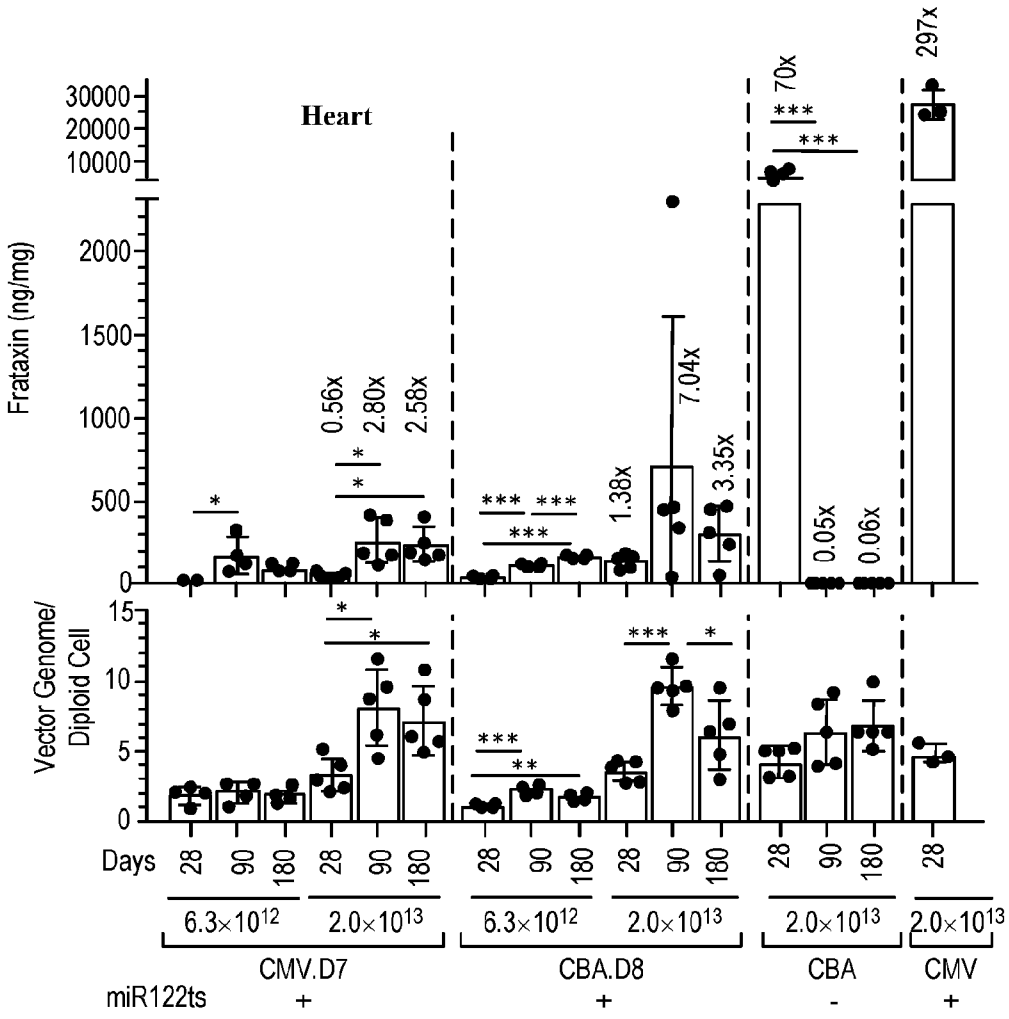
Heart
Frataxin (ng/mg)
30000
20000
10000
2000
1500
1000
500
0
0.56x
2.80x
2.58x
1.38x
7.04x
3.35x
70x
0.05x
0.06x
297x
Vector Genome/ Diploid Cell
15
10
5
0
Days
28
90
180
6.3×10^12
2.0×10^13
CMV.D7
CBA.D8
CBA
CMV
miR122ts
+
-

FIG. 3A

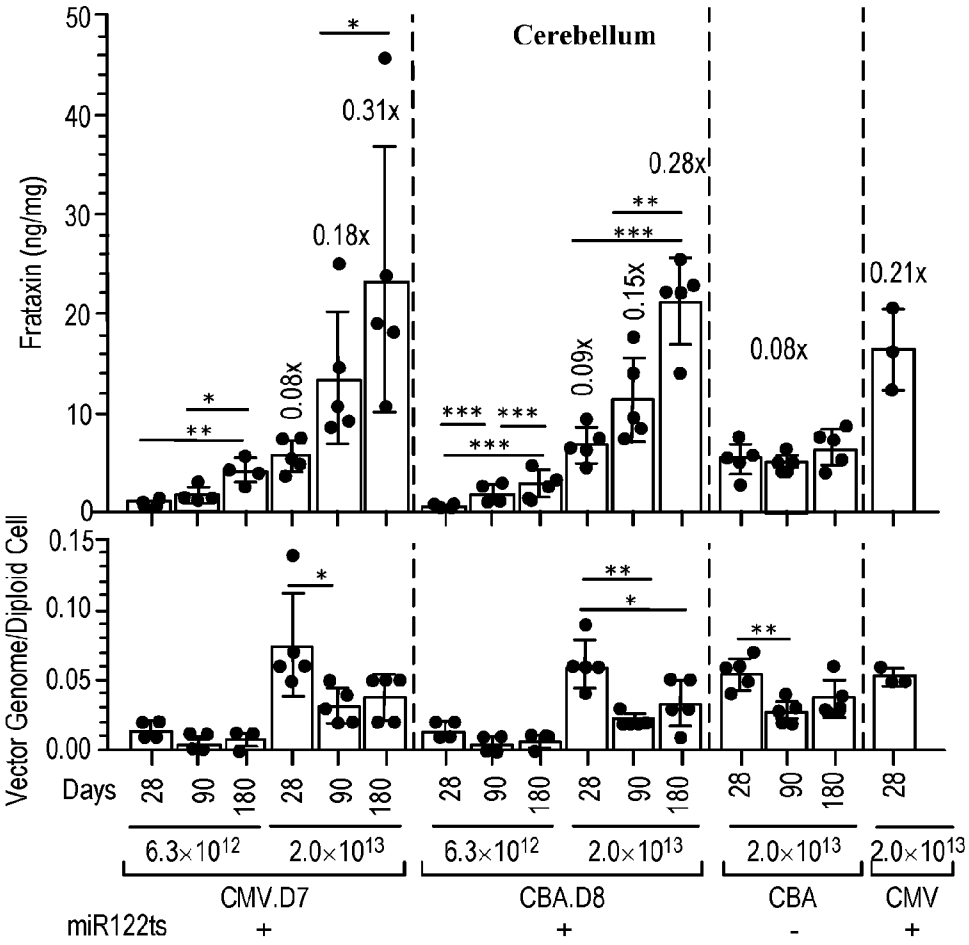
Cerebellum
Frataxin (ng/mg)
Vector Genome/Diploid Cell
0.31x
0.18x
0.08x
0.09x
0.15x
0.28x
0.08x
0.21x
Days
28
90
180
6.3×10^12
2.0×10^13
CMV.D7
CBA.D8
CBA
CMV
miR122ts
+
+
-
+

FIG. 3B

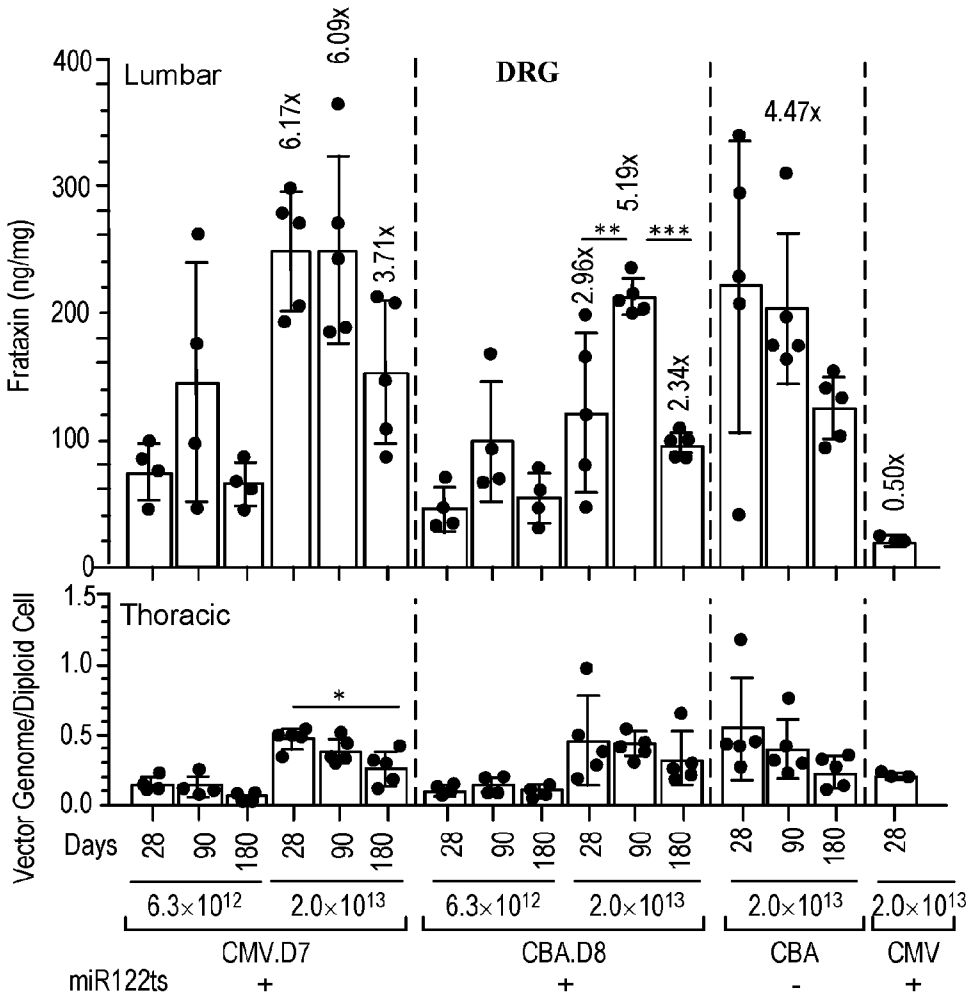
Lumbar
DRG
Frataxin (ng/mg)
400
300
200
100
0
6.17x
6.09x
3.71x
2.96x
**
5.19x
***
2.34x
4.47x
0.50x
Thoracic
Vector Genome/Diploid Cell
1.5
1.0
0.5
0.0
*
Days
28
90
180
6.3×10^12
2.0×10^13
CMV.D7
CBA.D8
CBA
CMV
miR122ts
+
+
-
+

FIG. 3C

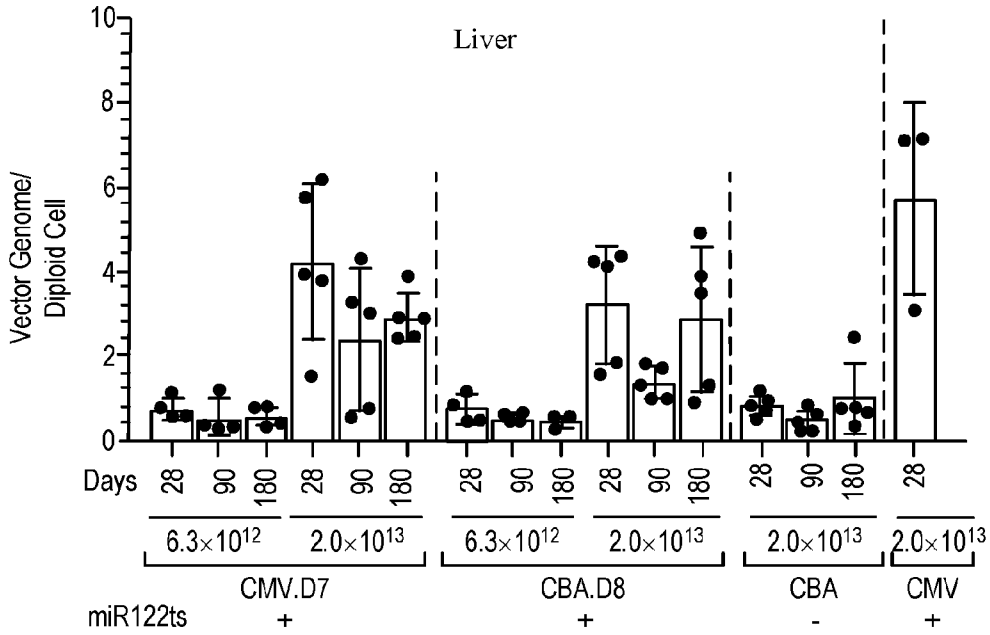
Liver
Vector Genome/ Diploid Cell
10
8
6
4
2
0
Days
28
90
180
28
90
180
28
90
180
28
90
180
28
90
180
28
6.3×10^12
2.0×10^13
6.3×10^12
2.0×10^13
2.0×10^13
2.0×10^13
CMV.D7
CBA.D8
CBA
CMV
miR122ts
+
+
-
+

FIG. 3D

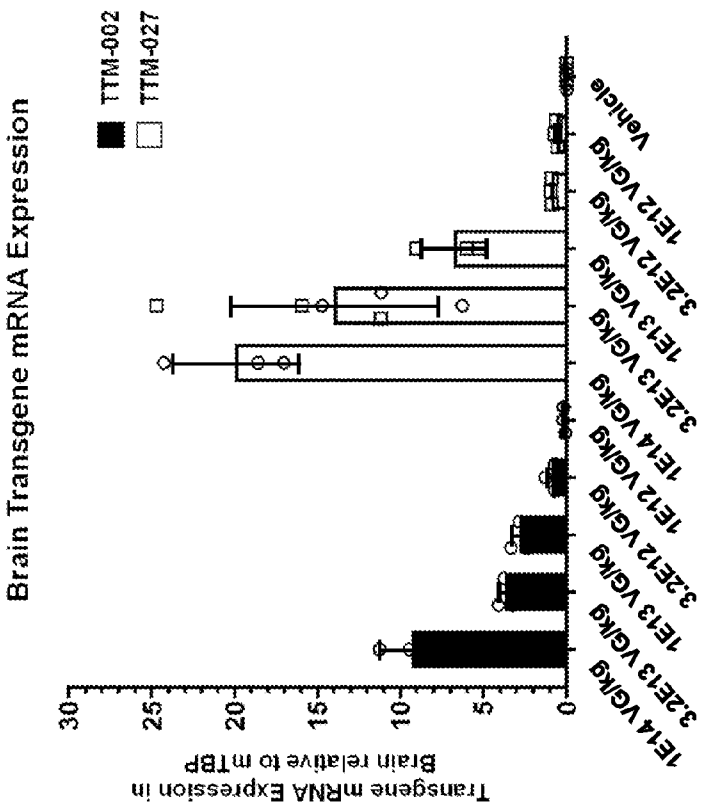
Brain Transgene mRNA Expression
TTM-002
TTM-027
Transgene mRNA Expression in Brain relative to mTBP
30
25
20
15
10
5
0
1E14 VG/kg
3.2E13 VG/kg
1E13 VG/kg
3.2E12 VG/kg
1E12 VG/kg
1E14 VG/kg
3.2E13 VG/kg
1E13 VG/kg
3.2E12 VG/kg
1E12 VG/kg
Vehicle

FIG. 4B

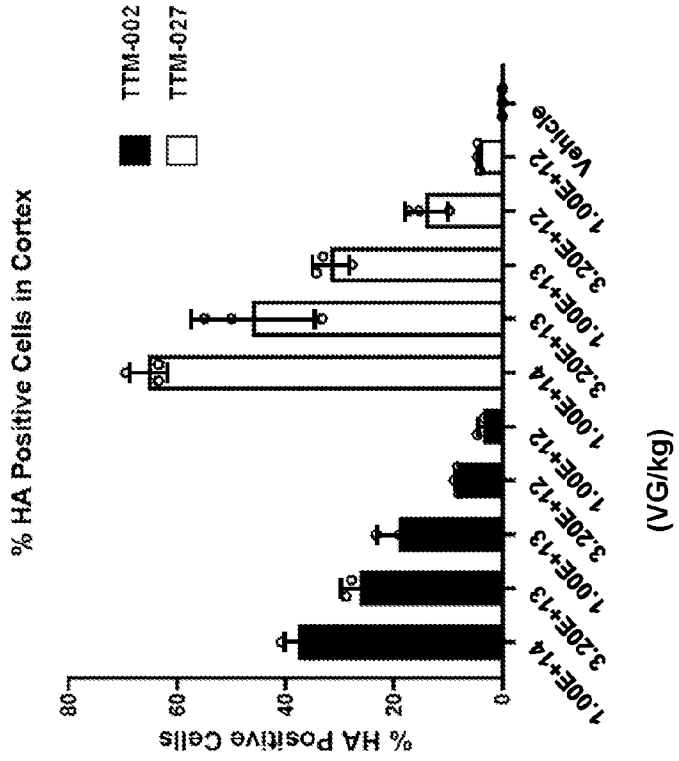
% HA Positive Cells in Cortex
TTM-002
TTM-027
% HA Positive Cells
80
60
40
20
0
1.00E+14
3.20E+13
1.00E+13
3.20E+12
1.00E+12
1.00E+14
3.20E+13
1.00E+13
3.20E+12
1.00E+12
Vehicle
(VG/kg)

FIG. 4A

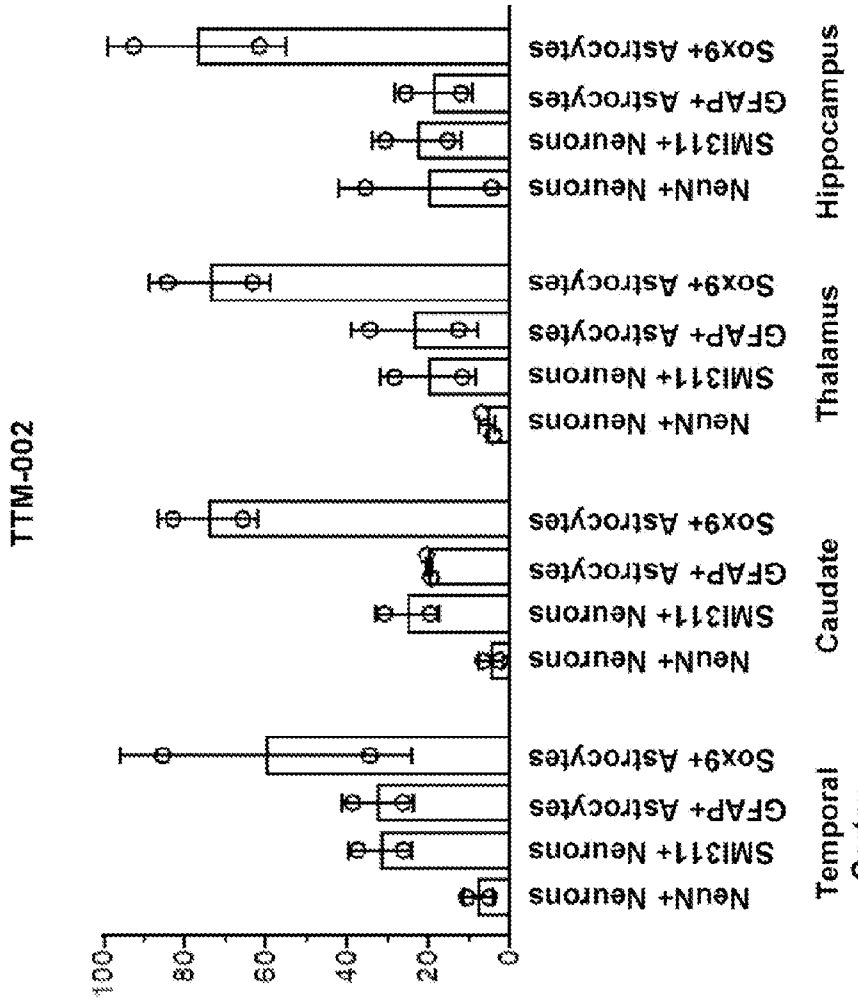
TTM-002
% HA+ Cells
100
80
60
40
20
0
Temporal Cortex
Caudate
Thalamus
Hippocampus
NeuN+ Neurons
SMI311+ Neurons
GFAP+ Astrocytes
Sox9+ Astrocytes

FIG. 5B

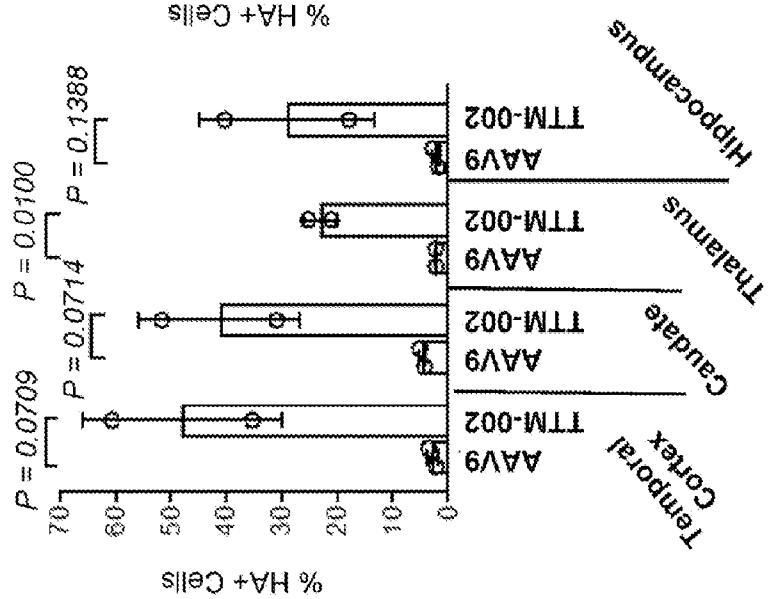
% HA+ Cells
70
60
50
40
30
20
10
0
P = 0.0709
P = 0.0714
P = 0.0100
P = 0.1388
Temporal Cortex
Caudate
Thalamus
Hippocampus
AAV9
TTM-002

FIG. 5A

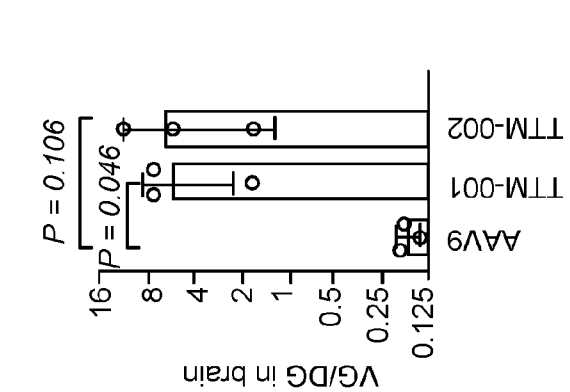

FIG. 6A

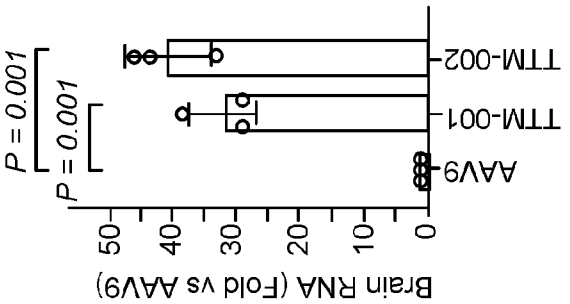

FIG. 6B

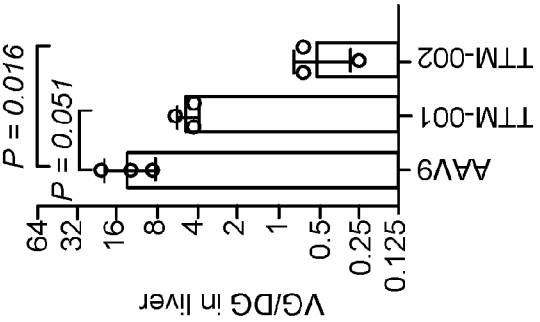

FIG. 6C

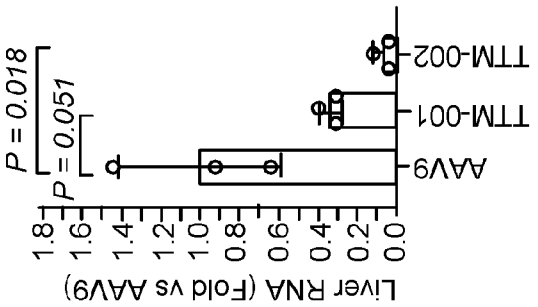

FIG. 6D