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(54) Titre : TRAITEMENT D'ETATS OPHTALMIQUES AVEC DES INHIBITEURS DE L'ANGIOPOIETINE 7 (ANGPTL7)
(54) Title: TREATMENT OF OPHTHALMIC CONDITIONS WITH ANGIOPOIETIN-LIKE 7 (ANGPTL7) INHIBITORS

(57) Abrégé/Abstract:

The present disclosure provides methods of treating patients having an ophthalmic condition, methods of identifying subjects having an increased risk of developing an ophthalmic condition, methods of detecting human angiopoietin like 7 (ANGPTL7) variant nucleic acid molecules and variant polypeptides, and ANGPTL7 variant nucleic acid molecules and variant polypeptides.



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(54) Title: TREATMENT OF OPHTHALMIC CONDITIONS WITH ANGIOPOIETIN-LIKE 7 (ANGPTL7) INHIBITORS

(57) Abstract: The present disclosure provides methods of treating patients having an ophthalmic condition, methods of identifying subjects having an increased risk of developing an ophthalmic condition, methods of detecting human angiopoietin like 7 (ANGPTL7) variant nucleic acid molecules and variant polypeptides, and ANGPTL7 variant nucleic acid molecules and variant polypeptides.

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**Treatment Of Ophthalmic Conditions With Angiopoietin-Like 7
(ANGPTL7) Inhibitors**

Reference To Sequence Listing

5 This application includes a Sequence Listing submitted electronically as a text file named 18923801602SEQ, created on January 18, 2020, with a size of 111 kilobytes. The Sequence Listing is incorporated herein by reference.

Field

10 The present disclosure relates generally to the treatment of patients having ophthalmic conditions with angiopoietin like 7 (ANGPTL7) inhibitors, methods of identifying subjects having an increased risk of developing ophthalmic conditions, methods of detecting ANGPTL7 variant nucleic acid molecules and variant polypeptides, and ANGPTL7 variant nucleic acid molecules and ANGPTL7 variant polypeptides.

15

Background

Glaucoma is a collection of disorders that damage the optic nerve of the eye and can result in partial vision loss and blindness. Several types of glaucoma exist, the primary form being open-angle glaucoma, whereby fluid within the eye builds up and increases the pressure 20 inside the eye (intraocular pressure; IOP) to a level that may damage the optic nerve. In low-tension or normal-tension glaucoma, optic nerve damage and narrowed side vision occur in people with normal ocular pressure. In angle-closure glaucoma, the fluid at the front of the eye cannot drain properly, which may lead to a sudden increase in ocular pressure. In congenital glaucoma, children are born with a defect in the eye that slows the normal drainage of fluid.

25 Glaucoma treatments include drug therapy, laser trabeculoplasty, and conventional surgery. While these treatments may save remaining vision, they do not improve sight already lost from glaucoma.

ANGPTL7 is a secreted glycoprotein structurally related to the angiopoietin family of growth factors. ANGPTL7 contains C-terminal (fibrinogen-like) and N-terminal (coiled) domains. 30 ANGPTL7 is predominantly found in the stromal layer of the cornea and the extracellular matrix of the trabecular meshwork.

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Summary

The present disclosure provides methods of treating a patient having increased IOP, the method comprising administering an ANGPTL7 inhibitor to the patient.

The present disclosure also provides methods of treating a patient having glaucoma, 5 the method comprising administering an ANGPTL7 inhibitor to the patient.

In some embodiments, the methods further comprise detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid 10 molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 15 according to SEQ ID NO:8. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or a cDNA molecule produced from an 20 mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an mRNA molecule having a nucleotide sequence 25 comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence 30 comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or a cDNA molecule produced from

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an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; an mRNA molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

10 In some embodiments, the detecting step comprises sequencing at least a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample.

15 In some embodiments, the detecting step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, and detecting the detectable label.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of: determining whether the patient 20 has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then administering or continuing to 25 administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard 30 dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule

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encoding the human ANGPTL7 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition.

Brief Description Of The Drawings

5 The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Figure 1 shows a Manhattan plot depicting association of rare (NAF<0.01), protein-altering variants (including those predicted to affect splicing) with IOP in individuals of

10 European descent in the meta-analysis of the UKB and GHS studies. Significance thresholds: 1x10⁻⁵ (blue line) and 5x10⁻⁸ (red line).

Figures 2A-2F show the association of Gln175His (Figure 2A, 2C, and 2E) and Arg177* (Figure 2B, Figure 2D, and Figure 2F) variants in ANGPTL7 with IOP and glaucoma in individuals of European descent; the effect for association with IOP is measured in standard deviation

15 units; association p-values were calculated using BOLT-LMM adjusted for age, age squared, sex, top principal components and, for UKB, genotyping array and assessment center (Figure 2A and 2B); boxplots representing Goldmann-correlated (IOPg) in the UK Biobank across genotypes (Figure 2C and 2D); Gln175His heterozygous and homozygous carriers have a 0.8-mmHg and 4.1-mmHg lower median IOPg, respectively, compared to non-carriers (Figure 2C); Arg177*

20 heterozygous carriers have a 1.4-mmHg lower IOPg compared to non-carriers (Figure 2D); association with glaucoma was conducted across four series for Gln175His and Arg177*. GHS VCRome: Geisinger ~60,000 individuals, captured with VCRome; GHS IDT: ~85,000 individuals, captured with IDT; UKB: UK Biobank; MSSM: Mt. Sinai Medical School BioMe Biobank; MDCS: Malmo Diet and Cancer Study (Figure 2E and 2F); AAF = alternative allele frequency.

25 Figure 3 shows missense and predicted loss-of-function (pLOF) variants in *ANGPTL7* and IOP levels in individuals of European descent. The plots represent Goldmann-correlated IOP (mean of both eyes) levels in carriers of 1 pLOF and 6 missense variants in *ANGPTL7* that are predicted deleterious by five different algorithms and have at least 4 carriers with IOP measurements in about 150,000 individuals in the UK Biobank for whom exome sequence data 30 are available. The median IOP level across carriers of all 34 pLOF and predicted-deleterious missense *ANGPTL7* variants (15.11 mmHg) is indicated by the red line, and the median IOP in non-variant carriers (15.51 mmHg) is indicated by the blue line. Magenta diamonds mark the

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median IOP in carriers of each variant. Beneath the plots is the median and interquartile range of IOP and the numbers of carriers that are glaucoma cases and controls for each variant.

Figures 4A-4E show ANGPTL7 expression in ocular tissues across species; RNA-sequencing-based expression levels (measured in transcripts per million, TPM) are highest in 5 cornea, trabecular meshwork (TM), and sclera in human (Figure 4A), and African green monkey (Figure 4B) eyes, and in cornea, TM, sclera, optic nerve, and choroid/RPE in C57BL/6J mice (Figure 4C). In situ hybridization (RNAscope) shows ANGPTL7/Angptl7 (red) expression in TM, cornea and sclera in human (Figure 4D) and murine (Figure 4E) eyes. DAPI staining (blue) counterstains cell nuclei. RPE: retinal pigmented epithelium; CB: ciliary body; SC: Schlemm's 10 canal; CM: ciliary muscle; AC: anterior chamber; TM: trabecular meshwork; RGC: retinal ganglion cell; INL: inner nuclear layer; ONL: outer nuclear layer.

Figure 5 shows dexamethasone (DEX)-induced gene expression changes in three human trabecular meshwork (hTM) primary cell lines from three independent human eyes, measured with quantitative PCR (qPCR); hTM cells were treated with DEX for 72 hours followed 15 by qPCR analysis; DEX treatment increased ANGPTL7 expression in two out of three HTM cell lines; Ctrl represents untreated cells and EtOH represents ethanol treatment; data are presented as means \pm standard error across two replicates, one-way ANOVA, *p=0.01, **p=0.001, ***p=0.0001.

Figure 6A shows increasing mAngptl7 levels in mouse eyes increases IOP. Murine 20 Angptl7 (mAngptl7) protein was injected into mouse eyes via intravitreal route and IOP was measured over time. After an initial drop, IOP was elevated in Angptl7-treated eyes compared to control eyes. Data are presented as means \pm SEM.

Figure 6B shows Increasing mAngptl7 levels in mouse eyes increases IOP. Murine 25 Angptl7 (mAngptl7) protein was injected into mouse eyes via intracameral route and IOP was measured over time. After an initial drop, IOP was elevated in Angptl7-treated eyes compared to control eyes. Data are presented as means \pm SEM.

Figure 7A shows association of Trp188* in ANGPTL7 with IOP in individuals of African ancestry across two cohorts;

Figure 7B shows association of Trp188* in ANGPTL7 with glaucoma in individuals of 30 African ancestry across two cohorts.

Figure 7C shows Meta-analysis of the European-enriched Arg177*, and the African-enriched Trp188*, pLOF variants in ANGPTL7 for IOP. The Arg177* variant is represented by the

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cohorts labeled 'EUR', which include only European ancestry individuals. The Trp188* variant is represented by the cohorts labeled 'AFR', which include only African ancestry individuals.

Figure 7D shows Meta-analysis of the European-enriched Arg177*, and the African-enriched Trp188*, pLOF variants in *ANGPTL7* for glaucoma. The Arg177* variant is represented by the cohorts labeled 'EUR', which include only European ancestry individuals. The Trp188* variant is represented by the cohorts labeled 'AFR', which include only African ancestry individuals.

Figure 8A and 8B show the expression of two variants of *ANGPTL7* (Gln175His and Arg177Stop) in HEK 293 whole cell lysates; Figure 8C and Figure 8D shows a drastic decrease of the Gln175His variant observed in the cell supernatant compared to the wild type *ANGPTL7*; Figure 8E shows Arg177Stop variant unable to be secreted in the supernatant.

Figure 9A shows an RT-PCR analysis of *ANGPTL7* wild type and variants at 48 hours from HEK293 transfection. Expression values are calculated relative to GAPDH housekeeping gene.

Figure 9B shows western blotting showing intracellular protein levels of *ANGPTL7* wild type, *ANGPTL7* Gln175His and *ANGPTL7* Arg177*.

Figure 9C shows ELISA assay showing intracellular protein levels of *ANGPTL7* wild type, *ANGPTL7* Gln175His and *ANGPTL7* Arg177*. For quantification each cell lysate was diluted 1:1,000.

Figure 9D shows western blotting showing extracellular protein levels of *ANGPTL7* wild type, *ANGPTL7* Gln175His and *ANGPTL7* Arg177*. The analysis were repeated on three independent biological replicates.

Figure 9E shows ELISA assay showing extracellular protein levels of *ANGPTL7* wild type, *ANGPTL7* Gln175His and *ANGPTL7* Arg177*. For quantification each supernatant was diluted 1:10,000. Western blotting and ELISA analysis were repeated on three independent biological replicates. Technical replicates (n=3) were run for RT-PCR and ELISA analysis.

Description

Various terms relating to aspects of the present disclosure are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art, unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

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Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order.

Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, 5 in any respect. This holds for any possible non-expressed basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

As used herein, the singular forms "a," "an" and "the" include plural referents unless 10 the context clearly dictates otherwise.

As used herein, the terms "subject" and "patient" are used interchangeably. A subject may include any animal, including mammals. Mammals include, but are not limited to, farm animals (such as, for example, horse, cow, pig), companion animals (such as, for example, dog, cat), laboratory animals (such as, for example, mouse, rat, rabbits), and non-human primates.

15 In some embodiments, the subject is a human.

As used herein, a "nucleic acid," a "nucleic acid molecule," a "nucleic acid sequence," a "polynucleotide," or an "oligonucleotide" can comprise a polymeric form of nucleotides of any length, can comprise DNA and/or RNA, and can be single-stranded, double-stranded, or multiple stranded. One strand of a nucleic acid also refers to its complement.

20 As used herein, the term "comprising" may be replaced with "consisting" or "consisting essentially of" in particular embodiments as desired.

An "isolated" nucleic acid molecule is a polynucleotide that is in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated nucleic acid molecule is substantially free of other polynucleotides, particularly other 25 polynucleotides of animal origin. It is preferred to provide the nucleic acid molecule in a highly purified form, i.e., greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same nucleic acid molecule in alternative physical forms, such as dimers or alternatively phosphorylated or derivatized forms.

30 Certain variations in the ANGPTL7 gene associate with a decreased risk of developing ophthalmic conditions, such as increased IOP and glaucoma, in human subjects. For example, a genetic alteration that changes the cytosine nucleotide of position 4,291 in the human

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ANGPTL7 reference (see, SEQ ID NO:1) to thymine or changes the guanine nucleotide of position 4,287 in the human ANGPTL7 reference (see, SEQ ID NO:1) to thymine has been observed to indicate that the human having such an alteration may have a decreased risk of developing ophthalmic conditions, such as increased IOP and glaucoma. Altogether, the genetic

5 analyses described herein indicate that particular variants in the ANGPTL7 gene associate with a decreased risk of developing ophthalmic conditions, such as increased IOP and glaucoma.

Therefore, human subjects that are ANGPTL7 reference that have an increased risk of developing an ophthalmic condition, such as increased IOP and glaucoma, may be treated such that the ophthalmic condition is prevented, the symptoms thereof are reduced, and/or

10 development of symptoms is repressed. Accordingly, the present disclosure provides isolated ANGPTL7 variant genomic nucleic acid molecules, variant mRNA molecule, and variant cDNA molecules. Additionally, the disclosure provides methods of leveraging the identification of such variants in subjects to identify or stratify risk in such subjects of developing ophthalmic conditions, such as increased IOP and glaucoma, or to diagnose subjects as having an increased

15 risk of developing ophthalmic conditions, such as increased IOP and glaucoma, such that subjects at risk or subjects with active disease may be treated accordingly. Accordingly, provided herein are ANGPTL7 loss-of-function variant nucleic acid molecules discovered to be associated with a decreased risk of developing ophthalmic conditions, such as increased IOP and glaucoma.

20 For purposes of the present disclosure, any particular human can be categorized as having one of three ANGPTL7 genotypes: i) ANGPTL7 reference; ii) heterozygous for an ANGPTL7 predicted loss-of-function variant, and iii) homozygous for an ANGPTL7 predicted loss-of-function variant. A human in the ANGPTL7 reference category does not have a copy of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule. A human in the

25 heterozygous ANGPTL7 predicted loss-of-function variant category has a single copy of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule. An ANGPTL7 predicted loss-of-function variant nucleic acid molecule is any ANGPTL7 nucleic acid molecule (such as, a genomic nucleic acid molecule, an mRNA molecule, or a cDNA molecule produced from the mRNA molecule) encoding an ANGPTL7 polypeptide having a partial loss-of-function, a

30 complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. A human who has an ANGPTL7 polypeptide having a partial loss-of-function (or predicted partial loss-of-function) is hypomorphic for ANGPTL7. The ANGPTL7 predicted loss-of-

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function variant nucleic acid molecule is believed to be any nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Lys192Gln, Phe161Ile, Trp188Stop, Arg340His, Arg220His, Asn302Lys, or Arg220Cys. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Arg177Stop, Lys192Gln, Phe161Ile, or Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, or Phe161Ile. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Trp188Stop, or Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Lys192Gln. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Phe161Ile. A human in the homozygous ANGPTL7 predicted loss-of-function variant category has two copies of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule.

For human subjects or patients that are genotyped or determined to be ANGPTL7 reference, such human subjects or patients have an increased risk of developing ophthalmic conditions, such as increased IOP, pre-glaucoma, glaucoma, and decreased corneal hysteresis. For human subjects or patients that are genotyped or determined to be either ANGPTL7 reference or heterozygous for an ANGPTL7 predicted loss-of-function variant, such human subjects or patients can be treated with an ANGPTL7 inhibitor.

The present disclosure provides methods of treating a patient having glaucoma, the methods comprising administering an ANGPTL7 inhibitor to the patient. In some embodiments, the glaucoma is primary open-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, congenital glaucoma, neovascular glaucoma, steroid-induced glaucoma, or glaucoma related to ocular trauma.

The present disclosure also provides methods of treating a patient having increased IOP, the methods comprising administering an ANGPTL7 inhibitor to the patient. In some embodiments, the increased IOP is corneal compensated IOP (IOPcc) or Goldmann-correlated IOP (IOPg).

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The present disclosure also provides methods of treating a patient having pre-glucoma, the methods comprising administering an ANGPTL7 inhibitor to the patient.

The present disclosure also provides methods of treating a patient having decreased corneal hysteresis, the methods comprising administering an ANGPTL7 inhibitor to the patient.

5 In some embodiments, the ANGPTL7 inhibitor comprises an antisense molecule.

Examples of antisense molecules include, but are not limited to, antisense nucleic acid molecules, small interfering RNAs (siRNAs), and short hairpin RNAs (shRNAs). Such antisense molecules can be designed to target any region of an ANGPTL7 mRNA. In some embodiments, the antisense RNA, siRNA, or shRNA hybridizes to a sequence within an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject. In some embodiments, the ANGPTL7 inhibitor comprises an antisense RNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject. In some embodiments, the ANGPTL7 inhibitor comprises an siRNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject.

10 In some embodiments, the ANGPTL7 inhibitor comprises an shRNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject. In some embodiments, the ANGPTL7 inhibitor comprises an shRNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject.

15 In some embodiments, the ANGPTL7 inhibitor comprises an shRNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject. In some embodiments, the ANGPTL7 inhibitor comprises an shRNA that hybridizes to an ANGPTL7 genomic nucleic acid molecule or mRNA molecule and decreases expression of the ANGPTL7 polypeptide in a cell in the subject.

In some embodiments, the ANGPTL7 inhibitor comprises a nuclease agent that induces 20 one or more nicks or double-strand breaks at a recognition sequence(s) or a DNA-binding protein that binds to a recognition sequence within an ANGPTL7 genomic nucleic acid molecule. The recognition sequence can be located within a coding region of the ANGPTL7 gene, or within 25 regulatory regions that influence the expression of the gene. A recognition sequence of the DNA-binding protein or nuclease agent can be located in an intron, an exon, a promoter, an enhancer, a regulatory region, or any non-protein coding region. The recognition sequence can include or be proximate to the start codon of the ANGPTL7 gene. For example, the recognition sequence can be located from about 10, 20, 30, 40, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of the start codon. As another example, two or more nuclease agents can be used, 30 each targeting a nuclease recognition sequence including or proximate to the start codon. As another example, two nuclease agents can be used, one targeting a nuclease recognition sequence including or proximate to the start codon, and one targeting a nuclease recognition sequence including or proximate to the stop codon, wherein cleavage by the nuclease agents

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can result in deletion of the coding region between the two nuclease recognition sequences.

Any nuclease agent that induces a nick or double-strand break into a desired recognition sequence can be used in the methods and compositions disclosed herein. Any DNA-binding protein that binds to a desired recognition sequence can be used in the methods and compositions disclosed herein.

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Suitable nuclease agents and DNA-binding proteins for use herein include, but are not limited to, zinc finger protein or zinc finger nuclease (ZFN) pair, Transcription Activator-Like Effector (TALE) protein or Transcription Activator-Like Effector Nuclease (TALEN), or Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) systems.

10 The length of the recognition sequence can vary, and includes, for example, recognition sequences that are about 30-36 bp for a zinc finger protein or ZFN pair (i.e., about 15-18 bp for each ZFN), about 36 bp for a TALE protein or TALEN, and about 20 bp for a CRISPR/Cas guide RNA.

15 In some embodiments, CRISPR/Cas systems can be used to modify an ANGPTL7 genomic nucleic acid molecule within a cell. The methods and compositions disclosed herein can employ CRISPR-Cas systems by utilizing CRISPR complexes (comprising a guide RNA (gRNA) complexed with a Cas protein) for site-directed cleavage of ANGPTL7 nucleic acid molecules.

20 Cas proteins generally comprise at least one RNA recognition or binding domain that can interact with gRNAs. Cas proteins can also comprise nuclease domains (such as, for example, DNase or RNase domains), DNA binding domains, helicase domains, protein-protein interaction domains, dimerization domains, and other domains. Suitable Cas proteins include, for example, a wild type Cas9 protein and a wild type Cpf1 protein (such as, for example, FnCpf1). A Cas protein can have full cleavage activity to create a double-strand break in an ANGPTL7 genomic nucleic acid molecule or it can be a nickase that creates a single-strand break 25 in an ANGPTL7 genomic nucleic acid molecule. Additional examples of Cas proteins include, but are not limited to, Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5e (CasD), Cas6, Cas6e, Cas6f, Cas7, Cas8a1, Cas8a2, Cas8b, Cas8c, Cas9 (Csn1 or Csx12), Cas10, Cas10d, CasF, CasG, CasH, CsY1, CsY2, CsY3, Cse1 (CasA), Cse2 (CasB), Cse3 (CasE), Cse4 (CasC), Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, 30 Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, and Cu1966, and homologs or modified versions thereof. Cas proteins can also be operably linked to heterologous polypeptides as fusion proteins. For example, a Cas protein can be fused to a cleavage domain,

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an epigenetic modification domain, a transcriptional activation domain, or a transcriptional repressor domain. Cas proteins can be provided in any form. For example, a Cas protein can be provided in the form of a protein, such as a Cas protein complexed with a gRNA. Alternately, a Cas protein can be provided in the form of a nucleic acid molecule encoding the Cas protein, 5 such as an RNA or DNA.

In some embodiments, targeted genetic modifications of ANGPTL7 genomic nucleic acid molecules can be generated by contacting a cell with a Cas protein and one or more gRNAs that hybridize to one or more gRNA recognition sequences within a target genomic locus in the ANGPTL7 genomic nucleic acid molecule. For example, a gRNA recognition sequence can be 10 located in a region of SEQ ID NO:1. In some embodiments, the gRNA recognition sequence includes or is proximate to a position corresponding to position 4,291 according to SEQ ID NO:1, position 4,287 according to SEQ ID NO:1, position 4,243 according to SEQ ID NO:1, position 4,325 according to SEQ ID NO:1, or position 4,336 according to SEQ ID NO:1. For example, the gRNA recognition sequence can be located from about 1000, 500, 400, 300, 200, 100, 50, 45, 15 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to position 4,291 according to SEQ ID NO:1. The gRNA recognition sequence can be located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to position 4,287 according to SEQ ID NO:1. The gRNA recognition sequence can be located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to position 4,243 according to SEQ ID NO:1. The gRNA 20 recognition sequence can be located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to position 4,325 according to SEQ ID NO:1. The gRNA recognition sequence can be located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to position 4,336 according to SEQ ID NO:1. As yet another example, a gRNA recognition 25 sequence can include or be proximate to the start codon of an ANGPTL7 genomic nucleic acid molecule or the stop codon of an ANGPTL7 genomic nucleic acid molecule. For example, the gRNA recognition sequence can be located from about 10, 20, 30, 40, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of the start codon or the stop codon.

30 The gRNA recognition sequences within a target genomic locus in an ANGPTL7 genomic nucleic acid molecule are located near a Protospacer Adjacent Motif (PAM) sequence, which is a 2-6 base pair DNA sequence immediately following the DNA sequence targeted by

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the Cas9 nuclease. The canonical PAM is the sequence 5'-NGG-3' where "N" is any nucleobase followed by two guanine ("G") nucleobases. gRNAs can transport Cas9 to anywhere in the genome for gene editing, but no editing can occur at any site other than one at which Cas9 recognizes PAM. In addition, 5'-NGA-3' can be a highly efficient non-canonical PAM for human 5 cells. Generally, the PAM is about 2-6 nucleotides downstream of the DNA sequence targeted by the gRNA. The PAM can flank the gRNA recognition sequence. In some embodiments, the gRNA recognition sequence can be flanked on the 3' end by the PAM. In some embodiments, the gRNA recognition sequence can be flanked on the 5' end by the PAM. For example, the cleavage site of Cas proteins can be about 1 to about 10, about 2 to about 5 base pairs, or three 10 base pairs upstream or downstream of the PAM sequence. In some embodiments (such as when Cas9 from *S. pyogenes* or a closely related Cas9 is used), the PAM sequence of the non-complementary strand can be 5'-NGG-3', where N is any DNA nucleotide and is immediately 3' of the gRNA recognition sequence of the non-complementary strand of the target DNA. As such, the PAM sequence of the complementary strand would be 5'-CCN-3', where N is any DNA 15 nucleotide and is immediately 5' of the gRNA recognition sequence of the complementary strand of the target DNA.

A gRNA is an RNA molecule that binds to a Cas protein and targets the Cas protein to a specific location within an ANGPTL7 genomic nucleic acid molecule. One exemplary gRNA is a gRNA effective to direct a Cas enzyme to bind to or cleave an ANGPTL7 genomic nucleic acid 20 molecule, wherein the gRNA comprises a DNA-targeting segment that hybridizes to a gRNA recognition sequence within the ANGPTL7 genomic nucleic acid molecule that includes or is proximate to a position corresponding to position 4,291 according to SEQ ID NO:1, or that includes or is proximate to a position corresponding to position 4,287 according to SEQ ID NO:1, or that includes or is proximate to a position corresponding to position 4,243 according to SEQ 25 ID NO:1, or that includes or is proximate to a position corresponding to position 4,325 according to SEQ ID NO:1, or that includes or is proximate to a position corresponding to position 4,336 according to SEQ ID NO:1. For example, a gRNA can be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of a position corresponding to position 30 4,291 according to SEQ ID NO:1. A gRNA can also be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of a position corresponding to position 4,287 according to

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SEQ ID NO:1. A gRNA can also be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of a position corresponding to position 4,243 according to SEQ ID NO:1. A gRNA can also be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of a position corresponding to position 4,325 according to SEQ ID NO:1. A gRNA can also be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of a position corresponding to position 4,336 according to SEQ ID NO:1. Other exemplary gRNAs 5 comprise a DNA-targeting segment that hybridizes to a gRNA recognition sequence within an ANGPTL7 genomic nucleic acid molecule that is located in a region of SEQ ID NO:1. Other exemplary gRNAs comprise a DNA-targeting segment that hybridizes to a gRNA recognition sequence within an ANGPTL7 genomic nucleic acid molecule that includes or is proximate to the start codon or the stop codon. For example, a gRNA can be selected such that it hybridizes 10 to a gRNA recognition sequence that is located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of the start codon or located from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 200, 300, 400, 500, or 1,000 nucleotides of the start codon or 15 stop codon. The design and synthesis of gRNAs are described in, for example, Mali et al., Science, 2013, 339, 823-826; Jinek et al., Science, 2012, 337, 816-821; Hwang et al., Nat. Biotechnol., 2013, 31, 227-229; Jiang et al., Nat. Biotechnol., 2013, 31, 233-239; and Cong et al., 20 Science, 2013, 339, 819-823. Suitable gRNAs can comprise from about 17 to about 23 nucleotides, from about 18 to about 22 nucleotides, or from about 19 to about 21 nucleotides. 20 In some embodiments, the gRNAs can comprise 20 nucleotides.

Examples of suitable gRNA recognition sequences of the human ANGPTL7 reference 25 gene are set forth in SEQ ID NOS:13-131 and 144-165 (see, Tables 1-9).

Table 1: Guide RNA Recognition Sequences Near ANGPTL7 Arg177Stop Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	CTGCAGGGACAGGAACAGGTTGG	13
+	CAGAGTATCCCCTCTGCTTCAGG	14
+	GGCTCTGCAGGGACAGGAACAGG	15
+	GCTTCAGGTGTTCTGTGACATGG	16
+	TGCAGGGACAGGAACAGGTTGGG	17

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+	TCTACTGGCTCTGCAGGGACAGG	18
-	CCTTCTACCGGGACTGGAAGCAG	19
-	CCGTGGGGACTTCTGGCTGGGA	20
-	CCGGGACTGGAAGCAGTACAAGC	21
-	CCTTGTCTCCTTCTACCGGGACT	22
-	CCACCGGCTCTCCAGACAGCCAA	23
-	CCGGCTCTCCAGACAGCCAACCC	24
+	TGGAGACTTCAGGCGGAGGCTGG	25
+	TGTGACATGGAGACTTCAGGCGG	26
+	TTCTGTGACATGGAGACTTCAGG	27
+	GACATGGAGACTTCAGGCGGAGG	28
-	CCATGACTGGACCAGTGCCACCA	29
-	CCCGGCTGCGTGTAGAGATGGAG	30
-	CCGGCTGCGTGTAGAGATGGAGG	31
-	CCAACCCGGCTGCGTGTAGAGAT	32
-	CCAGGGGCCCATGACTGGACCA	33
-	CCCCATGACTGGACCAGTGCCAC	34

Table 2: Guide RNA Recognition Sequences Near ANGPTL7 Gln175His Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
-	CTGCTTCCAGTCCCGGTAGAAGG	35
+	TTGTCTCCTTCTACCGGGACTGG	36
+	GCAGGGAGTGCACACATCTACTGG	37
+	GGACTGGAAGCAGTACAAGCAGG	38
+	GACATGGAGACTTCAGGCGGAGG	28
+	GTGGCCTTGTCTCCTTCTACCGG	39
+	TGGAGACTTCAGGCGGAGGCTGG	25
-	TACTCTGGTGAGGGACTTGCAGG	40
-	ACTCTGGTGAGGGACTTGCAGGG	41
-	GCTTGTACTGCTTCCAGTCCCGG	42
-	AGTCCCGGTAGAAGGGAGACAAGG	43

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+	CACACATCTACTGGCTCTGCAGG	44
-	CAAGGCCACTTTTCGTCTATGG	45
+	GACTGGAAGCAGTACAAGCAGGG	46
-	GCAGAGGGGATACTCTGGTGAGG	47
+	CAGAGTATCCCCTCTGCTTCAGG	14
+	TTCTGTGACATGGAGACTTCAGG	27
-	CTCTGGTGAGGGACTTGCAGGGG	48
-	CAGAGGGGATACTCTGGTGAGGG	49
-	ACTTTTCGTCTATGGATGATGG	50
+	TGGCCTTGTCTCCTTCTACCGGG	51
+	AAGCAGTACAAGCAGGGCTTGG	52
+	GCTTCAGGTGTTCTGTGACATGG	16
-	CTGAAGCAGAGGGGATACTCTGG	53
-	TCACAGAACACCTGAAGCAGAGG	54
+	ACACATCTACTGGCTCTGCAGGG	55
+	ATCATCCATAGACGAAAAAGTGG	56
+	TGTGACATGGAGACTTCAGGCGG	26
+	TCTACTGGCTCTGCAGGGACAGG	18

Table 3: Guide RNA Recognition Sequences Near ANGPTL7 Arg220His Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	ATGACCGCGTACAACACTCCGGGG	57
+	CATGACCGCGTACAACACTCCGGGG	58
-	GGCACCCCCGGAGTTGTACGCGG	59
-	GAGTTGTACGCGGTATGTGTGG	60
+	ACATGACCGCGTACAACACTCCGG	61
+	CACATGACCGCGTACAACACTCCGG	62
-	TTGTACGCGGTATGTGTGG	63
+	TTGTCTCCTCTACCGGGACTGG	36
-	CTGCTTCCAGTCCCGGTAGAAGG	35
+	TGGGGAACGAACACATCCACCGG	64

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+	GGACTGGAAGCAGTACAAGCAGG	38
-	GGTGGCACTGGTCCAGTCATGGG	65
-	CAGAATAGGAATGGCACCCCCGG	66
-	GTGGCACTGGTCCAGTCATGGGG	67
-	GCGGTCATGTGTGGTGGCACTGG	68
-	TGGTGGCACTGGTCCAGTCATGG	69
+	GTGGCCTTGTCTCCTTACCGG	39
+	GCAGCATCCGTGGGGACTTCTGG	70
+	CATCCGTGGGGACTTCTGGCTGG	71
-	GCTTGTACTGCTTCCAGTCCC GG	42
-	AGTCCCGGTAGAAGGAGACAAGG	43
+	GGCTCTCCAGACAGCCAACCCGG	72
+	ATCCGTGGGGACTTCTGGCTGG	73
+	GACTGGAAGCAGTACAAGCAGGG	46
-	TTGGCTGTCTGGAGAGGCCGGTGG	74
-	TGGTCCAGTCATGGGGCCCCTGG	75
-	GATTGTCTTGAATCAGAAATAGG	76
+	AACCCGGCTGCATGTAGAGATGG	77
-	CTCCATCTCTACATGCAGCCGGG	78
+	TGGCCTTGTCTCCTTACCGGG	51
+	AAGCAGTACAAGCAGGGCTTGG	52
+	TAGAGATGGAGGTAAGCACAAGG	79
+	TCCGTGGGGACTTCTGGCTGGGG	80

Table 4: Guide RNA Recognition Sequences Near ANGPTL7 Arg220Cys Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	ATGACCGCGTACAACACTCCGGGG	57
+	CATGACCGCGTACAACACTCCGGGG	58
-	GGCACCCCCGGAGTTGTACGCCGG	59
-	GAGTTGTACGCCGGTACGTGTGG	60
+	ACATGACCGCGTACAACACTCCGGG	61

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+	CACATGACCGCGTACAACCTCCGG	62
-	TTGTACGCGGTATGTGTGGTGG	63
+	TTGTCTCCTCTACCGGGACTGG	36
-	CTGCTTCCAGTCCCGTAGAAGG	35
+	TGGGAAACGAACACATCCACCGG	64
+	GGACTGGAAGCAGTACAAGCAGG	38
-	GGTGGCACTGGTCCAGTCATGGG	65
-	CAGAATAGGAATGGCACCCCCGG	66
-	GTGGCACTGGTCCAGTCATGGG	67
-	GCGGTCATGTGTGGTGGCACTGG	68
-	TGGTGGCACTGGTCCAGTCATGG	69
+	CATCCGTGGGGACTTCTGGCTGG	71
+	GCAGCATCCGTGGGGACTTCTGG	70
+	GTGGCCTTGTCTCCTCTACCGG	39
-	GCTTGTACTGCTTCCAGTCCCGG	42
+	GGCTCTCCAGACAGCCAACCCGG	72
-	AGTCCCGGTAGAAGGAGACAAGG	43
+	ATCCGTGGGGACTTCTGGCTGGG	73
+	GAUTGGAAGCAGTACAAGCAGGG	46
-	TGGTCCAGTCATGGGGCCCCCTGG	75
-	TTGGCTGTCTGGAGAGGCCGGTGG	74
-	GATTGTCTTGAATCAGAATAGG	76
-	ATCTCTACACACAGCCGGTTGG	81
+	AAGCAGTACAAGCAGGGCTTGG	52
+	TGGCCTTGTCTCCTCTACCGGG	51
+	TAGAGATGGAGGTAAGCACAAGG	79
+	TCCGTGGGGACTTCTGGCTGGGG	80
+	AACCCGGCTGTGTAGAGATGG	82
-	CCTCCATCTACACACAGCCGG	83

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Table 5: Guide RNA Recognition Sequences Near ANGPTL7 Asn302Lys Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	CAATGGAGTGTACTACCGCCTGG	84
+	AATGGAGTGTACTACCGCCTGGG	85
+	TACCTACTCCCTCAAACGGGTGG	86
-	TTTCATCTCCACCCGTTGAGGG	87
+	ACAGTCAACTTACTAGCACTGGG	88
-	TTTCATCTCCACCCGTTGAGGG	89
+	GGGTGAGCACAATAAGCACCTGG	90
+	ATGGCATCACCTGGTATGGCTGG	91
-	CTCCACCCGTTGAGGGAGTAGG	92
-	GGTGCTTATTGTGCTACCCAGG	93
+	CTAACTCCTTACCTGATGTCTGG	94
+	CACAGTCAACTTACTAGCACTGG	95
-	CAGTTGTACCAAGTAGGCCACCTGG	96
-	GATAGACCAGACATCAGGTAAGG	97
-	TCAGGTAAGGAGTTAGAGCCAGG	98
+	GATCTACCTACTCCCTCAAACGG	99
-	AGATCCATGCCAGCCATACCAGG	100
-	GCTTATTGTGCTACCCAGGCGG	101
-	CATACCAGGTGATGCCATCCAGG	102
+	ATCTACCTACTCCCTCAAACGGG	103
-	ACTGTGATAGACCAGACATCAGG	104
+	TTCTCATGCCAGGTGGCTACTGG	105
+	CTGGATGGCATCACCTGGTATGG	106
+	AGCACCTGGATGGCATCACCTGG	107
+	ATCACCTGGTATGGCTGGCATGG	108
-	GTAGTACACTCCATTGAGTTGG	109
+	GAGCACAATAAGCACCTGGATGG	110
-	CAGGTAAGGAGTTAGAGCCAGGG	111
+	CTGGGTCTGTTCTCATGCCAGG	112

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+	TTTGGTATTCTTCTGACCCTGG	113
-	GTCAGAAAGAATACCAAAACCGG	114
+	GGTCTGTTCTCATGCCAGGTGG	115

Table 6: Guide RNA Recognition Sequences Near ANGPTL7 Arg340His Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	CAATGGAGTGTACTACCGCCTGG	84
+	AATGGAGTGTACTACCGCCTGGG	85
-	GGCGGTAGTACACTCCATTGAGG	116
+	TACCTACTCCCTCAAACGGGTGG	86
-	GTA GTACACTCCATTGAGGTTGG	117
-	TTTCATCTCCACCCGTTGAGGG	87
-	TTTCATCTCCACCCGTTGAGGG	89
+	GGGTGAGCACAATAAGCACCTGG	90
+	ATGGCATCACCTGGTATGGCTGG	91
-	GGTGCTTATTGTGCTCACCCAGG	93
-	CTCCACCCGTTGAGGGAGTAGG	92
-	GTTTCTGTATCCGTGCTCCACGG	118
+	AAACTGAGACACGTGGAGACTGG	119
-	GCTTATTGTGCTCACCCAGGCGG	101
+	GATCTACCTACTCCCTCAAACGG	99
-	AGATCCATGCCAGCCATACCAGG	100
+	GCCTTAAAAGGAGGCTGCCGTGG	120
-	CATACCAGGTGATGCCATCCAGG	102
+	ATCTACCTACTCCCTCAAACGGG	103
+	GACACGTGGAGACTGGATGAGGG	121
-	TCCACGGCAGCCTCCTTTAAGG	122
+	CTGGATGGCATCACCTGGTATGG	106
+	AGCACCTGGATGGCATCACCTGG	107
+	ATCACCTGGTATGGCTGGCATGG	108
+	TGCACAGACTCCAACCTCAATGG	123

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+	GAGCACAATAAGCACCTGGATGG	110
+	AGACACGTGGAGACTGGATGAGG	124
+	AGACTTCAAGCCTAAAAGGAGG	125
-	TTTAAGGCTTGAAGTCTTCTGGG	126
-	AAGGCTTGAAGTCTTCTGGGTGG	127
-	TTTTAAGGCTTGAAGTCTTCTGG	128
+	GATACAGAAACTGAGACACGTGG	129
+	AAGGAGGGCTGCCGTGGAGCACGG	130
+	AGAAGACTTCAAGCCTAAAAGG	131

Table 7: Guide RNA Recognition Sequences Near ANGPTL7 Phe161Ile Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
-	ACAGAACACCTGAAGCAGAGGGG	144
-	ACAGAACACCTGAAGCAGAGGGG	145
-	CACAGAACACCTGAAGCAGAGGG	146
+	CAGAGTATCCCCCTCTGCTTCAGG	147
-	ACTCTGGTGAGGGACTTGCAGGG	148
-	TACTCTGGTGAGGGACTTGCAGG	149
-	GCAGAGGGGATACTCTGGTGAGG	150
+	GCTTCAGGTGTTCTGTGACATGG	151
-	CAGAGGGGATACTCTGGTGAGGG	152

Table 8: Guide RNA Recognition Sequences Near ANGPTL7 Trp188STOP Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	TTGTCTCCTTCTACCGGGACTGG	153
+	GTGGCCTTGTCTCCTTCTACCGG	154
+	TGGCCTTGTCTCCTTCTACCGGG	155
+	GACTGGAAGCAGTACAAGCAGGG	156
+	GGACTGGAAGCAGTACAAGCAGG	157
-	CTGCTTCCAGTCCCGGTAGAAGG	158
-	GCTTGTACTGCTTCCAGTCCCGG	159

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-	AGTCCCGGTAGAAGGAGACAAGG	160
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Table 9: Guide RNA Recognition Sequences Near ANGPTL7 Lys192Gln Variation

Strand	Guide RNA Recognition Sequence	SEQ ID NO:
+	GACTGGAAGCAGTACAAGCAGGG	156
+	GGACTGGAAGCAGTACAAGCAGG	157
-	GGACTGGAAGCAGTACAAGC	159
+	AAGCAGTACAAGCAGGGCTTGG	161
+	CAGGGCTTGGCAGCATCCGTGG	162
+	AGGGCTTGGCAGCATCCGTGGG	163
+	GGGCTTGGCAGCATCCGTGGGG	164
-	TCCCCAGCCAGAAGTCCCCACGG	165

The Cas protein and the gRNA form a complex, and the Cas protein cleaves the target

5 ANGPTL7 genomic nucleic acid molecule. The Cas protein can cleave the nucleic acid molecule at a site within or outside of the nucleic acid sequence present in the target ANGPTL7 genomic nucleic acid molecule to which the DNA-targeting segment of a gRNA will bind. For example, formation of a CRISPR complex (comprising a gRNA hybridized to a gRNA recognition sequence and complexed with a Cas protein) can result in cleavage of one or both strands in or near (such as, for example, within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, or more base pairs from) the nucleic acid sequence present in the ANGPTL7 genomic nucleic acid molecule to which a DNA-targeting segment of a gRNA will bind.

10 Such methods can result, for example, in an ANGPTL7 genomic nucleic acid molecule in which a region of SEQ ID NO:1 is disrupted, the start codon is disrupted, the stop codon is disrupted, or the coding sequence is deleted. Optionally, the cell can be further contacted with one or more additional gRNAs that hybridize to additional gRNA recognition sequences within the target genomic locus in the ANGPTL7 genomic nucleic acid molecule. By contacting the cell with one or more additional gRNAs (such as, for example, a second gRNA that hybridizes to a second gRNA recognition sequence), cleavage by the Cas protein can create two or more 15 double-strand breaks or two or more single-strand breaks.

20 In some embodiments, the ANGPTL7 inhibitor comprises a small molecule. In some embodiments, the ANGPTL7 inhibitor is 6,11-dihydro[1]benzothiopyrano[4,3-b]indole

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(PD146176), 2-bromophenol, 2,4-dibromophenol, 2-(1-thienyl)ethyl-3,4-dihydroxybenzylidenecyanoacetate (TEDC), 4,4'-(2,3-dimethyl-1,4-butanediyl)bis-1,2-benzenediol (nordihydroguaiaretic acid), or cinnamyl-3,4-dihydroxy-a-cyanocinnamate (CDC).

In some embodiments, the methods further comprise detecting the presence or

5 absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient. As used throughout the present disclosure an “ANGPTL7 predicted loss-of-function variant nucleic acid molecule” is any ANGPTL7 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding an ANGPTL7 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. For example, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes 10 ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, or Phe161Ile. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Trp188Stop, or Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 15 Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Lys192Gln. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Phe161Ile.

20 In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or iii) a cDNA molecule produced from an mRNA 25 molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

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In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to 5 position 525 according to SEQ ID NO:6; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9

In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising an 10 adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; ii) an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

15 In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or iii) a cDNA molecule produced from an mRNA 20 molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a 25 cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; ii) an mRNA molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

30 In some embodiments, when the patient is ANGPTL7 reference, the patient is also administered a therapeutic agent that treats or inhibits an ophthalmic condition in a standard dosage amount. In some embodiments, when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, the patient is also administered a therapeutic agent that

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treats or inhibits an ophthalmic condition in a dosage amount that is the same as or lower than the standard dosage amount.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an

5 ophthalmic condition, the method comprising the steps of: determining whether the patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then: i) administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then:

10 i) administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference.

15 In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of: determining whether the patient

20 has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8; by: obtaining or having

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obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of: determining whether the patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9; by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to

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administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7

5 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an

10 ophthalmic condition, the method comprising the steps of: determining whether the patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is:

i) a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; ii) an mRNA

15 molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138; by: obtaining or having obtained a biological sample from the patient; and performing or having performed a

20 genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous

25 for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7

30 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

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The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of: determining whether the patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human

5 ANGPTL7 polypeptide, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or iii) a cDNA molecule produced from an mRNA
10 molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139; by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the
15 patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition
20 in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is
25 heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of treating a patient with a therapeutic agent that treats or inhibits an ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of: determining whether the patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human

30 ANGPTL7 polypeptide, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; ii) an mRNA

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molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140; by: obtaining or having 5 obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and when the patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, 10 and administering to the patient an ANGPTL7 inhibitor; and when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; wherein the presence of a genotype having the ANGPTL7 15 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7 polypeptide indicates the patient has a reduced risk of developing the ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any 20 ANGPTL7 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding an ANGPTL7 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. For example, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, 25 Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Trp188Stop, or Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His. In some 30 embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Lys192Gln. In some

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embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Phe161Ile.

Detecting the presence or absence of any of the ANGPTL7 predicted loss-of-function variant nucleic acid molecules described herein in a biological sample from a patient and/or 5 determining whether a patient has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*.

In some embodiments, the determining step, detecting step, or genotyping assay 10 comprises sequencing at least a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule, the ANGPTL7 mRNA molecule, or the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises variation(s) that cause a loss-of-function (partial or complete) or are predicted to cause a loss-of-function (partial or complete). For example, in some embodiments, the detection step, detecting step, or genotyping assay 15 comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. When the 20 sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, then the ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When 25 the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, then the

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ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the 5 nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,291 according to SEQ ID NO:2; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:5; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to 10 position 529 according to SEQ ID NO:8; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,291 according to SEQ ID NO:2; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 529 according to SEQ ID NO:5; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to 15 position 529 according to SEQ ID NO:8; and c) determining whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5; and/or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

In some embodiments, the determining step, detecting step, or genotyping assay 20 comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the 25 complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,291 according to SEQ 30 ID NO:2, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic

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acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

5 In some embodiments, the determining step, detecting step, or genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to 10 position 4,291 according to SEQ ID NO:2, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and 15 detecting the detectable label.

In some embodiments, the determining step, detecting step, or genotyping assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; 20 ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. When the 25 sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position 30 corresponding to position 525 according to SEQ ID NO:6, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a

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thymine at a position corresponding to position 525 according to SEQ ID NO:9, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step, detecting step, or genotyping assay 5 comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,287 according to SEQ ID NO:3; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:6; and/or iii) a portion of the nucleotide 10 sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:9; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,287 according to SEQ ID NO:3; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 525 according to SEQ ID NO:6; and/or iii) 15 the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 525 according to SEQ ID NO:9; and c) determining whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6; and/or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

20 In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; and/or iii) 25 a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid 30 molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID

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NO:6, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises 5 reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence 10 of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position 15 corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or genotyping assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a 20 position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:135; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a 25 position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the 30 sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function

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variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

5 In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:138; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,243 according to SEQ ID NO:132; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 481 according to SEQ ID NO:135; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 481 according to SEQ ID NO:138; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) adenine at a position corresponding to position 481 according to SEQ ID NO:138.

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In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ

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ID NO:132, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 5 481 according to SEQ ID NO:138, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or genotyping assay 20 comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according 25 to SEQ ID NO:136, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,325 according 30 to SEQ ID NO:133, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an

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adenine at a position corresponding to position 563 according to SEQ ID NO:136, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according 5 to SEQ ID NO:139, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a 10 position corresponding to position 4,325 according to SEQ ID NO:133; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; b) extending the primer at least 15 through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,325 according to SEQ ID NO:133; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 563 according to SEQ ID NO:136 and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 563 according to SEQ ID NO:139; and c) determining 20 whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

In some embodiments, the determining step, detecting step, or genotyping assay 25 comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) an adenine at a position corresponding to position 563 30 according to SEQ ID NO:139 or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a

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nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a 5 position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the 10 mRNA into a cDNA prior to the amplifying step.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence 15 of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a 20 position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or genotyping assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a 25 position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:137; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a 30 position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a cytosine at a position corresponding to position 4,336 according

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to SEQ ID NO:134, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, then the

5 ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

10 In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,336 according to SEQ ID NO:134; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position

15 corresponding to position 574 according to SEQ ID NO:137; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:140; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,336 according to SEQ ID NO:134; ii) the position of the

20 nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 574 according to SEQ ID NO:137; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 574 according to SEQ ID NO:140; and c) determining whether the extension product of the primer comprises: i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; ii) a cytosine at a position

25 corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a cytosine at a position corresponding 30 to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement

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thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the determining step, detecting step, or genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:139, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and detecting the detectable label.

In any of these embodiments, the nucleic acid molecule can be present within a cell obtained from the human subject.

In any of the embodiments described herein, the ophthalmic condition is increased IOP, pre-glaucoma, glaucoma, or decreased corneal hysteresis. In some embodiments, the ophthalmic condition is increased IOP. In some embodiments, the increased IOP is IOPcc or IOPg. In some embodiments, the ophthalmic condition is pre-glaucoma. In some embodiments, the ophthalmic condition is glaucoma. In some embodiments, the glaucoma is primary open-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, congenital glaucoma,

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neovascular glaucoma, steroid-induced glaucoma, or glaucoma related to ocular trauma. In some embodiments, the ophthalmic condition is decreased corneal hysteresis.

For human subjects or patients that are genotyped or determined to be either ANGPTL7 reference or heterozygous for an ANGPTL7 predicted loss-of-function variant, such 5 human subjects or patients can be treated with an ANGPTL7 inhibitor, as described herein.

Examples of therapeutic agents that treat or inhibit the ophthalmic condition include, but are not limited to: a prostaglandin, a beta blocker, an alpha-adrenergic agonist, a carbonic anhydrase inhibitor, a rho kinase inhibitor, or a miotic or cholinergic agent.

In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic 10 condition is a prostaglandin. In some embodiments, the prostaglandin is Xalatan[®] (latanoprost), Travatan Z[®] (travoprost), Zioptan[®] (tafluprost), Lumigan[®] (bimatoprost), or Vyzulta[®] (latanoprostene bunod).

In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic 15 condition is a beta blocker. In some embodiments, the beta blocker is Betimol[®], Istalol[®], or Timoptic[®] (timolol) or Betoptic[®] (betaxolol).

In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic condition is an alpha-adrenergic agonist. In some embodiments, the alpha-adrenergic agonist is Iopidine[®] (apraclonidine) or Alphagan[®] or Qoliana[®] (brimonidine).

In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic 20 condition is a carbonic anhydrase inhibitor. In some embodiments, the carbonic anhydrase inhibitor is Trusopt[®] (dorzolamide) or Azopt[®] (brinzolamide).

In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic condition is a rho kinase inhibitor. In some embodiments, the rho kinase inhibitor is Rhopressa[®] (netarsudil).

25 In some embodiments, the therapeutic agent that treats or inhibits the ophthalmic condition is a miotic or cholinergic agent. In some embodiments, the miotic or cholinergic agent is Isopto[®] Carpine (pilocarpine).

In some embodiments, the dose of the therapeutic agents that treat or inhibit the ophthalmic condition can be reduced by about 10%, by about 20%, by about 30%, by about 30 40%, by about 50%, by about 60%, by about 70%, by about 80%, or by about 90% for patients or human subjects that are heterozygous for an ANGPTL7 predicted loss-of-function variant (i.e., a lower than the standard dosage amount) compared to patients or human subjects that

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are ANGPTL7 reference (who may receive a standard dosage amount). In some embodiments, the dose of the therapeutic agents that treat or inhibit the ophthalmic condition can be reduced by about 10%, by about 20%, by about 30%, by about 40%, or by about 50%. In addition, the dose of therapeutic agents that treat or inhibit the ophthalmic condition in 5 patients or human subjects that are heterozygous for an ANGPTL7 predicted loss-of-function variant can be administered less frequently compared to patients or human subjects that are ANGPTL7 reference.

Administration of the therapeutic agents that treat or inhibit the ophthalmic condition and/or ANGPTL7 inhibitors can be repeated, for example, after one day, two days, three days, 10 five days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, eight weeks, two months, or three months. The repeated administration can be at the same dose or at a different dose. The administration can be repeated once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more. For example, according to certain dosage regimens a patient can receive therapy for a prolonged 15 period of time such as, for example, 6 months, 1 year, or more.

Administration of the therapeutic agents that treat or inhibit the ophthalmic condition and/or ANGPTL7 inhibitors can occur by any suitable route including, but not limited to, parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, 20 intraperitoneal, topical, intranasal, or intramuscular. Pharmaceutical compositions for administration are desirably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically and pharmaceutically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. The term "pharmaceutically acceptable" means that the carrier, diluent, excipient, or auxiliary is compatible with the other 25 ingredients of the formulation and not substantially deleterious to the recipient thereof.

The terms "treat", "treating", and "treatment" and "prevent", "preventing", and "prevention" as used herein, refer to eliciting the desired biological response, such as a therapeutic and prophylactic effect, respectively. In some embodiments, a therapeutic effect 30 comprises one or more of a decrease/reduction in an ophthalmic condition, a decrease/reduction in the severity of an ophthalmic condition (such as, for example, a reduction or inhibition of development or an ophthalmic condition), a decrease/reduction in

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symptoms and ophthalmic condition-related effects, delaying the onset of symptoms and ophthalmic condition-related effects, reducing the severity of symptoms of the ophthalmic condition-related effects, reducing the severity of an acute episode, reducing the number of symptoms and ophthalmic condition-related effects, reducing the latency of symptoms and ophthalmic condition-related effects, an amelioration of symptoms and ophthalmic condition-related effects, reducing secondary symptoms, reducing secondary infections, preventing relapse to an ophthalmic condition, decreasing the number or frequency of relapse episodes, increasing latency between symptomatic episodes, increasing time to sustained progression, expediting remission, inducing remission, augmenting remission, speeding recovery, or increasing efficacy of or decreasing resistance to alternative therapeutics, and/or an increased survival time of the affected host animal, following administration of the agent or composition comprising the agent. A prophylactic effect may comprise a complete or partial avoidance/inhibition or a delay of ophthalmic condition development/progression (such as, for example, a complete or partial avoidance/inhibition or a delay), and an increased survival time of the affected host animal, following administration of a therapeutic protocol. Treatment of an ophthalmic condition encompasses the treatment of patients already diagnosed as having any form of the ophthalmic condition at any clinical stage or manifestation, the delay of the onset or evolution or aggravation or deterioration of the symptoms or signs of the ophthalmic condition, and/or preventing and/or reducing the severity of the ophthalmic condition.

In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises positions corresponding to any positions that are C-terminal to position 176 according to SEQ ID NO:11. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises positions corresponding to any positions that are C-terminal to position 176 according to SEQ ID NO:11.

In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 175 according to SEQ ID NO:10 or SEQ ID NO:12. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 175 according to SEQ ID NO:10 or SEQ ID NO:12.

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In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 161 according to SEQ ID NO:141 or SEQ ID NO:10. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for 5 detecting the presence of a polypeptide that comprises a position corresponding to position 161 according to SEQ ID NO:141 or SEQ ID NO:10.

In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises positions corresponding to any positions that are C-terminal to position 187 according to SEQ ID NO:142. In some embodiments, the detecting step comprises 10 sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises positions corresponding to any positions that are C-terminal to position 187 according to SEQ ID NO:142.

In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 192 according to SEQ ID 15 NO:143 or SEQ ID NO:10. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 192 according to SEQ ID NO:143 or SEQ ID NO:10.

The present disclosure also provides methods of identifying a human subject having an 20 increased risk for developing an ophthalmic condition, wherein the method comprises: determining or having determined in a biological sample obtained from the subject the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as a genomic nucleic acid molecule, mRNA molecule, and/or cDNA molecule) encoding a human ANGPTL7 polypeptide; wherein: i) when the human subject lacks an ANGPTL7 predicted 25 loss-of-function variant nucleic acid molecule (i.e., the human subject is genotypically categorized as an ANGPTL7 reference), then the human subject has an increased risk for developing an ophthalmic condition; and ii) when the human subject has an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (i.e., the human subject is categorized as heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an 30 ANGPTL7 predicted loss-of-function variant), then the human subject has a decreased risk for developing an ophthalmic condition. Having a single copy of an ANGPTL7 predicted loss-of-

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function variant nucleic acid molecule confers protection to a human subject from developing an ophthalmic condition.

Without intending to be limited to any particular theory or mechanism of action, it is believed that a single copy of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (i.e., heterozygous for an ANGPTL7 predicted loss-of-function variant) confers protection to a human subject from developing an ophthalmic condition, and it is also believed that having two copies of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (i.e., homozygous for an ANGPTL7 predicted loss-of-function variant) may confer more protection of a human subject from developing an ophthalmic condition, relative to a human subject with a single copy. Thus, in some embodiments, a single copy of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule may not be completely protective, but instead, may be partially or incompletely protective of a human subject from developing an ophthalmic condition. While not desiring to be bound by any particular theory, there may be additional factors or molecules involved in the development of ophthalmic conditions that are still present in a human subject having a single copy of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule, thus resulting in less than complete protection from the development of an ophthalmic condition.

The present disclosure also provides methods of identifying a human subject having an increased risk for developing an ophthalmic condition, wherein the method comprises:

20 detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; wherein: when the human subject is ANGPTL7 reference, then the human subject has an increased risk for developing an ophthalmic condition; and when the human subject is heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an ANGPTL7 predicted loss-of-function variant, then the human subject has a

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decreased risk for developing an ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of identifying a human subject having an increased risk for developing an ophthalmic condition, wherein the method comprises: detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; wherein: when the human subject is ANGPTL7 reference, then the human subject has an increased risk for developing an ophthalmic condition; and when the human subject is heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an ANGPTL7 predicted loss-of-function variant, then the human subject has a decreased risk for developing an ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of identifying a human subject having an increased risk for developing an ophthalmic condition, wherein the method comprises: detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481

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according to SEQ ID NO:138, or the complement thereof; wherein: when the human subject is ANGPTL7 reference, then the human subject has an increased risk for developing an ophthalmic condition; and when the human subject is heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an ANGPTL7 predicted loss-of-function variant, then the 5 human subject has a decreased risk for developing an ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of identifying a human subject having an increased risk for developing an ophthalmic condition, wherein the method comprises: 10 detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) an 15 mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; wherein: when the human subject is 20 ANGPTL7 reference, then the human subject has an increased risk for developing an ophthalmic condition; and when the human subject is heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an ANGPTL7 predicted loss-of-function variant, then the human subject has a decreased risk for developing an ophthalmic condition. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is 25 heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of identifying a human subject having an increased risk for developing an ophthalmic condition, wherein the method comprises: detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient, 30 wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: i) a genomic nucleic acid molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) an

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mRNA molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; or iii) a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574

5 according to SEQ ID NO:140, or the complement thereof; wherein: when the human subject is ANGPTL7 reference, then the human subject has an increased risk for developing an ophthalmic condition; and when the human subject is heterozygous for an ANGPTL7 predicted loss-of-function variant or homozygous for an ANGPTL7 predicted loss-of-function variant, then the human subject has a decreased risk for developing an ophthalmic condition. In some

10 embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any ANGPTL7 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding an ANGPTL7 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. For example, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, or Phe161Ile. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Trp188Stop, or Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Lys192Gln. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Phe161Ile.

30 In any of the embodiments described herein, the ophthalmic condition is increased IOP, pre-glaucoma, glaucoma, or decreased corneal hysteresis. In some embodiments, the ophthalmic condition is increased IOP. In some embodiments, the increased IOP is IOPcc or

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IOPg. In some embodiments, the ophthalmic condition is pre-glaucoma. In some embodiments, the ophthalmic condition is glaucoma. In some embodiments, the glaucoma is primary open-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, congenital glaucoma, neovascular glaucoma, steroid-induced glaucoma, or glaucoma related to ocular trauma. In 5 some embodiments, the ophthalmic condition is decreased corneal hysteresis.

Determining or having determined in a sample obtained from the subject the presence or absence of the particular nucleic acid molecules can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some 10 embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*.

In some embodiments, the determining step comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleotide sequence of the 15 ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. When the sequenced portion of the ANGPTL7 20 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 529 25 according to SEQ ID NO:5, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

30 In some embodiments, the determining step comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,291

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according to SEQ ID NO:2; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:5; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:8; b) extending 5 the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,291 according to SEQ ID NO:2; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 529 according to SEQ ID NO:5; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 529 according to SEQ ID NO:8; and c) determining 10 whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5; and/or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

In some embodiments, the determining step comprises: a) amplifying at least a portion 15 of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; b) 20 labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and d) detecting the detectable label. In some embodiments, the 25 nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

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In some embodiments, the determining step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,287

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according to SEQ ID NO:3; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:6; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:9; b) extending 5 the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,287 according to SEQ ID NO:3; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 525 according to SEQ ID NO:6; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 525 according to SEQ ID NO:9; and c) determining 10 whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6; and/or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

In some embodiments, the determining step comprises: a) amplifying at least a portion 15 of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; b) 20 labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and d) detecting the detectable label. In some embodiments, the 25 nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

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In some embodiments, the determining step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and detecting the detectable label.

In some embodiments, determining step comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:135; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step comprises: a) contacting the biological sample with a primer hybridizing to i) a portion of the nucleotide sequence of the ANGPTL7

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genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:138; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,243 according to SEQ ID NO:132; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 481 according to SEQ ID NO:135; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 481 according to SEQ ID NO:138; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) adenine at a position corresponding to position 481 according to SEQ ID NO:138.

In some embodiments, the determining step comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

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In some embodiments, the determining step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7

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genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID NO:133; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,325 according to SEQ ID NO:133; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 563 according to SEQ ID NO:136 and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 563 according to SEQ ID NO:139; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

In some embodiments, the determining step comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139 or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

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In some embodiments, the determining step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:137; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the determining step comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7

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genomic nucleic acid molecule that is proximate to a position corresponding to position 4,336 according to SEQ ID NO:134; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:140; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,336 according to SEQ ID NO:134; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 574 according to SEQ ID NO:137; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 574 according to SEQ ID NO:140; and c) determining whether the extension product of the primer comprises: i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

In some embodiments, the determining step comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

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In some embodiments, the determining step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and detecting the detectable label.

In any of these embodiments, the nucleic acid molecule can be present within a cell obtained from the human subject.

In some embodiments, the human subject is further treated with a therapeutic agent that treats or inhibits the ophthalmic condition and/or an ANGPTL7 inhibitor, as described herein. For example, when the human subject is ANGPTL7 reference, and therefore has an increased risk for developing an ophthalmic condition, the human subject is administered an ANGPTL7 inhibitor. In some embodiments, such a patient is also administered a therapeutic agent that treats or inhibits the ophthalmic condition. In some embodiments, when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, the patient is administered the therapeutic agent that treats or inhibits the ophthalmic condition in a dosage amount that is the same as or lower than the standard dosage amount, and is also administered an ANGPTL7 inhibitor. In some embodiments, the patient is ANGPTL7 reference. In some embodiments, the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant.

The present disclosure also provides methods of detecting the presence of an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule, an ANGPTL7 predicted loss-of-function variant mRNA molecule, and/or an ANGPTL7 predicted loss-of-function variant cDNA molecule in a biological sample from a subject human. It is understood that gene sequences within a population and mRNA molecules encoded by such genes can vary due to polymorphisms such as single-nucleotide polymorphisms. The sequences provided herein for the ANGPTL7 variant genomic nucleic acid molecule, ANGPTL7 variant mRNA molecule, and ANGPTL7 variant cDNA molecule are only exemplary sequences. Other

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sequences for the ANGPTL7 variant genomic nucleic acid molecule, variant mRNA molecule, and variant cDNA molecule are also possible.

The biological sample can be derived from any cell, tissue, or biological fluid from the subject. The sample may comprise any clinically relevant tissue, such as a bone marrow sample,

5 a tumor biopsy, a fine needle aspirate, or a sample of bodily fluid, such as blood, gingival crevicular fluid, plasma, serum, lymph, ascitic fluid, cystic fluid, or urine. In some cases, the sample comprises a buccal swab. The sample used in the methods disclosed herein will vary based on the assay format, nature of the detection method, and the tissues, cells, or extracts that are used as the sample. A biological sample can be processed differently depending on the
10 assay being employed. For example, when detecting any ANGPTL7 variant nucleic acid molecule, preliminary processing designed to isolate or enrich the sample for the genomic DNA can be employed. A variety of known techniques may be used for this purpose. When detecting the level of any ANGPTL7 variant mRNA, different techniques can be used enrich the biological sample with mRNA. Various methods to detect the presence or level of a mRNA or the presence
15 of a particular variant genomic DNA locus can be used.

In some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the human subject to determine whether an ANGPTL7 genomic nucleic acid molecule, an ANGPTL7 mRNA molecule, or an ANGPTL7 cDNA molecule in the biological sample

20 comprises one or more variations that cause a loss-of-function (partial or complete) or are predicted to cause a loss-of-function (partial or complete). For example, in some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the subject to determine whether an ANGPTL7 nucleic acid molecule in the biological sample comprises a
25 nucleotide sequence comprising: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof, ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof, or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof.
In some embodiments, the method is an *in vitro* method.

30 In some embodiments, the methods of detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule) in a human

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subject, comprise: performing an assay on a biological sample obtained from the human subject, which assay determines whether a nucleic acid molecule in the biological sample comprises a nucleotide sequence that encodes: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2 (genomic nucleic acid molecule), ii) a uracil at a 5 position corresponding to position 529 according to SEQ ID NO:5 (mRNA molecule), or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8 (cDNA molecule). In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising an ANGPTL7 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse 10 transcribing the mRNA into cDNA, and performing an assay on the biological sample that determines that a position of the ANGPTL7 genomic nucleic acid molecule, mRNA, or cDNA encodes a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, respectively. Such assays can 15 comprise, for example determining the identity of these positions of the particular ANGPTL7 nucleic acid molecule. In some embodiments, the method is an *in vitro* method.

In some embodiments, the assay comprises sequencing at least a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule, the ANGPTL7 mRNA molecule, or the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced 20 portion comprises one or more variations that cause a loss-of-function (partial or complete). For example, in some embodiments, the assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID 25 NO:5, or the complement thereof; or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, then the ANGPTL7 genomic nucleic acid molecule in 30 the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid

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molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,291 according to SEQ ID NO:2; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:5; or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:8; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,291 according to SEQ ID NO:2; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 529 according to SEQ ID NO:5; or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 529 according to SEQ ID NO:8; and c) determining whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8. In some embodiments, the assay comprises sequencing the entire nucleic acid molecule. In some embodiments, only an ANGPTL7 genomic nucleic acid molecule is analyzed. In some embodiments, only an ANGPTL7 mRNA is analyzed. In some embodiments, only an ANGPTL7 cDNA obtained from ANGPTL7 mRNA is analyzed.

In some embodiments, the assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; b) labeling the amplified

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nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and detecting the detectable label. Alteration-specific polymerase chain reaction techniques can be used to detect mutations such as SNPs in a nucleic acid sequence. Alteration-specific primers can be used because the DNA polymerase will not extend when a mismatch with the template is present.

In some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the subject to determine whether an ANGPTL7 nucleic acid molecule in the biological sample comprises a nucleotide sequence comprising: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof, ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement

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thereof, or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the method is an *in vitro* method.

In some embodiments, the methods of detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule) in a human subject, comprise: performing an assay on a biological sample obtained from the human subject, which assay determines whether a nucleic acid molecule in the biological sample comprises a nucleotide sequence that encodes: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3 (genomic nucleic acid molecule), ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6 (mRNA molecule), or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9 (cDNA molecule).

In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising an ANGPTL7 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse transcribing the mRNA into cDNA, and performing an assay on the biological sample that determines that a position of the ANGPTL7 genomic nucleic acid molecule, mRNA, or cDNA encodes a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position corresponding to position 525 according to SEQ ID NO:9, respectively. Such assays can comprise, for example determining the identity of these positions of the particular ANGPTL7 nucleic acid molecule. In some embodiments, the method is an *in vitro* method.

In some embodiments, the assay comprises sequencing at least a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule, the ANGPTL7 mRNA molecule, or the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises one or more variations that cause a loss-of-function (partial or complete).

For example, in some embodiments, the assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the

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sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,287 according to SEQ ID NO:3; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:6; or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:9; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,287 according to SEQ ID NO:3; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 525 according to SEQ ID NO:6; or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 525 according to SEQ ID NO:9; and c) determining whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9. In some embodiments, the assay comprises sequencing the entire nucleic acid molecule. In some embodiments, only an ANGPTL7 genomic nucleic acid molecule is analyzed. In some embodiments, only an ANGPTL7 mRNA is analyzed. In some embodiments, only an ANGPTL7 cDNA obtained from ANGPTL7 mRNA is analyzed.

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In some embodiments, the assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or the nucleotide sequence of the amplified nucleic acid molecule comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and detecting the detectable label. Alteration-specific polymerase chain reaction techniques can be used to detect mutations such as SNPs in a nucleic acid sequence. Alteration-specific primers can be used because the DNA polymerase will not extend when a mismatch with the template is present.

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In some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the subject to determine whether an ANGPTL7 nucleic acid molecule in the biological sample comprises a nucleotide sequence comprising: i) an adenine at a position

5 corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof, ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof, or iii) an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the method is an *in vitro* method.

10 In some embodiments, the methods of detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule) in a human subject, comprise: performing an assay on a biological sample obtained from the human subject, which assay determines whether a nucleic acid molecule in the biological sample

15 comprises a nucleotide sequence that encodes i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) an adenine at a position corresponding to position 481 according to SEQ ID NO:138. In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for

20 example, obtaining a biological sample from the subject comprising an ANGPTL7 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse transcribing the mRNA into cDNA, and performing an assay on the biological sample that determines that a position of the ANGPTL7 genomic nucleic acid molecule, mRNA, or cDNA encodes an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, an adenine at a position

25 corresponding to position 481 according to SEQ ID NO:135, an adenine at a position corresponding to position 481 according to SEQ ID NO:138, respectively. Such assays can comprise, for example determining the identity of these positions of the particular ANGPTL7 nucleic acid molecule. In some embodiments, the method is an *in vitro* method.

In some embodiments, the assay comprises sequencing at least a portion of: i) the 30 nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) the nucleotide sequence of the ANGPTL

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mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:135; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the assay comprises: a) contacting the biological sample with a primer hybridizing to i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:138; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,243 according to SEQ ID NO:132; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 481 according to SEQ ID NO:135; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 481 according to SEQ ID NO:138; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) adenine at a position corresponding to position 481 according to SEQ ID NO:138.

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In some embodiments, the assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) an adenine at a position corresponding to position 481 according to SEQ ID NO:135; and/or iii) an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and detecting the detectable label.

In some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the subject to determine whether an ANGPTL7 nucleic acid molecule in the biological sample comprises a nucleotide sequence comprising: i) an adenine at a position

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corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof, ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof, or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the method is an *in vitro* method.

5 In some embodiments, the methods of detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule) in a human subject, comprise: performing an assay on a biological sample obtained from the human 10 subject, which assay determines whether a nucleic acid molecule in the biological sample comprises a nucleotide sequence that encodes i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139. In some embodiments, the biological sample 15 comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising an ANGPTL7 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse transcribing the mRNA into cDNA, and performing an assay on the biological sample that determines that a position of the ANGPTL7 genomic nucleic acid molecule, mRNA, or cDNA encodes an adenine at a position corresponding 20 to position 4,325 according to SEQ ID NO:133, an adenine at a position corresponding to position 563 according to SEQ ID NO:136, an adenine at a position corresponding to position 563 according to SEQ ID NO:139, respectively. Such assays can comprise, for example determining the identity of these positions of the particular ANGPTL7 nucleic acid molecule. In some embodiments, the method is an *in vitro* method.

25 In some embodiments, the assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or 30 iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID

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NO:139, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID NO:133; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,325 according to SEQ ID NO:133; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 563 according to SEQ ID NO:136 and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 563 according to SEQ ID NO:139; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136; and/or iii) an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

In some embodiments, the assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: i) an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) an adenine at a position

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corresponding to position 563 according to SEQ ID NO:139 or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid molecule comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and detecting the detectable label.

In some embodiments, the methods of detecting a human ANGPTL7 predicted loss-of-function variant nucleic acid molecule in a human subject comprise assaying a biological sample obtained from the subject to determine whether an ANGPTL7 nucleic acid molecule in the biological sample comprises a nucleotide sequence comprising: i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof, ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof, or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the method is an *in vitro* method.

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In some embodiments, the methods of detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule) in a human subject, comprise: performing an assay on a biological sample obtained from the human subject, which assay determines whether a nucleic acid molecule in the biological sample comprises a nucleotide sequence that encodes i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140. In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising an ANGPTL7 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse transcribing the mRNA into cDNA, and performing an assay on the biological sample that determines that a position of the ANGPTL7 genomic nucleic acid molecule, mRNA, or cDNA encodes an a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, respectively. Such assays can comprise, for example determining the identity of these positions of the particular ANGPTL7 nucleic acid molecule. In some embodiments, the method is an in vitro method.

In some embodiments, the assay comprises sequencing at least a portion of: i) the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:137; or the complement thereof; and/or iii) the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. When the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule. When the sequenced portion of the ANGPTL7 mRNA molecule in the

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biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule. When the sequenced portion of the

5 ANGPTL7 cDNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

In some embodiments, the assay comprises: a) contacting the biological sample with a primer hybridizing to: i) a portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,336 according to SEQ

10 ID NO:134; ii) a portion of the nucleotide sequence of the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a portion of the nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:140; b) extending the primer at least through: i) the position of the nucleotide sequence of the ANGPTL7 genomic nucleic acid

15 molecule corresponding to position 4,336 according to SEQ ID NO:134; ii) the position of the nucleotide sequence of the ANGPTL7 mRNA molecule corresponding to position 574 according to SEQ ID NO:137; and/or iii) the position of the nucleotide sequence of the ANGPTL7 cDNA molecule corresponding to position 574 according to SEQ ID NO:140; and c) determining whether the extension product of the primer comprises: i) a cytosine at a position

20 corresponding to position 4,336 according to SEQ ID NO:134; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

In some embodiments, the assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion

25 comprises: i) a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; and/or iii) a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support

30 comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: i) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position

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corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; ii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; and/or iii) the nucleic acid sequence of the amplified nucleic acid molecule comprising a cytosine at a 5 position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and d) detecting the detectable label. In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the assay comprises: contacting the nucleic acid molecule in 10 the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to: the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; the nucleotide sequence of the amplified nucleic acid molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; and/or the nucleotide sequence of the amplified nucleic acid 15 molecule comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and detecting the detectable label.

In some embodiments, the nucleic acid molecule in the sample is mRNA and the mRNA 20 is reverse-transcribed into a cDNA prior to the amplifying step. In some embodiments, the nucleic acid molecule is present within a cell obtained from the human subject.

The ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any ANGPTL7 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding an ANGPTL7 polypeptide having a partial loss-of- 25 function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. For example, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule can be any nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes 30 ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, or Phe161Ile. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Gln175His, Trp188Stop, or Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-

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function variant nucleic acid molecule encodes ANGPTL7 Gln175His. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Arg177Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Trp188Stop. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Lys192Gln. In some embodiments, the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encodes ANGPTL7 Phe161Ile.

In some embodiments, the assay comprises contacting the biological sample with a primer or probe, such as an alteration-specific primer or alteration-specific probe, that 10 specifically hybridizes to an ANGPTL7 variant genomic sequence, variant mRNA sequence, or variant cDNA sequence and not the corresponding ANGPTL7 reference sequence under stringent conditions, and determining whether hybridization has occurred.

In some embodiments, the assay comprises RNA sequencing (RNA-Seq). In some 15 embodiments, the assays also comprise reverse transcribing mRNA into cDNA, such as by the reverse transcriptase polymerase chain reaction (RT-PCR).

In some embodiments, the methods utilize probes and primers of sufficient nucleotide length to bind to the target nucleotide sequence and specifically detect and/or identify a polynucleotide comprising an ANGPTL7 variant genomic nucleic acid molecule, variant mRNA molecule, or variant cDNA molecule. The hybridization conditions or reaction conditions can be 20 determined by the operator to achieve this result. This nucleotide length may be any length that is sufficient for use in a detection method of choice, including any assay described or exemplified herein. Such probes and primers can hybridize specifically to a target nucleotide sequence under high stringency hybridization conditions. Probes and primers may have complete nucleotide sequence identity of contiguous nucleotides within the target nucleotide 25 sequence, although probes differing from the target nucleotide sequence and that retain the ability to specifically detect and/or identify a target nucleotide sequence may be designed by conventional methods. Accordingly, probes and primers can share about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% sequence identity or complementarity to the nucleotide 30 sequence of the target nucleic acid molecule.

In some embodiments, to determine whether the ANGPTL7 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof,

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within a biological sample comprises a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2 (genomic nucleic acid molecule), or a uracil at a position corresponding to position 529 according to SEQ ID NO:5 (mRNA molecule), or a thymine at a position corresponding to position 529 according to SEQ ID NO:8 (cDNA

5 molecule), the biological sample may be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, and a second primer derived from the
10 3' flanking sequence adjacent to a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8 to produce an amplicon that is indicative of the presence of the SNP at positions comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or a uracil at a
15 position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty
20 thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising a thymine at a position
25 corresponding to position 4,291 according to SEQ ID NO:2, or a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

In some embodiments, to determine whether the ANGPTL7 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof,
30 within a biological sample comprises a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3 (genomic nucleic acid molecule), or a uracil at a position corresponding to position 525 according to SEQ ID NO:6 (mRNA molecule),

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or a thymine at a position corresponding to position 525 according to SEQ ID NO:9 (cDNA molecule), the biological sample may be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or a uracil at a position

5 corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position corresponding to position 525 according to SEQ ID NO:9, and a second primer derived from the 3' flanking sequence adjacent to a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position corresponding to position 525 according to SEQ ID NO:9

10 to produce an amplicon that is indicative of the presence of the SNP at positions comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position corresponding to position 525 according to SEQ ID NO:9. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair

15 to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position

20 a position corresponding to position 525 according to SEQ ID NO:9, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

25 In some embodiments, to determine whether a ANGPTL7 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132 (genomic nucleic acid molecule), or an adenine at a position corresponding to position 481 according to SEQ ID NO:135 (mRNA molecule), or an adenine at a position corresponding to position 481 according to SEQ ID NO:138 (cDNA molecule), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent

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to an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or an adenine at a position corresponding to position 481 according to SEQ ID NO:138, and a second primer derived from the 3' flanking sequence adjacent to an adenine at a position corresponding to 5 position 4,243 according to SEQ ID NO:132, or an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or an adenine at a position corresponding to position 481 according to SEQ ID NO:138 to produce an amplicon that is indicative of the presence of the SNP at positions encoding an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or an adenine at a position corresponding to position 481 10 according to SEQ ID NO:135, or an adenine at a position corresponding to position 481 according to SEQ ID NO:138. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base 15 pairs. Optionally, the primer pair flanks a region including positions comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or an adenine at a position corresponding to position 481 according to SEQ ID NO:138, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising an adenine at a position 20 corresponding to position 4,243 according to SEQ ID NO:132, or an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

In some embodiments, to determine whether a ANGPTL7 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, 25 within a biological sample comprises a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133 (genomic nucleic acid molecule), or an adenine at a position corresponding to position 563 according to SEQ ID NO:136 (mRNA molecule), or an adenine at a position corresponding to position 563 according to SEQ ID NO:139 (cDNA molecule), the biological sample can be subjected to an amplification method 30 using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or an adenine

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at a position corresponding to position 563 according to SEQ ID NO:139, and a second primer derived from the 3' flanking sequence adjacent to an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or an adenine at a position corresponding to position 563 according to SEQ ID NO:139 to produce an amplicon that is indicative of the presence of the SNP at positions encoding an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or an adenine at a position corresponding to position 563 according to SEQ ID NO:139. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or an adenine at a position corresponding to position 563 according to SEQ ID NO:139, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

In some embodiments, to determine whether a ANGPTL7 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134 (genomic nucleic acid molecule), or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137 (mRNA molecule), or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140 (cDNA molecule), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, and a second primer derived from the 3' flanking sequence adjacent to a cytosine at a position corresponding to

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position 4,336 according to SEQ ID NO:134, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140 to produce an amplicon that is indicative of the presence of the SNP at positions encoding a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose, such as the PCR primer analysis tool in Vector NTI version 10 (Informax Inc., Bethesda Md.); PrimerSelect (DNASTAR Inc., Madison, Wis.); and Primer3 (Version 0.4.0[®], 1991, Whitehead Institute for Biomedical Research, Cambridge, Mass.). Additionally, the sequence can be visually scanned and primers manually identified using known guidelines.

A variety of techniques are available in the art including, for example, nucleic acid sequencing, nucleic acid hybridization, and nucleic acid amplification. Illustrative examples of nucleic acid sequencing techniques include, but are not limited to, chain terminator (Sanger) sequencing and dye terminator sequencing.

Other methods involve nucleic acid hybridization methods other than sequencing, including using labeled primers or probes directed against purified DNA, amplified DNA, and fixed cell preparations (fluorescence in situ hybridization (FISH)). In some methods, a target nucleic acid molecule may be amplified prior to or simultaneous with detection. Illustrative

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examples of nucleic acid amplification techniques include, but are not limited to, polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), and nucleic acid sequence based amplification (NASBA). Other methods include, but are not limited to, ligase chain reaction, strand displacement amplification, and thermophilic SDA (tSDA).

5 In hybridization techniques, stringent conditions can be employed such that a probe or primer will specifically hybridize to its target. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target sequence to a detectably greater degree than to other non-target sequences, such as, at least 2-fold, at least 3-fold, at least 4-fold, or more over background, including over 10-fold over background. In some embodiments,
10 a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 2-fold. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 3-fold. In some embodiments, a polynucleotide
15 primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 4-fold. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by over 10-fold over background. Stringent conditions are sequence-dependent and will be
20 different in different circumstances.

Appropriate stringency conditions which promote DNA hybridization, for example, 6X sodium chloride/sodium citrate (SSC) at about 45°C., followed by a wash of 2X SSC at 50°C, are known or can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Typically, stringent conditions for hybridization and detection will be those in which the salt concentration is less than about 1.5 M Na⁺ ion, typically about 0.01 to 1.0 M Na⁺ ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (such as, for example, 10 to 50 nucleotides) and at least about 60°C for longer probes (such as, for example, greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Optionally, wash buffers may comprise about 0.1% to about 1% SDS. Duration of hybridization is generally less than about 24 hours, usually about 4 to about 12 hours. The duration of the wash time will be at least a length of time sufficient to reach equilibrium.

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The present disclosure also provides methods of detecting the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide comprising performing an assay on a sample obtained from a human subject to determine whether an ANGPTL7 polypeptide in the subject contains one or more variations that causes the polypeptide to have a loss-of-function

5 (partial or complete). For example, in some embodiments, the methods detect the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide, such as, for example, the ANGPTL7 Arg177Stop variant polypeptide, and comprise performing an assay on a sample obtained from a human subject to determine whether an ANGPTL7 polypeptide in the sample terminates at a position corresponding to position 176 according to SEQ ID NO:11. In some

10 embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises positions corresponding to any positions that are C-terminal to position 176 according to SEQ ID NO:11 (such polypeptides are reference; an absence of such positions indicates that the polypeptide terminates at least at position 176 and is a predicted loss-of-function variant ANGPTL7 polypeptide). In some embodiments, the detecting step comprises

15 sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that terminates at a position corresponding to position 176 according to SEQ ID NO:11.

The present disclosure also provides isolated nucleic acid molecules that hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:2), ANGPTL7 variant

20 mRNA molecules (such as SEQ ID NO:5), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:8). In some embodiments, the isolated nucleic acid molecules hybridize to the portion of the ANGPTL7 nucleic acid molecule that includes a position corresponding to position 4,291 according to SEQ ID NO:2, or includes a position corresponding to position 529 according to SEQ ID NO:5 or SEQ ID NO:8.

25 In some embodiments, the methods detect the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide, such as, for example, the ANGPTL7 Gln175His variant polypeptide, and comprise performing an assay on a sample obtained from a human subject to determine whether an ANGPTL7 polypeptide in the sample comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the

30 detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 175 according to SEQ ID NO:10 or SEQ ID NO:12. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some

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embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 175 according to SEQ ID NO:10 or SEQ ID NO:12.

The present disclosure also provides isolated nucleic acid molecules that hybridize to
5 ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:3), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:6), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:9). In some embodiments, the isolated nucleic acid molecules hybridize to the portion of the ANGPTL7 nucleic acid molecule that includes a position corresponding to position 4,287 according to SEQ ID NO:3, or includes a position corresponding to position 525 according to
10 SEQ ID NO:6 or SEQ ID NO:9.

In some embodiments, the methods detect the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide, such as, for example, the ANGPTL7 Phe161Ile variant polypeptide, and comprise performing an assay on a sample obtained from a human subject to determine whether an ANGPTL7 polypeptide in the sample comprises an isoleucine
15 at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 161 according to SEQ ID NO:10 or SEQ ID NO:141. In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a
20 polypeptide that comprises a position corresponding to position 161 according to SEQ ID NO:10 or SEQ ID NO:141.

The present disclosure also provides isolated nucleic acid molecules that hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:132), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:135), and/or ANGPTL7 variant cDNA molecules (such as
25 SEQ ID NO:138). In some embodiments, the isolated nucleic acid molecules hybridize to the portion of the ANGPTL7 nucleic acid molecule that includes a position corresponding to position 4,243 according to SEQ ID NO:132, or includes a position corresponding to position 481 according to SEQ ID NO:135 or SEQ ID NO:138.

In some embodiments, the methods detect the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide, such as, for example, the ANGPTL7 Trp188Stop variant polypeptide, and comprise performing an assay on a sample obtained from a human subject to determine whether an ANGPTL7 polypeptide in the sample terminates at a position
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corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises positions corresponding to any positions that are C-terminal to position 187 according to SEQ ID NO:142 (such polypeptides are reference; an absence of such positions indicates that the 5 polypeptide terminates at least at position 187 and is a predicted loss-of-function variant ANGPTL7 polypeptide). In some embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that terminates at a position corresponding to position 187 according to SEQ ID NO:142.

10 The present disclosure also provides isolated nucleic acid molecules that hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:133), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:136), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:139). In some embodiments, the isolated nucleic acid molecules hybridize to the portion of the ANGPTL7 nucleic acid molecule that includes a position corresponding to 15 position 4,325 according to SEQ ID NO:133, or includes a position corresponding to position 563 according to SEQ ID NO:136 or SEQ ID NO:139.

16 In some embodiments, the methods detect the presence of a human ANGPTL7 predicted loss-of-function variant polypeptide, such as, for example, the ANGPTL7 Lys192Gln variant polypeptide, and comprise performing an assay on a sample obtained from a human 20 subject to determine whether an ANGPTL7 polypeptide in the sample comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 192 according to SEQ ID NO:10 or SEQ ID NO:143. In some 25 embodiments, the detecting step comprises sequencing the entire polypeptide. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 192 according to SEQ ID NO:10 or SEQ ID NO:143.

30 The present disclosure also provides isolated nucleic acid molecules that hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:134), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:137), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:140). In some embodiments, the isolated nucleic acid molecules hybridize to the portion of the ANGPTL7 nucleic acid molecule that includes a position corresponding to

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position 4,336 according to SEQ ID NO:134, or includes a position corresponding to position 574 according to SEQ ID NO:137 or SEQ ID NO:140.

In some embodiments, such isolated nucleic acid molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, at least about 60, at least about 65, at least about 70, at least about 75, at least about 80, at least about 85, at least about 90, at least about 95, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 2000, at least about 3000, at least about 4000, or at least about 5000 nucleotides. In some embodiments, such isolated nucleic acid molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, or at least about 25 nucleotides. In preferred embodiments, the isolated nucleic acid molecules comprise or consist of at least about 18 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of at least about 15 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 10 to about 35, from about 10 to about 30, from about 10 to about 25, from about 12 to about 30, from about 12 to about 28, from about 12 to about 24, from about 15 to about 30, from about 15 to about 25, from about 18 to about 30, from about 18 to about 25, from about 18 to about 24, or from about 18 to about 22 nucleotides. In preferred embodiments, the isolated nucleic acid molecules comprise or consist of from about 18 to about 30 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of at least about 15 nucleotides to at least about 35 nucleotides.

In some embodiments, such isolated nucleic acid molecules hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:2), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:5), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:8) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or

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exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

In some embodiments, the isolated nucleic acid molecules hybridize to at least about 5 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:2), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:5), and/or ANGPTL7 variant cDNA molecules (such as SEQ 10 ID NO:8). In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 35 nucleotides.

15 In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the portion comprises a position corresponding to: position 4,291 according to SEQ ID NO:2, or the
20 complement thereof; position 529 according to SEQ ID NO:5, or the complement thereof; or position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments,
25 the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 4,289 to 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide
30 sequence comprising a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide

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sequence comprising positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof.

In some embodiments, such isolated nucleic acid molecules hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:3), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:6), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:9) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

In some embodiments, the isolated nucleic acid molecules hybridize to at least about 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:3), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:6), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:9). In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 35 nucleotides.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the portion comprises a position corresponding to: position 4,287 according to SEQ ID NO:3, or the

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complement thereof; position 525 according to SEQ ID NO:6, or the complement thereof; or position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to 5 position 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer 10 comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 523 to 525 according to SEQ ID NO:6, 15 or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a 20 portion of a nucleotide sequence comprising positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof.

In some embodiments, such isolated nucleic acid molecules hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:132), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:135), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:138) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

30 In some embodiments, the isolated nucleic acid molecules hybridize to at least about 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least

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about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:132), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:135), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:138). In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 35 nucleotides.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the portion comprises a position corresponding to: position 4,243 according to SEQ ID NO:132, or the complement thereof; position 481 according to SEQ ID NO:135, or the complement thereof; or position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is

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complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof.

In some embodiments, such isolated nucleic acid molecules hybridize to ANGPTL variant genomic nucleic acid molecules (such as SEQ ID NO:133), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:136), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:139) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

In some embodiments, the isolated nucleic acid molecules hybridize to at least about 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:133), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:136), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:139). In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 35 nucleotides.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the portion comprises a position corresponding to: position 4,325 according to SEQ ID NO:133, or the complement thereof; position 563 according to SEQ ID NO:136, or the complement thereof; or position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a

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nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 562 to 564 according to SEQ ID NO:139, or the complement thereof.

In some embodiments, such isolated nucleic acid molecules hybridize to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:134), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:137), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:140) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

In some embodiments, the isolated nucleic acid molecules hybridize to at least about 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to ANGPTL7 variant genomic nucleic acid molecules (such as SEQ ID NO:134), ANGPTL7 variant mRNA molecules (such as SEQ ID NO:137), and/or ANGPTL7 variant cDNA molecules (such as SEQ ID NO:140). In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to

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about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of from about 15 to about 35 nucleotides.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or 5 alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the portion comprises a position corresponding to: position 4,336 according to SEQ ID NO:134, or the complement thereof; position 574 according to SEQ ID NO:137, or the complement thereof; or position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, 10 the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising 15 positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the alteration-specific probe or alteration- 20 specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to position 574 25 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof.

In some embodiments, the alteration-specific probes and alteration-specific primers 30 comprise DNA. In some embodiments, the alteration-specific probes and alteration-specific primers comprise RNA.

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In some embodiments, the probes and primers described herein (including alteration-specific probes and alteration-specific primers) have a nucleotide sequence that specifically hybridizes to any of the nucleic acid molecules disclosed herein, or the complement thereof. In some embodiments, the probes and primers specifically hybridize to any of the nucleic acid molecules disclosed herein under stringent conditions.

In some embodiments, the primers, including alteration-specific primers, can be used in second generation sequencing or high throughput sequencing. In some instances, the primers, including alteration-specific primers, can be modified. In particular, the primers can comprise various modifications that are used at different steps of, for example, Massive Parallel Signature Sequencing (MPSS), Polony sequencing, and 454 Pyrosequencing. Modified primers can be used at several steps of the process, including biotinylated primers in the cloning step and fluorescently labeled primers used at the bead loading step and detection step. Polony sequencing is generally performed using a paired-end tags library wherein each molecule of DNA template is about 135 bp in length. Biotinylated primers are used at the bead loading step and emulsion PCR. Fluorescently labeled degenerate nonamer oligonucleotides are used at the detection step. An adaptor can contain a 5'-biotin tag for immobilization of the DNA library onto streptavidin-coated beads.

The probes and primers described herein can be used to detect the C4,291T variation within the ANGPTL7 variant genomic nucleic acid molecule (such as, for example, according to SEQ ID NO:2), or the C529U variation within the ANGPTL7 variant mRNA molecule (such as, for example, according to SEQ ID NO:5), or the C529T variation within the ANGPTL7 variant cDNA molecule (such as, for example, according to SEQ ID NO:8). For example, the primers can be used to amplify ANGPTL7 variant genomic nucleic acid molecules or a fragment thereof comprising the C4,291T variation. The primers can also be used to amplify ANGPTL7 variant mRNA or a fragment thereof comprising the C529U variation. The primers can also be used to amplify ANGPTL7 variant cDNA or a fragment thereof comprising the C529T variation.

The probes and primers described herein can be used to detect the G4,287T variation within the ANGPTL7 variant genomic nucleic acid molecule (such as, for example, according to SEQ ID NO:3), or the G525U variation within the ANGPTL7 variant mRNA molecule (such as, for example, according to SEQ ID NO:6), or the G525T variation within the ANGPTL7 variant cDNA molecule (such as, for example, according to SEQ ID NO:9). For example, the primers can be used to amplify ANGPTL7 variant genomic nucleic acid molecules or a fragment thereof

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comprising the G4,287T variation. The primers can also be used to amplify ANGPTL7 variant mRNA or a fragment thereof comprising the G525U variation. The primers can also be used to amplify ANGPTL7 variant cDNA or a fragment thereof comprising the G525T variation.

The probes and primers described herein can be used to detect the T4,243A variation 5 within the ANGPTL7 variant genomic nucleic acid molecule (such as, for example, according to SEQ ID NO:132), or the U481A variation within the ANGPTL7 variant mRNA molecule (such as, for example, according to SEQ ID NO:135), or the T481A variation within the ANGPTL7 variant cDNA molecule (such as, for example, according to SEQ ID NO:138). For example, the primers can be used to amplify ANGPTL7 variant genomic nucleic acid molecules or a fragment thereof 10 comprising the T4,243A variation. The primers can also be used to amplify ANGPTL7 variant mRNA or a fragment thereof comprising the U481A variation. The primers can also be used to amplify ANGPTL7 variant cDNA or a fragment thereof comprising the T481A variation.

The probes and primers described herein can be used to detect the G4,325A variation 15 within the ANGPTL7 variant genomic nucleic acid molecule (such as, for example, according to SEQ ID NO:133), or the G563A variation within the ANGPTL7 variant mRNA molecule (such as, for example, according to SEQ ID NO:136), or the G563A variation within the ANGPTL7 variant cDNA molecule (such as, for example, according to SEQ ID NO:139). For example, the primers can be used to amplify ANGPTL7 variant genomic nucleic acid molecules or a fragment thereof 20 comprising the G4,325A variation. The primers can also be used to amplify ANGPTL7 variant mRNA or a fragment thereof comprising the G563A variation. The primers can also be used to amplify ANGPTL7 variant cDNA or a fragment thereof comprising the G563A variation.

The probes and primers described herein can be used to detect the A4,336C variation 25 within the ANGPTL7 variant genomic nucleic acid molecule (such as, for example, according to SEQ ID NO:134), or the A574C variation within the ANGPTL7 variant mRNA molecule (such as, for example, according to SEQ ID NO:137), or the A574C variation within the ANGPTL7 variant cDNA molecule (such as, for example, according to SEQ ID NO:140). For example, the primers can be used to amplify ANGPTL7 variant genomic nucleic acid molecules or a fragment thereof 30 comprising the A4,336C variation. The primers can also be used to amplify ANGPTL7 variant mRNA or a fragment thereof comprising the A574C variation. The primers can also be used to amplify ANGPTL7 variant cDNA or a fragment thereof comprising the A574C variation.

The present disclosure also provides pairs of primers comprising any of the primers described above. If one of the primers' 3'-ends hybridizes to a cytosine at a position

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corresponding to position 4,291 (rather than thymine) (comparing SEQ ID NO:1 and SEQ ID NO:2) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference genomic nucleic acid molecule. Conversely, if one of the primers' 3'-ends hybridizes to a thymine at a position

5 corresponding to position 4,291 (rather than cytosine) (comparing SEQ ID NO:1 and SEQ ID NO:2) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant genomic nucleic acid molecule. In some embodiments, the nucleotide of the primer complementary to the thymine at a position corresponding to position 4,291 in SEQ ID NO:2 can be at the 3' end of the primer.

10 In addition, if one of the primers' 3'-ends hybridizes to a cytosine at a position corresponding to position 529 (rather than uracil) (comparing SEQ ID NO:4 and SEQ ID NO:5) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference mRNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to a uracil at a position corresponding to position 529 (rather than cytosine)

15 (comparing SEQ ID NO:4 and SEQ ID NO:5) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant mRNA molecule. In some embodiments, the nucleotide of the primer complementary to the uracil at a position corresponding to position 529 in SEQ ID NO:5 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes to a cytosine at a position corresponding to

20 position 529 (rather than thymine) (comparing SEQ ID NO:7 and SEQ ID NO:8) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference cDNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to a thymine at a position corresponding to position 529 (rather than cytosine)

25 (comparing SEQ ID NO:7 and SEQ ID NO:8) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant cDNA molecule. In some embodiments, the nucleotide of the primer complementary to the thymine at a position corresponding to position 529 in SEQ ID NO:8 can be at the 3' end of the primer.

In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 genomic nucleic acid molecule, wherein the portion

30 comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 genomic

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nucleic acid molecule comprising SEQ ID NO:2 at a portion comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 mRNA molecule, 5 wherein the portion comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 mRNA molecule comprising SEQ ID NO:5 at a portion comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or which hybridizes to the 10 complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 cDNA molecule, wherein the portion comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an 15 ANGPTL7 cDNA molecule comprising SEQ ID NO:8 at a portion comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or which hybridizes to the complement of this nucleic acid molecule.

If one of the primers' 3'-ends hybridizes to a guanine at a position corresponding to position 4,287 (rather than thymine) (comparing SEQ ID NO:1 and SEQ ID NO:3) in a particular 20 ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference genomic nucleic acid molecule. Conversely, if one of the primers' 3'-ends hybridizes to a thymine at a position corresponding to position 4,287 (rather than guanine) (comparing SEQ ID NO:1 and SEQ ID NO:3) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the 25 presence of the ANGPTL7 variant genomic nucleic acid molecule. In some embodiments, the nucleotide of the primer complementary to the thymine at a position corresponding to position 4,287 in SEQ ID NO:3 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes to a guanine at a position corresponding to position 525 (rather than uracil) (comparing SEQ ID NO:4 and SEQ ID NO:6) in a particular ANGPTL7 mRNA molecule, then the 30 presence of the amplified fragment would indicate the presence of an ANGPTL7 reference mRNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to a uracil at a position corresponding to position 525 (rather than guanine) (comparing SEQ ID NO:4 and SEQ ID NO:6)

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in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant mRNA molecule. In some embodiments, the nucleotide of the primer complementary to the uracil at a position corresponding to position 525 in SEQ ID NO:6 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends 5 hybridizes to a guanine at a position corresponding to position 525 (rather than thymine) (comparing SEQ ID NO:7 and SEQ ID NO:9) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference cDNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to a thymine at a position corresponding to position 525 (rather than guanine) (comparing SEQ ID NO:7 and SEQ ID NO:9) 10 in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant cDNA molecule. In some embodiments, the nucleotide of the primer complementary to the thymine at a position corresponding to position 525 in SEQ ID NO:9 can be at the 3' end of the primer.

In some embodiments, the probes or primers comprise a nucleotide sequence which 15 hybridizes to a portion of an ANGPTL7 genomic nucleic acid molecule, wherein the portion comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 genomic nucleic acid molecule comprising SEQ ID NO:3 at a portion comprising a thymine at a position 20 corresponding to position 4,287 according to SEQ ID NO:3, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 mRNA molecule, wherein the portion comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or which hybridizes to the complement of this nucleic acid molecule. In some 25 embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 mRNA molecule comprising SEQ ID NO:6 at a portion comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 cDNA molecule, 30 wherein the portion comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an

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ANGPTL7 cDNA molecule comprising SEQ ID NO:9 at a portion comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or which hybridizes to the complement of this nucleic acid molecule.

If one of the primers' 3'-ends hybridizes to a thymine at a position corresponding to 5 position 4,243 (rather than adenine) (comparing SEQ ID NO:1 and SEQ ID NO:132) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference genomic nucleic acid molecule. Conversely, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 4,243 (rather than thymine) (comparing SEQ ID NO:1 and SEQ ID NO:132) in a 10 particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 variant genomic nucleic acid molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 4,243 according to SEQ ID NO:132 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes to a uracil at a position corresponding to 15 position 481 (rather than adenine) (comparing SEQ ID NO:4 and SEQ ID NO:135) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference mRNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 481 (rather than uracil) (comparing SEQ ID NO:4 and SEQ ID NO:135) in a particular ANGPTL7 mRNA molecule, then the 20 presence of the amplified fragment would indicate the presence of the ANGPTL7 variant mRNA molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 481 according to SEQ ID NO:135 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes to a thymine at a position corresponding to position 481 (rather than adenine) (comparing SEQ ID NO:7 and SEQ ID 25 NO:138) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference cDNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 481 (rather than thymine) (comparing SEQ ID NO:4 and SEQ ID NO:138) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of the 30 ANGPTL7 variant cDNA molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 481 according to SEQ ID NO:138 can be at the 3' end of the primer.

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In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 genomic nucleic acid molecule, wherein the portion comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or which hybridizes to the complement of this nucleic acid molecule. In some 5 embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 genomic nucleic acid molecule comprising SEQ ID NO:132 at a portion comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132 or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 mRNA 10 molecule, wherein the portion comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 mRNA molecule comprising SEQ ID NO:135 at a portion comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or which 15 hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 cDNA molecule, wherein the portion comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which 20 hybridizes to an ANGPTL7 cDNA molecule comprising SEQ ID NO:138 at a portion comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or which hybridizes to the complement of this nucleic acid molecule.

If one of the primers' 3'-ends hybridizes to a guanine at a position corresponding to 25 position 4,325 (rather than adenine) (comparing SEQ ID NO:1 and SEQ ID NO:133) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference genomic nucleic acid molecule. Conversely, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 4,325 (rather than guanine) (comparing SEQ ID NO:1 and SEQ ID NO:133) in a 30 particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant genomic nucleic acid molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 4,325 according to SEQ ID NO:133 can be at the 3' end of the

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primer. In addition, if one of the primers' 3'-ends hybridizes to a guanine at a position corresponding to position 563 (rather than adenine) (comparing SEQ ID NO:4 and SEQ ID NO:136) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference mRNA molecule. Conversely, if one of

5 the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 563 (rather than guanine) (comparing SEQ ID NO:4 and SEQ ID NO:136) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant mRNA molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 563 according to SEQ ID
10 NO:136 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes to a guanine at a position corresponding to position 563 (rather than adenine) (comparing SEQ ID NO:7 and SEQ ID NO:139) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference cDNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding
15 to position 563 (rather than guanine) (comparing SEQ ID NO:7 and SEQ ID NO:139) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant cDNA molecule. In some embodiments, the nucleotide of the primer complementary to the adenine at a position corresponding to position 563 according to SEQ ID NO:139 can be at the 3' end of the primer.

20 In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 genomic nucleic acid molecule, wherein the portion comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an
25 ANGPTL7 genomic nucleic acid molecule comprising SEQ ID NO:133 at a portion comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133 or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 mRNA molecule, wherein the portion comprises an adenine at a position corresponding to position
30 563 according to SEQ ID NO:136, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 mRNA molecule comprising SEQ ID NO:136 at a portion comprising

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an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 cDNA molecule, wherein the portion comprises an adenine at a position corresponding to position

5 563 according to SEQ ID NO:139, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 cDNA molecule comprising SEQ ID NO:139 at a portion comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or which hybridizes to the complement of this nucleic acid molecule.

10 If one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 4,336 (rather than cytosine) (comparing SEQ ID NO:1 and SEQ ID NO:134) in a particular ANGPTL7 genomic nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference genomic nucleic acid molecule. Conversely, if one of the primers' 3'-ends hybridizes to a cytosine at a position corresponding to 15 position 4,336 (rather than adenine) (comparing SEQ ID NO:1 and SEQ ID NO:134) in a particular ANGPTL7 nucleic acid molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant genomic nucleic acid molecule. In some embodiments, the nucleotide of the primer complementary to the cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134 can be at the 3' end of the primer.

20 In addition, if one of the primers' 3'-ends hybridizes to an adenine at a position corresponding to position 574 (rather than cytosine) (comparing SEQ ID NO:4 and SEQ ID NO:137) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference mRNA molecule. Conversely, if one of the primers' 3'-ends hybridizes to a cytosine at a position corresponding to position 574 (rather 25 than adenine) (comparing SEQ ID NO:4 and SEQ ID NO:137) in a particular ANGPTL7 mRNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant mRNA molecule. In some embodiments, the nucleotide of the primer complementary to the cytosine at a position corresponding to position 574 according to SEQ ID NO:137 can be at the 3' end of the primer. In addition, if one of the primers' 3'-ends hybridizes 30 to an adenine at a position corresponding to position 574 (rather than cytosine) (comparing SEQ ID NO:7 and SEQ ID NO:140) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of an ANGPTL7 reference cDNA molecule.

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Conversely, if one of the primers' 3'-ends hybridizes to a cytosine at a position corresponding to position 574 (rather than adenine) (comparing SEQ ID NO:7 and SEQ ID NO:140) in a particular ANGPTL7 cDNA molecule, then the presence of the amplified fragment would indicate the presence of the ANGPTL7 variant cDNA molecule. In some embodiments, the nucleotide of the 5 primer complementary to the cytosine at a position corresponding to position 574 according to SEQ ID NO:140 can be at the 3' end of the primer.

In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 genomic nucleic acid molecule, wherein the portion comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, 10 or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 genomic nucleic acid molecule comprising SEQ ID NO:134 at a portion comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134 or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers 15 comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 mRNA molecule, wherein the portion comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 mRNA molecule comprising SEQ ID NO:137 at a portion comprising a cytosine at a 20 position corresponding to position 574 according to SEQ ID NO:137, or which hybridizes to the complement of this nucleic acid molecule. In some embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to a portion of an ANGPTL7 cDNA molecule, wherein the portion comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or which hybridizes to the complement of this nucleic acid molecule. In some 25 embodiments, the probes or primers comprise a nucleotide sequence which hybridizes to an ANGPTL7 cDNA molecule comprising SEQ ID NO:140 at a portion comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or which hybridizes to the complement of this nucleic acid molecule.

In the context of the disclosure "specifically hybridizes" means that the probe or 30 primer (such as, for example, the alteration-specific probe or alteration-specific primer) does not hybridize to a nucleic acid sequence encoding an ANGPTL7 reference genomic nucleic acid

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molecule, an ANGPTL7 reference mRNA molecule, and/or an ANGPTL7 reference cDNA molecule.

In some embodiments, the probes (such as, for example, an alteration-specific probe) comprise a label. In some embodiments, the label is a fluorescent label, a radiolabel, or biotin.

5 The present disclosure also provides supports comprising a substrate to which any one or more of the probes disclosed herein is attached. Solid supports are solid-state substrates or supports with which molecules, such as any of the probes disclosed herein, can be associated. A form of solid support is an array. Another form of solid support is an array detector. An array detector is a solid support to which multiple different probes have been coupled in an array, 10 grid, or other organized pattern. A form for a solid-state substrate is a microtiter dish, such as a standard 96-well type. In some embodiments, a multiwell glass slide can be employed that normally contains one array per well.

15 The present disclosure also provides molecular complexes comprising or consisting of any of the ANGPTL7 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein and any of the alteration-specific primers or alteration-specific probes described herein. In some embodiments, the ANGPTL7 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, in the molecular complexes are single-stranded. In some 20 embodiments, the ANGPTL7 nucleic acid molecule is any of the genomic nucleic acid molecules described herein. In some embodiments, the ANGPTL7 nucleic acid molecule is any of the mRNA molecules described herein. In some embodiments, the ANGPTL7 nucleic acid molecule is any of the cDNA molecules described herein. In some embodiments, the molecular complex comprises or consists of any of the ANGPTL7 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein 25 and any of the alteration-specific primers described herein. In some embodiments, the molecular complex comprises or consists of any of the ANGPTL7 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein and any of the alteration-specific probes described herein. In some embodiments, the molecular complex comprises an alteration-specific probe or an alteration- 30 specific primer comprising a label. In some embodiments, the label is a fluorescent label, a radiolabel, or biotin. In some embodiments, the molecular complex further comprises a non-human polymerase.

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The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the polypeptide terminates at a position corresponding to position 176 according to SEQ ID NO:11, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes an

5 ANGPTL7 polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated nucleic acid molecule encodes an

10 ANGPTL7 polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according

15 to SEQ ID NO:11. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 96% sequence

20 identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:11, and terminates at a position corresponding to position 176 according to SEQ ID NO:11.

25 In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide comprising SEQ ID NO:11. In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide consisting of SEQ ID NO:11.

The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the polypeptide

30 comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90%, at least

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about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated nucleic acid molecule encodes

5 an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175
10 according to SEQ ID NO:12. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 96% sequence
15 identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:12, and comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12.

20 In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide comprising SEQ ID NO:12. In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide consisting of SEQ ID NO:12.

The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the polypeptide
25 comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated nucleic acid
30 molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least

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about 90% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:141, and comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141.

In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide comprising SEQ ID NO:141. In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide consisting of SEQ ID NO:141.

The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the polypeptide terminates at a position corresponding to position 187 according to SEQ ID NO:142, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187

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according to SEQ ID NO:142. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated nucleic acid molecule encodes 5 an ANGPTL7 polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:142, and terminates at a position corresponding to position 187 10 according to SEQ ID NO:142.

In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide comprising SEQ ID NO:142. In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide consisting of SEQ ID NO:142.

The present disclosure also provides isolated nucleic acid molecules comprising a 15 nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the polypeptide comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at 20 least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:143, and comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:143, and comprises a glutamine at a position corresponding to 25 position 192 according to SEQ ID NO:143. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:143, and comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that 30 has at least about 94% sequence identity to SEQ ID NO:143, and comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid

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sequence that has at least about 96% sequence identity to SEQ ID NO:143, and comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated nucleic acid molecule encodes an ANGPTL7 polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:143, and

5 comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143.

In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide comprising SEQ ID NO:143. In some embodiments, the nucleic acid molecule encodes an ANGPTL7 polypeptide consisting of SEQ ID NO:143.

The nucleotide sequence of an ANGPTL7 reference genomic nucleic acid molecule is set forth in SEQ ID NO:1. Referring to SEQ ID NO:1, position 4,291 of the ANGPTL7 reference genomic nucleic acid molecule is a cytosine. Referring to SEQ ID NO:1, position 4,287 of the ANGPTL7 reference genomic nucleic acid molecule is a guanine. Referring to SEQ ID NO:1, position 4,243 of the ANGPTL7 reference genomic nucleic acid molecule is a thymine. Referring to SEQ ID NO:1, position 4,325 of the ANGPTL7 reference genomic nucleic acid molecule is a guanine. Referring to SEQ ID NO:1, position 4,336 of the ANGPTL7 reference genomic nucleic acid molecule is an adenine.

A variant genomic nucleic acid molecule of ANGPTL7 exists, wherein the cytosine at position 4,291 (referring to the reference genomic sequence set forth in SEQ ID NO:1) is replaced with a thymine. The nucleotide sequence of this ANGPTL7 variant genomic nucleic acid molecule is set forth in SEQ ID NO:2.

Another variant genomic nucleic acid molecule of ANGPTL7 exists, wherein the guanine at position 4,287 (referring to the reference genomic sequence set forth in SEQ ID NO:1) is replaced with a thymine. The nucleotide sequence of this ANGPTL7 variant genomic nucleic acid molecule is set forth in SEQ ID NO:3.

25 Another variant genomic nucleic acid molecule of ANGPTL7 exists, wherein the thymine at position 4,243 (referring to the reference genomic sequence set forth in SEQ ID NO:1) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant genomic nucleic acid molecule is set forth in SEQ ID NO:132.

Another variant genomic nucleic acid molecule of ANGPTL7 exists, wherein the

30 guanine at position 4,325 (referring to the reference genomic sequence set forth in SEQ ID NO:1) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant genomic nucleic acid molecule is set forth in SEQ ID NO:133.

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Another variant genomic nucleic acid molecule of ANGPTL7 exists, wherein the adenine at position 4,336 (referring to the reference genomic sequence set forth in SEQ ID NO:1) is replaced with a cytosine. The nucleotide sequence of this ANGPTL7 variant genomic nucleic acid molecule is set forth in SEQ ID NO:134.

5 The present disclosure provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 (C4,291T) according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human
10 ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 (C4,291T) according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 (C4,291T)
15 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a TGA codon at positions corresponding to positions 4,289 to 4,291 according to SEQ ID NO:2.

20 In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:2, and comprise a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:2, and comprise a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic
25 nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:2, and comprise a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:2, and comprise a thymine at a position
30 corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:2, and comprise a thymine at a position

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corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:2, and comprise a

thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the

5 complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:2, and comprise a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

10 In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions corresponding to positions 4,289 to 4,291 according to SEQ

15 ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions corresponding to positions 4,289 to 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments,

the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that

20 has at least about 92% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions corresponding to positions 4,289 to 4,291 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules

comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions corresponding to positions 4,289 to 4,291

25 according to SEQ ID NO:2, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions

corresponding to positions 4,289 to 4,291 according to SEQ ID NO:2, or the complement

thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or

30 consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:2, and comprise a TGA codon at positions corresponding to positions 4,289 to 4,291 according to

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SEQ ID NO:2, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:2. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID 5 NO:2.

The present disclosure also provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 (G4,287T) according to SEQ ID NO:3, or the complement thereof. In some embodiments, 10 the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 (G4,287T) according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide 15 sequence comprises a thymine at a position corresponding to position 4,287 (G4,287T) according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a CAT codon at positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3.

20 In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:3, and comprise a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or 25 the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:3, and comprise a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% 30 sequence identity to SEQ ID NO:3, and comprise a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that

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has at least about 94% sequence identity to SEQ ID NO:3, and comprise a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:3, and comprise a

5 thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:3, and comprise a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof. Herein, if reference is made to percent sequence

10 identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments,

15 the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to

20 SEQ ID NO:3, and comprise a CAT codon at positions corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions

25 corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions

30 corresponding to positions 4,285 to 4,287 according to SEQ ID NO:3, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:3, and comprise a CAT codon at positions corresponding to positions 4,285 to 4,287 according to

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SEQ ID NO:3, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:3. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID 5 NO:3.

The present disclosure also provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243 (T4,243A) according to SEQ ID NO:132, or the complement thereof. In some 10 embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243 (T4,243A) according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the 15 nucleotide sequence comprises an adenine at a position corresponding to position 4,243 (T4,243A) according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an ATC codon at positions corresponding to positions 4,243 to 4,245 according to SEQ ID NO:132.

20 In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, 25 or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least 30 about 92% sequence identity to SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a

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nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to 5 SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:132, and comprise an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof.

10 Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least 15 about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:132, and comprise an ATC codon at positions corresponding to positions 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:132, and comprise an ATC codon at positions corresponding to 20 positions 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:132, and comprise an ATC codon at positions corresponding to 25 positions 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:132, and comprise an ATC codon at positions corresponding to 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:132, and comprise an ATC codon at 30 positions corresponding to 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to

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SEQ ID NO:132, and comprise an ATC codon at positions corresponding to positions 4,243 to 4,245 according to SEQ ID NO:132, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

5 In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO: 132. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:132.

10 The present disclosure also provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 (G4,325A) according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 (G4,325A) according to SEQ ID NO:133, or 15 the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 (G4,325A) according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human 20 ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133.

25 In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 30 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:133, and comprise an adenine at a position

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corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least 5 about 98% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least 10 about 98% sequence identity to SEQ ID NO:133, and comprise an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise or 15 consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:133, and comprise a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% 20 sequence identity to SEQ ID NO:133, and comprise a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:133, and comprise a TAG 25 codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:133, and comprise a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. In some embodiments, the 30 isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:133, and comprise a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement

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thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:133, and comprise a TAG codon at positions corresponding to positions 4,324 to 4,326 according to SEQ ID NO:133, or the complement thereof. Herein, if reference is made to 5 percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO: 133. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:133.

10 The present disclosure also provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 (A4,336C) according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence 15 encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 (A4,336C) according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 20 (A4,336C) according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134.

In some embodiments, the isolated genomic nucleic acid molecules comprise or 25 consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules 30 comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic

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nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that

5 has at least about 94% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ

10 ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:134, and comprise a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred

15 over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:134, and

20 comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:134, and comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some

25 embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:134, and comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to

30 SEQ ID NO:134, and comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has

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at least about 96% sequence identity to SEQ ID NO:134, and comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID 5 NO:134, and comprise a CAG codon at positions corresponding to positions 4,336 to 4,338 according to SEQ ID NO:134, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID 10 NO: 134. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:134.

The genomic nucleic acid molecules can be from any organism. For example, the genomic nucleic acid molecules can be human or an ortholog from another organism, such as a non-human mammal, a rodent, a mouse, or a rat. It is understood that gene sequences within a 15 population can vary due to polymorphisms such as single-nucleotide polymorphisms. The examples provided herein are only exemplary sequences. Other sequences are also possible.

In some embodiments, the isolated genomic nucleic acid molecules comprise less than the entire genomic DNA sequence. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of at least about 15, at least about 20, at least about 25, at least 20, about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 2000, at least about 3000, at least about 4000, or at least about 5000 contiguous nucleotides of any one or more of 25 SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:132, SEQ ID NO:133, and/or SEQ ID NO:134. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of at least about 1000 to at least about 2000 contiguous nucleotides of any one or more of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:132, SEQ ID NO:133, and/or SEQ ID NO:134. In some embodiments, these isolated genomic nucleic acid molecules comprise the thymine at a position corresponding to 30 position 4,291 according to SEQ ID NO:2, or comprise the thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or comprise the adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or comprise the adenine at a

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position corresponding to position 4,325 according to SEQ ID NO:133, or comprise the cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134.

The nucleotide sequence of an ANGPTL7 reference mRNA molecule is set forth in SEQ ID NO:4. Referring to SEQ ID NO:4, position 529 of the ANGPTL7 reference mRNA molecule is a cytosine. Referring to SEQ ID NO:4, position 525 of the ANGPTL7 reference mRNA molecule is a guanine. Referring to SEQ ID NO:4, position 481 of the ANGPTL7 reference mRNA molecule is a uracil. Referring to SEQ ID NO:4, position 563 of the ANGPTL7 reference mRNA molecule is a guanine. Referring to SEQ ID NO:4, position 574 of the ANGPTL7 reference mRNA molecule is an adenine.

10 A variant mRNA molecule of ANGPTL7 exists, wherein the cytosine at position 529 (referring to the reference mRNA sequence set forth in SEQ ID NO:4) is replaced with a uracil. The nucleotide sequence of this ANGPTL7 variant mRNA molecule is set forth in SEQ ID NO:5.

Another variant mRNA molecule of ANGPTL7 exists, wherein the guanine at position 525 (referring to the reference mRNA sequence set forth in SEQ ID NO:4) is replaced with a uracil. The nucleotide sequence of this ANGPTL7 variant mRNA molecule is set forth in SEQ ID NO:6.

Another variant mRNA molecule of ANGPTL7 exists, wherein the uracil at position 481 (referring to the reference mRNA sequence set forth in SEQ ID NO:4) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant mRNA molecule is set forth in SEQ ID NO:135.

Another variant mRNA molecule of ANGPTL7 exists, wherein the guanine at position 563 (referring to the reference mRNA sequence set forth in SEQ ID NO:4) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant mRNA molecule is set forth in SEQ ID NO:136.

25 Another variant mRNA molecule of ANGPTL7 exists, wherein the adenine at position 574 (referring to the reference mRNA sequence set forth in SEQ ID NO:4) is replaced with a cytosine. The nucleotide sequence of this ANGPTL7 variant mRNA molecule is set forth in SEQ ID NO:137.

The present disclosure provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules

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comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the

5 nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5.

10 In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:5, and

15 comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:5, and

20 comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:5, and

25 comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:5, and comprise a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher

30 percentages of sequence identity are preferred over the lower ones.

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In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:5, and comprise a UGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:5, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:5. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:5.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules

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consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein
5 the nucleotide sequence comprises a CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:6.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%,
10 at least about 98%, or at least about 99% sequence identity to SEQ ID NO:6, and comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:6, and comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the
15 complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:6, and comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:6, and
20 comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:6, and comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist
25 of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:6, and comprise a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise or consist of a
30 nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:6, and comprise a

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CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:6, and comprise a CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID

5 NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:6, and comprise a CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94%
10 sequence identity to SEQ ID NO:6, and comprise a CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:6, or the complement thereof. In some
embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that
has at least about 96% sequence identity to SEQ ID NO:6, and comprise a CAU codon at
positions corresponding to positions 523 to 525 according to SEQ ID NO:6, or the complement
15 thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a
nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:6, and
comprise a CAU codon at positions corresponding to positions 523 to 525 according to SEQ ID
NO:6, or the complement thereof. Herein, if reference is made to percent sequence identity,
the higher percentages of sequence identity are preferred over the lower ones.

20 In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:6. In some
embodiments, the isolated mRNA molecules consist of SEQ ID NO:6.

The present disclosure also provides isolated mRNA molecules comprising or consisting
of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide
sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID
25 NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules
comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the
nucleotide sequence comprises an adenine at a position corresponding to position 481
according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated
mRNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide,
30 wherein the nucleotide sequence comprises an adenine at a position corresponding to position
481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the
isolated mRNA molecules comprise or consist of a nucleotide sequence encoding a human

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ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an AUC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:135.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:135, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:135, and comprise an AUC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID

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NO:135, and comprise an AUC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:135, and comprise an AUC codon at positions corresponding to 5 positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:135, and comprise an AUC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist 10 of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:135, and comprise an AUC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:135, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:135, and comprise an AUC codon at positions corresponding to positions 481 to 483 15 according to SEQ ID NO:135, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:135. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:135.

20 The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the 25 nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the 30 isolated mRNA molecules comprise or consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136.

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In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:136, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated

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mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that 5 has at least about 94% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID 10 NO:136, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:136, and comprise a UAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:136, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the 15 lower ones.

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:136. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:136.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID 20 NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA 25 molecules comprise or consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at

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least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:137, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:137, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:137, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:137, and comprise a CAG codon at positions corresponding to

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positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:137, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the 5 complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:137, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to 10 SEQ ID NO:137, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:137, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

15 In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:137. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:137.

The mRNA molecules can be from any organism. For example, the mRNA molecules can be human or an ortholog from another organism, such as a non-human mammal, a rodent, a mouse, or a rat. It is understood that mRNA sequences within a population can vary due to 20 polymorphisms such as single-nucleotide polymorphisms. The examples provided herein are only exemplary sequences. Other sequences are also possible.

In some embodiments, the isolated mRNA molecules comprise less than the entire mRNA sequence. In some embodiments, the isolated mRNA molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 12, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 25 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 200, at least about 300, at least about 400, or at least about 500 contiguous nucleotides of any one or more of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:135, SEQ ID NO:136, and/or SEQ ID NO:137. In some embodiments, the isolated mRNA molecules comprise or consist of at least about 400 to at least about 500 contiguous nucleotides of any one or more 30 of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:135, SEQ ID NO:136, and/or SEQ ID NO:137. In some embodiments, these isolated mRNA molecules comprise the uracil at the position corresponding to position 529 according to SEQ ID NO:5, or the uracil at the position

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corresponding to position 525 according to SEQ ID NO:6, or the adenine at the position corresponding to position 481 according to SEQ ID NO:135, or the adenine at the position corresponding to position 563 according to SEQ ID NO:136, or the cytosine at the position corresponding to position 574 according to SEQ ID NO:137.

5 The nucleotide sequence of an ANGPTL7 reference cDNA molecule is set forth in SEQ ID NO:7. Referring to SEQ ID NO:7, position 529 of the ANGPTL7 reference cDNA molecule is a cytosine. Referring to SEQ ID NO:7, position 525 of the ANGPTL7 reference cDNA molecule is a guanine. Referring to SEQ ID NO:7, position 481 of the ANGPTL7 reference cDNA molecule is a thymine. Referring to SEQ ID NO:7, position 563 of the ANGPTL7 reference cDNA molecule is a 10 guanine. Referring to SEQ ID NO:7, position 574 of the ANGPTL7 reference cDNA molecule is an adenine.

A variant cDNA molecule of ANGPTL7 exists, wherein the cytosine at position 529 (referring to the reference cDNA sequence set forth in SEQ ID NO:7) is replaced with a thymine. The nucleotide sequence of this ANGPTL7 variant cDNA molecule is set forth in SEQ ID NO:8.

15 Another variant cDNA molecule of ANGPTL7 exists, wherein the guanine at position 525 (referring to the reference cDNA sequence set forth in SEQ ID NO:7) is replaced with a thymine. The nucleotide sequence of this ANGPTL7 variant cDNA molecule is set forth in SEQ ID NO:9.

Another variant cDNA molecule of ANGPTL7 exists, wherein the thymine at position 20 481 (referring to the reference cDNA sequence set forth in SEQ ID NO:7) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant cDNA molecule is set forth in SEQ ID NO:138.

Another variant cDNA molecule of ANGPTL7 exists, wherein the guanine at position 25 563 (referring to the reference cDNA sequence set forth in SEQ ID NO:7) is replaced with an adenine. The nucleotide sequence of this ANGPTL7 variant cDNA molecule is set forth in SEQ ID NO:139.

Another variant cDNA molecule of ANGPTL7 exists, wherein the adenine at position 30 574 (referring to the reference cDNA sequence set forth in SEQ ID NO:7) is replaced with a cytosine. The nucleotide sequence of this ANGPTL7 variant cDNA molecule is set forth in SEQ ID NO:140.

The present disclosure provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide

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sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, 5 wherein the nucleotide sequence comprises a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, 15 at least about 98%, or at least about 99% sequence identity to SEQ ID NO:8, and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:8, and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or 20 the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:8, and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:8, 25 and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:8, and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or 30 consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:8, and comprise a thymine at a position corresponding to position 529 according to SEQ ID NO:8,

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or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:8, and comprise a TGA codon at positions corresponding to positions 529 to 531 according to SEQ ID NO:8, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:8. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:8.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the

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nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525

5 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9.

In some embodiments, the isolated cDNA molecules comprise or consist of a

10 nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:9, and comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:9, and

15 comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:9, and comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9,

20 or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:9, and comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:9,

25 and comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:9, and comprise a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof. Herein, if reference is made to percent sequence identity, the

30 higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at

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least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:9, and comprise a CAT codon at positions corresponding to positions 523 to 525 according to SEQ ID NO:9, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:9. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:9.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position

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481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138.

5 In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 99% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:138, and comprise an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

30 In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or

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the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:138, and comprise an ATC codon at positions corresponding to positions 481 to 483 according to SEQ ID NO:138, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

20 In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:138. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:138.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7

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polypeptide, wherein the nucleotide sequence comprises a TAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:139.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:139, and comprise an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:139, and comprise a TAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID

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NO:139, and comprise a TAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:139, and comprise a TAG codon at positions corresponding to 5 positions 562 to 564 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:139, and comprise a TAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist 10 of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:139, and comprise a TAG codon at positions corresponding to positions 562 to 564 according to SEQ ID NO:139, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:139, and comprise a TAG codon at positions corresponding to positions 562 to 564 15 according to SEQ ID NO:139, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:139. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:139.

20 The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the 25 nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules consist of a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated 30 cDNA molecules comprise a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140.

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In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:140, and comprise a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated

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cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that 5 has at least about 94% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID 10 NO:140, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:140, and comprise a CAG codon at positions corresponding to positions 574 to 576 according to SEQ ID NO:140, or the complement thereof. Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the 15 lower ones.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:140. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:140.

The cDNA molecules can be from any organism. For example, the cDNA molecules can be human or an ortholog from another organism, such as a non-human mammal, a rodent, a 20 mouse, or a rat. It is understood that cDNA sequences within a population can vary due to polymorphisms such as single-nucleotide polymorphisms. The examples provided herein are only exemplary sequences. Other sequences are also possible.

In some embodiments, the isolated cDNA molecules comprise less than the entire cDNA sequence. In some embodiments, the isolated cDNA molecules comprise or consist of at 25 least about 5, at least about 8, at least about 10, at least about 12, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 200, at least about 300, at least about 400, or at least about 500 contiguous nucleotides of any one or more of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:138, SEQ ID 30 NO:139, and/or SEQ ID NO:139. In some embodiments, the isolated cDNA molecules comprise or consist of at least about 400 to at least about 500 contiguous nucleotides of any one or more of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:138, SEQ ID NO:139, and/or SEQ ID NO:139. In some

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embodiments, these isolated cDNA molecules comprise the thymine at the position corresponding to position 529 according to SEQ ID NO:8. In some embodiments, these isolated cDNA molecules comprise the thymine at the position corresponding to position 525 according to SEQ ID NO:9. In some embodiments, these isolated cDNA molecules comprise the adenine at the position corresponding to position 481 according to SEQ ID NO:138. In some embodiments, these isolated cDNA molecules comprise the adenine at the position corresponding to position 563 according to SEQ ID NO:139. In some embodiments, these isolated cDNA molecules comprise the cytosine at the position corresponding to position 574 according to SEQ ID NO:140.

The present disclosure also provides fragments of any of the isolated genomic nucleic acid molecules, mRNA molecules, or cDNA molecules disclosed herein. In some embodiments, the fragments comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, at least about 60, at least about 65, at least about 70, at least about 75, at least about 80, at least about 85, at least about 90, at least about 95, or at least about 100 contiguous residues of any of the nucleic acid molecules disclosed herein, or any complement thereof. In this regard, the longer fragments are preferred over the shorter ones.

In some embodiments, the fragments comprise or consist of at least about 20, at least about 25, at least about 30, or at least about 35 contiguous residues of any of the nucleic acid molecules disclosed herein, or any complement thereof. In some embodiments, the fragments comprise or consist of the portion of the nucleic acid molecule that includes a position corresponding to position 4,291 according to SEQ ID NO:2, or includes a position corresponding to position 529 according to SEQ ID NO:5 or SEQ ID NO:8. In some embodiments, the fragments comprise or consist of the portion of the nucleic acid molecule that includes a position corresponding to position 4,287 according to SEQ ID NO:3, or includes a position corresponding to position 525 according to SEQ ID NO:6 or SEQ ID NO:9. In some embodiments, the fragments comprise or consist of the portion of the nucleic acid molecule that includes a position corresponding to position 4,243 according to SEQ ID NO:132, or includes a position corresponding to position 481 according to SEQ ID NO:135 or SEQ ID NO:138. In some

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embodiments, the fragments comprise or consist of the portion of the nucleic acid molecule that includes a position corresponding to position 4,325 according to SEQ ID NO:133, or includes a position corresponding to position 563 according to SEQ ID NO:136 or SEQ ID NO:139. In some embodiments, the fragments comprise or consist of the portion of the nucleic acid molecule that includes a position corresponding to position 4,336 according to SEQ ID NO:134, or includes a position corresponding to position 574 according to SEQ ID NO:137 or SEQ ID NO:140. Such fragments may be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein.

Also provided herein are functional polynucleotides that can interact with the disclosed nucleic acid molecules. Functional polynucleotides are nucleic acid molecules that have a specific function, such as binding a target molecule or catalyzing a specific reaction. Examples of functional polynucleotides include, but are not limited to, antisense molecules, aptamers, ribozymes, triplex forming molecules, and external guide sequences. The functional polynucleotides can act as effectors, inhibitors, modulators, and stimulators of a specific activity possessed by a target molecule, or the functional polynucleotides can possess a *de novo* activity independent of any other molecules.

The isolated nucleic acid molecules disclosed herein can comprise RNA, DNA, or both RNA and DNA. The isolated nucleic acid molecules can also be linked or fused to a heterologous nucleic acid sequence, such as in a vector, or a heterologous label. For example, the isolated nucleic acid molecules disclosed herein can be within a vector or as an exogenous donor sequence comprising the isolated nucleic acid molecule and a heterologous nucleic acid sequence. The isolated nucleic acid molecules can also be linked or fused to a heterologous label, such as a fluorescent label.

The label can be directly detectable (such as, for example, fluorophore) or indirectly detectable (such as, for example, hapten, enzyme, or fluorophore quencher). Such labels can be detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. Such labels include, for example, radiolabels, pigments, dyes, chromogens, spin labels, and fluorescent labels. The label can also be, for example, a chemiluminescent substance; a metal-containing substance; or an enzyme, where there occurs an enzyme-dependent secondary generation of signal. The term “label” can also refer to a “tag” or hapten that can

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bind selectively to a conjugated molecule such that the conjugated molecule, when added subsequently along with a substrate, is used to generate a detectable signal. For example, biotin can be used as a tag along with an avidin or streptavidin conjugate of horseradish peroxidase (HRP) to bind to the tag, and examined using a calorimetric substrate (such as, for example, tetramethylbenzidine (TMB)) or a fluorogenic substrate to detect the presence of HRP. Exemplary labels that can be used as tags to facilitate purification include, but are not limited to, myc, HA, FLAG or 3XFLAG, 6XHis or polyhistidine, glutathione-S-transferase (GST), maltose binding protein, an epitope tag, or the Fc portion of immunoglobulin. Numerous labels include, for example, particles, fluorophores, haptens, enzymes and their calorimetric, fluorogenic and chemiluminescent substrates and other labels.

The disclosed nucleic acid molecules can comprise, for example, nucleotides or non-natural or modified nucleotides, such as nucleotide analogs or nucleotide substitutes. Such nucleotides include a nucleotide that contains a modified base, sugar, or phosphate group, or that incorporates a non-natural moiety in its structure. Examples of non-natural nucleotides include, but are not limited to, dideoxynucleotides, biotinylated, aminated, deaminated, alkylated, benzylated, and fluorophor-labeled nucleotides.

The nucleic acid molecules disclosed herein can also comprise one or more nucleotide analogs or substitutions. A nucleotide analog is a nucleotide which contains a modification to either the base, sugar, or phosphate moieties. Modifications to the base moiety include, but are not limited to, natural and synthetic modifications of A, C, G, and T/U, as well as different purine or pyrimidine bases such as, for example, pseudouridine, uracil-5-yl, hypoxanthin-9-yl (I), and 2-aminoadenin-9-yl. Modified bases include, but are not limited to, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (such as, for example, 5-bromo), 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

Nucleotide analogs can also include modifications of the sugar moiety. Modifications to the sugar moiety include, but are not limited to, natural modifications of the ribose and

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deoxy ribose as well as synthetic modifications. Sugar modifications include, but are not limited to, the following modifications at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl, and alkynyl may be substituted or unsubstituted C₁₋₁₀alkyl or C₂₋₁₀alkenyl, and C₂₋₁₀alkynyl. Exemplary 2' sugar modifications also 5 include, but are not limited to, -O[(CH₂)_nO]_mCH₃, -O(CH₂)_nOCH₃, -O(CH₂)_nNH₂, -O(CH₂)_nCH₃, -O(CH₂)_n-ONH₂, and -O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. Other 10 modifications at the 2' position include, but are not limited to, C₁₋₁₀alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for 15 improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. Similar modifications may also be made at other positions on the sugar, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and 20 the 5' position of 5' terminal nucleotide. Modified sugars can also include those that contain modifications at the bridging ring oxygen, such as CH₂ and S. Nucleotide sugar analogs can also have sugar mimetics, such as cyclobutyl moieties in place of the pentofuranosyl sugar.

Nucleotide analogs can also be modified at the phosphate moiety. Modified phosphate 25 moieties include, but are not limited to, those that can be modified so that the linkage between two nucleotides contains a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl and other alkyl phosphonates including 3'-alkylene phosphonate and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. These phosphate or modified phosphate linkage between two nucleotides can be through a 3'-5' linkage or a 2'-5' linkage, and the linkage can contain inverted polarity such as 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts, and free acid forms are also included. Nucleotide substitutes also include peptide nucleic acids (PNAs).

The present disclosure also provides vectors comprising any one or more of the nucleic 30 acid molecules disclosed herein. In some embodiments, the vectors comprise any one or more of the nucleic acid molecules disclosed herein and a heterologous nucleic acid. The vectors can be viral or nonviral vectors capable of transporting a nucleic acid molecule. In some

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embodiments, the vector is a plasmid or cosmid (such as, for example, a circular double-stranded DNA into which additional DNA segments can be ligated). In some embodiments, the vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome.

Expression vectors include, but are not limited to, plasmids, cosmids, retroviruses,

5 adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus and tobacco mosaic virus, yeast artificial chromosomes (YACs), Epstein-Barr (EBV)-derived episomes, and other expression vectors known in the art.

Desired regulatory sequences for mammalian host cell expression can include, for example, viral elements that direct high levels of polypeptide expression in mammalian cells,

10 such as promoters and/or enhancers derived from retroviral LTRs, cytomegalovirus (CMV) (such as, for example, CMV promoter/enhancer), Simian Virus 40 (SV40) (such as, for example, SV40 promoter/enhancer), adenovirus, (such as, for example, the adenovirus major late promoter (AdMLP)), polyoma and strong mammalian promoters such as native immunoglobulin and actin promoters. Methods of expressing polypeptides in bacterial cells or fungal cells (such as, for 15 example, yeast cells) are also well known. A promoter can be, for example, a constitutively active promoter, a conditional promoter, an inducible promoter, a temporally restricted promoter (such as, for example, a developmentally regulated promoter), or a spatially restricted promoter (such as, for example, a cell-specific or tissue-specific promoter).

Percent identity (or percent complementarity) between particular stretches of

20 nucleotide sequences within nucleic acid molecules or amino acid sequences within polypeptides can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs (Altschul *et al.*, J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 7, 649-656) or by using the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 25 Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482-489). Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

The present disclosure also provides compositions comprising any one or more of the isolated nucleic acid molecules, genomic nucleic acid molecules, mRNA molecules, and/or cDNA

30 molecules disclosed herein. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the compositions comprise a carrier and/or excipient.

Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres,

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poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules. A carrier may comprise a buffered salt solution such as PBS, HBSS, etc.

The amino acid sequence of an ANGPTL7 reference polypeptide is set forth in SEQ ID NO:10. Referring to SEQ ID NO:10, the ANGPTL7 reference polypeptide is 346 amino acids in length. Referring to SEQ ID NO:10, position 175 is a glutamine. Referring to SEQ ID NO:10, position 177 is an arginine. Referring to SEQ ID NO:10, position 161 is a phenylalanine.

Referring to SEQ ID NO:10, position 188 is a tryptophan. Referring to SEQ ID NO:10, position 192 is a lysine.

An ANGPTL7 variant polypeptide exists (p.Arg177Stop or Arg177Stop), the amino acid sequence of which is set forth in SEQ ID NO:11. Referring to SEQ ID NO:11, the ANGPTL7 variant polypeptide is 176 amino acids in length. Referring to SEQ ID NO:11, position 177 does not exist due to a truncation at position 176.

Another ANGPTL7 variant polypeptide exists (Gln175His or Q175H), the amino acid sequence of which is set forth in SEQ ID NO:12. Referring to SEQ ID NO:12, the ANGPTL7 variant polypeptide is 346 amino acids in length. Referring to SEQ ID NO:12, position 175 is a histidine.

Another ANGPTL7 variant polypeptide exists (Phe161Ile or F161I), the amino acid sequence of which is set forth in SEQ ID NO:141. Referring to SEQ ID NO:141, the ANGPTL7 variant polypeptide is 346 amino acids in length. Referring to SEQ ID NO:141, position 161 is an isoleucine.

Another ANGPTL7 variant polypeptide exists (p.Trp188Stop or Trp188Stop), the amino acid sequence of which is set forth in SEQ ID NO:142. Referring to SEQ ID NO:142, the ANGPTL7 variant polypeptide is 187 amino acids in length. Referring to SEQ ID NO:142, position 187 is an aspartic acid. This variant is a result of a replacement of a guanine with an adenine at position 563 of the reference mRNA molecule or cDNA molecule (see, SEQ ID NO:4 and SEQ ID NO:7, respectively, for reference mRNA and cDNA sequences).

Another ANGPTL7 variant polypeptide exists (Lys192Gln or K192Q), the amino acid sequence of which is set forth in SEQ ID NO:143. Referring to SEQ ID NO:143, the ANGPTL7 variant polypeptide is 346 amino acids in length. Referring to SEQ ID NO:143, position 192 is a glutamine.

The present disclosure provides isolated human ANGPTL7 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about

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93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 90% identical to SEQ

5 ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 94% identical to SEQ

10 ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 98% identical to SEQ

15 ID NO:11, and terminating at a position corresponding to position 176 according to SEQ ID NO:11.

In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide comprises SEQ ID NO:11. In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide consists of SEQ ID NO:11.

20 The present disclosure also provides isolated human ANGPTL7 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:12, and comprising a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 90% identical to SEQ ID NO:12, and comprising a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:12, and comprising a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In

25 some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:12, and comprising a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated

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human ANGPTL7 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:12, and comprising a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:12, and comprising a histidine 5 at a position corresponding to position 175 according to SEQ ID NO:12.

In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide comprises SEQ ID NO:12. In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide consists of SEQ ID NO:12.

The present disclosure also provides isolated human ANGPTL7 polypeptides having an 10 amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:141, and comprising an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 90% 15 identical to SEQ ID NO:141, and comprising an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:141, and comprising an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:141, and comprising an isoleucine at a 20 position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:141, and comprising an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:141, and comprising an isoleucine at a position corresponding to position 161 according to SEQ ID 25 NO:141.

In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide comprises SEQ ID NO:141. In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide consists of SEQ ID NO:141.

The present disclosure also provides isolated human ANGPTL7 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about

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93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 90% identical to SEQ

5 ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 94% identical to SEQ
10 ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 98% identical to SEQ
15 ID NO:142, and terminating at a position corresponding to position 187 according to SEQ ID NO:142.

In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide comprises SEQ ID NO:142. In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide consists of SEQ ID NO:142.

20 The present disclosure also provides isolated human ANGPTL7 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:143, and comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the
25 isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 90% identical to SEQ ID NO:143, and comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:143, and comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143.
30 In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:143, and comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the

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isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:143, and comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. In some embodiments, the isolated human ANGPTL7 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:143, and 5 comprising a glutamine at a position corresponding to position 192 according to SEQ ID NO:143.

In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide comprises SEQ ID NO:143. In some embodiments, the amino acid sequence of the isolated human ANGPTL7 polypeptide consists of SEQ ID NO:143.

In some embodiments, the isolated polypeptides comprise or consist of at least about 10 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, or at least about 600 contiguous amino acids of any one or more of SEQ ID NO:11, 15 SEQ ID NO:12, SEQ ID NO:141, SEQ ID NO:142, and/or SEQ ID NO:143. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated polypeptides comprise a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated polypeptides comprise an isoleucine at a position corresponding to position 161 20 according to SEQ ID NO:141. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated polypeptides comprise a glutamine at a position corresponding to position 192 according to SEQ ID NO:143.

In some embodiments, the isolated polypeptides comprise or consist of an amino acid 25 sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to at least about 8, at least about 10, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at 30 least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, or at

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least about 600 contiguous amino acids of any one or more of SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:141, SEQ ID NO:142, and/or SEQ ID NO:143. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 176 according to SEQ ID NO:11.

In some embodiments, the isolated polypeptides comprise a histidine at a position

5 corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated polypeptides comprise an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated polypeptides comprise a glutamine at a position corresponding to position 192 according to

10 SEQ ID NO:143.

In some embodiments, the isolated polypeptides comprise or consist of an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to at least about 8, at least about 10, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, or at least about 600 contiguous amino acids of any one or more of SEQ ID NO:11, SEQ ID

20 NO:12, SEQ ID NO:141, SEQ ID NO:142, and/or SEQ ID NO:143. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 176 according to SEQ ID NO:11. In some embodiments, the isolated polypeptides comprise a histidine at a position corresponding to position 175 according to SEQ ID NO:12. In some embodiments, the isolated polypeptides comprise an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. In some embodiments, the isolated polypeptides terminate at a position corresponding to position 187 according to SEQ ID NO:142. In some embodiments, the isolated polypeptides comprise a glutamine at a position corresponding to position 192 according to SEQ ID NO:143.

The isolated polypeptides disclosed herein can comprise an amino acid sequence of a naturally occurring ANGPTL7 polypeptide, or can comprise a non-naturally occurring sequence. In some embodiments, the naturally occurring sequence can differ from the non-naturally

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occurring sequence due to conservative amino acid substitutions. For example, the sequence can be identical with the exception of conservative amino acid substitutions.

In some embodiments, the isolated polypeptides comprise non-natural or modified amino acids or peptide analogs. For example, there are numerous D-amino acids or amino acids 5 which have a different functional substituent than the naturally occurring amino acids.

The present disclosure also provides nucleic acid molecules encoding any of the polypeptides disclosed herein. This includes all degenerate sequences related to a specific polypeptide sequence (i.e., all nucleic acids having a sequence that encodes one particular polypeptide sequence as well as all nucleic acids, including degenerate nucleic acids, encoding 10 the disclosed variants and derivatives of the protein sequences). Thus, while each particular nucleic acid sequence may not be written out herein, each and every sequence is in fact disclosed and described herein through the disclosed polypeptide sequences.

The present disclosure also provides compositions comprising any one or more of the nucleic acid molecules and/or any one or more of the polypeptides disclosed herein. In some 15 embodiments, the compositions comprise a carrier. Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules.

The present disclosure also provides methods of producing any of the ANGPTL 20 polypeptides or fragments thereof disclosed herein. Such ANGPTL7 polypeptides or fragments thereof can be produced by any suitable method.

The present disclosure also provides cells comprising any one or more of the nucleic acid molecules and/or any one or more of the polypeptides disclosed herein. The cells can be *in vitro*, *ex vivo*, or *in vivo*. Nucleic acid molecules can be linked to a promoter and other regulatory sequences so they are expressed to produce an encoded protein.

25 In some embodiments, the cell is a totipotent cell or a pluripotent cell such as, for example, an embryonic stem (ES) cell such as a rodent ES cell, a mouse ES cell, or a rat ES cell. In some embodiments, the cell is a primary somatic cell, or a cell that is not a primary somatic cell. The cell can be from any source. For example, the cell can be a eukaryotic cell, an animal cell, a plant cell, or a fungal (such as, for example, yeast) cell. Such cells can be fish cells or bird cells, 30 or such cells can be mammalian cells, such as human cells, non-human mammalian cells, rodent cells, mouse cells or rat cells. Mammals include, but are not limited to, humans, non-human primates, monkeys, apes, cats dogs, horses, bulls, deer, bison, sheep, rodents (such as, for

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example, mice, rats, hamsters, guinea pigs), livestock (such as, for example, bovine species such as cows, steer, etc.; ovine species such as sheep, goats, etc.; and porcine species such as pigs and boars). The term “non-human animal” excludes humans.

The nucleotide and amino acid sequences listed in the accompanying sequence listing 5 are shown using standard letter abbreviations for nucleotide bases, and three-letter code for amino acids. The nucleotide sequences follow the standard convention of beginning at the 5' end of the sequence and proceeding forward (i.e., from left to right in each line) to the 3' end. Only one strand of each nucleotide sequence is shown, but the complementary strand is understood to be included by any reference to the displayed strand. The amino acid sequence 10 follows the standard convention of beginning at the amino terminus of the sequence and proceeding forward (i.e., from left to right in each line) to the carboxy terminus.

As used herein, the phrase “corresponding to” or grammatical variations thereof when used in the context of the numbering of a particular nucleotide or nucleotide sequence or position refers to the numbering of a specified reference sequence when the particular 15 nucleotide or nucleotide sequence is compared to a reference sequence (such as, for example, SEQ ID NO:1, SEQ ID NO:4, or SEQ ID NO:7). In other words, the residue (such as, for example, nucleotide or amino acid) number or residue (such as, for example, nucleotide or amino acid) position of a particular polymer is designated with respect to the reference sequence rather than by the actual numerical position of the residue within the particular nucleotide or 20 nucleotide sequence. For example, a particular nucleotide sequence can be aligned to a reference sequence by introducing gaps to optimize residue matches between the two sequences. In these cases, although the gaps are present, the numbering of the residue in the particular nucleotide or nucleotide sequence is made with respect to the reference sequence to which it has been aligned.

25 For example, a nucleic acid molecule comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2 means that if the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule is aligned to the sequence of SEQ ID NO:2, the ANGPTL7 sequence has a thymine residue at the position that corresponds to 30 position 4,291 of SEQ ID NO:2. The same applies for mRNA molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, and

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cDNA molecules comprising a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8. In other words, these phrases refer to a nucleic acid molecule encoding an ANGPTL7 polypeptide, wherein the genomic nucleic acid molecule has a nucleotide sequence that comprises a thymine residue that is homologous to the thymine residue at position 4,291 of SEQ ID NO:2 (or wherein the mRNA molecule has a nucleotide sequence that comprises a uracil residue that is homologous to the uracil residue at position 529 of SEQ ID NO:5, or wherein the cDNA molecule has a nucleotide sequence that comprises a thymine residue that is homologous to the thymine residue at position 529 of SEQ ID NO:8). Herein, such a sequence is also referred to as “ANGPTL7 sequence with the C4,291T alteration” or “ANGPTL7 sequence with the C4,291T variation” referring to genomic nucleic acid molecules (or “ANGPTL7 sequence with the C529U alteration” or “ANGPTL7 sequence with the C529U variation” referring to mRNA molecules, and “ANGPTL7 sequence with the C529T alteration” or “ANGPTL7 sequence with the C529T variation” referring to cDNA molecules).

As described herein, a position within an ANGPTL7 genomic nucleic acid molecule that corresponds to position 4,291 according to SEQ ID NO:2 can be identified by performing a sequence alignment between the nucleotide sequence of a particular ANGPTL7 nucleic acid molecule and the nucleotide sequence of SEQ ID NO:2. A variety of computational algorithms exist that can be used for performing a sequence alignment to identify a nucleotide position that corresponds to, for example, position 4,291 in SEQ ID NO:2. For example, by using the NCBI BLAST algorithm (Altschul et al., Nucleic Acids Res., 1997, 25, 3389-3402) or CLUSTALW software (Sievers and Higgins, Methods Mol. Biol., 2014, 1079, 105-116) sequence alignments may be performed. However, sequences can also be aligned manually.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the

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nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; or an ANGPTL7 polypeptide that terminates at a position corresponding to position 176 according to SEQ ID NO:11. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or

5 inhibit an ophthalmic condition described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 according to SEQ 10 ID NO:2, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 15 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; or an ANGPTL7 polypeptide that terminates at a position corresponding to position 176 according to SEQ ID NO:11. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

20 The present disclosure also provides ANGPTL7 inhibitors for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; an mRNA molecule having a nucleotide 25 sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; or an 30 ANGPTL7 polypeptide that terminates at a position corresponding to position 176 according to SEQ ID NO:11. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

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The present disclosure also provides ANGPTL7 inhibitors for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; or an ANGPTL7 polypeptide that terminates at a position corresponding to position 176 according to SEQ ID NO:11. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; or an ANGPTL7 polypeptide that comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 according to SEQ

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ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; or an ANGPTL7 polypeptide that comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

10 The present disclosure also provides ANGPTL7 inhibitors for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; or an 15 ANGPTL7 polypeptide that comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

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The present disclosure also provides ANGPTL7 inhibitors for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human 25 subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; a cDNA molecule having a nucleotide 30 sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or

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the complement thereof; or an ANGPTL7 polypeptide that comprises a histidine at a position corresponding to position 175 according to SEQ ID NO:12. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; or an ANGPTL7 polypeptide that comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; or an ANGPTL7 polypeptide that comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

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The present disclosure also provides ANGPTL7 inhibitors for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243
5 according to SEQ ID NO:132, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a
10 position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; or an ANGPTL7 polypeptide that comprises an isoleucine at a position corresponding to position 161 according to SEQ ID NO:141. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides ANGPTL7 inhibitors for use in the preparation of a
15 medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide,
20 wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; or an ANGPTL7 polypeptide that comprises an isoleucine
25 at a position corresponding to position 161 according to SEQ ID NO:141. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence
30 encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human

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ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563

5 according to SEQ ID NO:139, or the complement thereof; or an ANGPTL7 polypeptide that terminates at a position corresponding to position 187 according to SEQ ID NO:142. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an mRNA molecule having a nucleotide sequence 10 encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; or an 15 ANGPTL7 polypeptide that terminates at a position corresponding to position 187 according to SEQ ID NO:142. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition described herein.

The present disclosure also provides ANGPTL7 inhibitors for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement 20

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thereof; or an ANGPTL7 polypeptide that terminates at a position corresponding to position 187 according to SEQ ID NO:142. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides ANGPTL7 inhibitors for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, 5 wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; or an ANGPTL7 polypeptide that terminates at a position 10 corresponding to position 187 according to SEQ ID NO:142. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

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The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the treatment of an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence 20 encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according 25 to SEQ ID NO:140, or the complement thereof; or an ANGPTL7 polypeptide that comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic 30 agents that treat or inhibit an ophthalmic condition described herein.

The present disclosure also provides therapeutic agents that treat or inhibit an ophthalmic condition for use in the preparation of a medicament for treating an ophthalmic

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condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; an mRNA molecule having a nucleotide sequence 5 encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; or an 10 ANGPTL7 polypeptide that comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. The therapeutic agents that treat or inhibit an ophthalmic condition can be any of the therapeutic agents that treat or inhibit an ophthalmic condition 15 described herein.

The present disclosure also provides ANGPTL7 inhibitors for use in the treatment of an 20 ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; an mRNA molecule having a 25 nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; or an ANGPTL7 polypeptide that comprises a glutamine at a position corresponding to 30 position 192 according to SEQ ID NO:143. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

The present disclosure also provides ANGPTL7 inhibitors for use in the preparation of a medicament for treating an ophthalmic condition in a human subject, wherein the human subject has: a genomic nucleic acid molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; an 35 mRNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide,

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wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human ANGPTL7 polypeptide, wherein the nucleotide sequence comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; or an ANGPTL7 polypeptide that comprises a glutamine at a position corresponding to position 192 according to SEQ ID NO:143. The ANGPTL7 inhibitors can be any of the ANGPTL7 inhibitors described herein.

All patent documents, websites, other publications, accession numbers and the like cited above or below are incorporated by reference in their entirety for all purposes to the same extent as if each individual item were specifically and individually indicated to be so incorporated by reference. If different versions of a sequence are associated with an accession number at different times, the version associated with the accession number at the effective filing date of this application is meant. The effective filing date means the earlier of the actual filing date or filing date of a priority application referring to the accession number if applicable.

Likewise, if different versions of a publication, website or the like are published at different times, the version most recently published at the effective filing date of the application is meant unless otherwise indicated. Any feature, step, element, embodiment, or aspect of the present disclosure can be used in combination with any other feature, step, element, embodiment, or aspect unless specifically indicated otherwise. Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

The following examples are provided to describe the embodiments in greater detail. They are intended to illustrate, not to limit, the claimed embodiments. The following examples provide those of ordinary skill in the art with a disclosure and description of how the compounds, compositions, articles, devices and/or methods described herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the scope of any claims. Efforts have been made to ensure accuracy with respect to numbers (such as, for example, amounts, temperature, etc.), but some errors and deviations may be accounted for.

Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

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Examples

Example 1: Exome Sequencing Analysis

Exome sequencing and analysis at the Regeneron Genetics Center in conjunction with the UK Biobank (UKB) 50K exome dataset identified that the putative loss-of-function variant, p.Arg177Stop, significantly associates with decreased IOP (Table 10). Table 11 shows the association of the M1 mask, which is an aggregate of all pLOFs ($\leq 1\%$ alt. allele frequency) within ANGPTL7, with IOP. This result supports the single variant pLOF association shown in Table 10 as 27/29 carriers have the p.Arg177Stop variant shown in Table 10.

Table 10

Phenotype	Dataset	Effect (CI) sd	Pvalue	AAF	N RR/RA/AA
IOPcc	50k Exome	-0.40 (-0.78, -0.03)	3.490E-02	0.04%	33,616 33,589/27/0
IOPg	50k Exome	-0.56 (-0.93, -0.19)	3.22E-03	0.04%	33,618 33,591/27/0

10

Table 11

Name	Dataset	Phenotype	Effect (CI) sd	Pvalue	AAF	N RR/RA/AA
M1.1	50k Exome	IOPcc	-0.38 (-0.74, -0.01)	4.2E-02	0.04%	33,616 33,587/29/0
	50k Exome	IOPg	-0.49 (-0.85, -0.13)	7.5E-03	0.04%	33,618 33,589/29/0

Additional exome sequencing and analysis at the Regeneron Genetics Center in conjunction with the Geisinger Health System 60k (GHS60k), GHS30k and/or UKB were carried out, the results of which are shown in Tables 12-17.

15

Association of a missense (p.Gln175His) variant in ANGPTL7 with glaucoma in the imputed dataset in GHS60k, GHS30k and UKB, and the meta-analysis of the three cohorts is shown in Table 12. The direction of effect (decreased IOP) of p.Gln175His is the same as the direction of effect of the pLOF p.Arg177Stop variant shown in Tables 10 and 11 suggesting that the Gln175His change acts to reduce the function of ANGPTL7.

20

Table 12

Phenotype	Dataset	OR (95% CI)	Pval	AAF
Glaucoma	META	0.734 (0.632,0.853)	5.59E-05	0.0069
Glaucoma	UKB_Imputed_EUR	0.688 (0.574,0.825)	5.35E-05	0.0076

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Glaucoma	GHS_GSA_Imputed_EUR	0.612 (0.288,1.302)	2.02E-01	0.0021
Glaucoma	GHS_Omni_Imputed_EUR	0.959 (0.681,1.349)	8.09E-01	0.0028

Table 12 (cont.)

Phenotype	Dataset	Direction	Ncase RR RA AA	Nctrl RR RA AA
Glaucoma	META	---	14,493 14,373 120 0	528,025 520,720 7,274 31
Glaucoma	UKB_Imputed_EUR	-	8,624 8,537 87 0	452,880 445,957 6,892 31
Glaucoma	GHS_GSA_Imputed_EUR	-	975 971 4 0	26,065 25,955 110 0
Glaucoma	GHS_Omni_Imputed_EUR	-	4,894 4,865 29 0	49,080 48,808 272 0

Association of the missense (p.Gln175His) variant with IOPg in the imputed dataset in

5 GHS60k, GHS30k and UKB, and the meta-analysis of the three cohorts is shown in Table 13.

Table 13

Phenotype	Dataset	Effect (95% CI)	Pval
IOPg	META	-0.221 (-0.269,-0.173)	1.16E-19
IOPg	UKB_Imputed_EUR	-0.234 (-0.284,-0.184)	6.40E-20
IOPg	GHS_GSA_Imputed_EUR	-0.249 (-0.6,0.102)	0.16
IOPg	GHS_Omni_Imputed_EUR	-0.061 (-0.233,0.111)	0.48

Table 13 (cont.)

Phenotype	Dataset	AAF	Direction	N RR RA AA
IOPg	META	0.0069	---	111,548 110019 1523 6
IOPg	UKB_Imputed_EUR	0.0077	-	92,484 91,073 1,405 6
IOPg	GHS_GSA_Imputed_EUR	0.0025	-	4,135 4,114 21 0
IOPg	GHS_Omni_Imputed_EUR	0.0032	-	14,929 14,832 97 0

10 Association of the missense (p.Gln175His) variant with IOPg in the exome dataset in

GHS60k, GHS30k and UKB, and the meta-analysis of the three cohorts is shown in Table 14.

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Table 14

Phenotype	Dataset	Effect (95% CI)	Pval
IOPg	META	-0.143 (-0.213,-0.073)	6.77E-05
IOPg	UKB_50K_Exome_EUR	-0.156 (-0.24,-0.072)	2.70E-04
IOPg	GHS_IDT_Exome_EUR	-0.24 (-0.53,0.051)	1.10E-01
IOPg	GHS_VCRome_Exome_EUR	-0.081 (-0.224,0.062)	2.70E-01

Table 14 (cont.)

Phenotype	Dataset	AAF	Direction	N RR RA AA
IOPg	META	0.0073	---	52,925 52,159 762 4
IOPg	UKB_50K_Exome_EUR	0.0079	-	33,618 33,088 526 4
IOPg	GHS_IDT_Exome_EUR	0.0055	-	4,187 4,141 46 0
IOPg	GHS_VCRome_Exome_EUR	0.0063	-	15,120 14,930 190 0

Association of the missense (p.Gln175His) variant with glaucoma in the exome dataset

in GHS60k, GHS30k and UKB, and the meta-analysis of the three cohorts is shown in Table 15.

Table 15

Phenotype	Dataset	OR (95% CI)	pval	AAF
Glaucoma	META	0.822 (0.655,1.032)	9.16E-02	0.0063
Glaucoma	UKB_50K_Exome_EUR	0.726 (0.436,1.209)	2.19E-01	0.0077
Glaucoma	GHS_IDT_Exome_EUR	0.745 (0.388,1.431)	3.77E-01	0.0050
Glaucoma	GHS_VCRome_Exome_EUR	0.875 (0.651,1.176)	3.76E-01	0.0057

Table 15 (cont.)

Phenotype	Dataset	Direction	Ncase RR RA AA	Nctrl RR RA AA
Glaucoma	META	---	6,967 6,899 67 1	121,924 120,377 1,539 8
Glaucoma	UKB_50K_Exome_EUR	-	1,021 1,010 11 0	45,766 45,060 702 4
Glaucoma	GHS_IDT_Exome_EUR	-	984 977 7 0	26,402 26,137 262 3
Glaucoma	GHS_VCRome_Exome_EUR	-	4,962 4,912 49 1	49,756 49,180 575 1

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Association of the M1.1 (pLOF variants \leq 1% AAF) mask in ANGPTL7 with IOPg in burden test is shown in Table 16.

Table 16

Phenotype	Dataset	Effect (95% CI)	Pval	AAF
IOPg	META	-0.512 (-0.827,-0.197)	1.46E-03	0.00039
IOPg	UKB_50K_Exome_EUR	-0.49 (-0.85,-0.131)	7.50E-03	0.00043
IOPg	GHS_IDT_Exome_EUR	NA	NA	NA
IOPg	GHS_VCRome_Exome_EUR	-0.582 (-1.236,0.072)	8.10E-02	0.00030

5

Table 16 (cont.)

Phenotype	Dataset	Direction	N RR RA AA
IOPg	META	-?-	48,738 48,700 38 0
IOPg	UKB_50K_Exome_EUR	-	33,618 33,589 29 0
IOPg	GHS_IDT_Exome_EUR	NA	NA
IOPg	GHS_VCRome_Exome_EUR	-	15,120 15,111 9 0

Association of the missense (p.Gln175His) variant with IOPcc in the exome and genotyped/imputed datasets in UKB is shown in Table H.

10

Table 17

Phenotype	Dataset	Effect (95% CI)	Pval
IOPcc	UKB_50K_Exome_EUR	-0.13 (-0.214, -0.045)	2.6E-02
IOPcc	UKB_Imputed_EUR	-0.179 (-0.23, -0.128)	5.4E-12

Table 17 (cont.)

Phenotype	Dataset	AAF	N RR RA AA
IOPcc	UKB_50K_Exome_EUR	0.0079	33,616 33,087 525 4
IOPcc	UKB_Imputed_EUR	0.0077	92,629 91,217 1,406 6

15

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Example 2: Genetic and Functional Studies Identify ANGPTL7 as a Therapeutic Target for Glaucoma

Study design and participants

Association tests using data from 5 cohorts were carried out. The cohorts included: 1)

5 The UK Biobank (UKB) is a large prospective study where > 500,000 individuals aged 40 to 69 years were recruited over 4 years, and extensive data on lifestyle, environment, medical history, physical measures and DNA samples, were collected. For genome-wide association conducted on the whole UKB cohort, 92,672 European and 4,179 African ancestry participants with IOP measurements were included in the IOP analyses. In glaucoma association analyses, 10 8,639 cases and 453,746 controls of European, and 371 cases and 9,361 controls of African ancestry were included. For exome-wide association conducted on about 150,000 UKB participants that have been sequenced, 47,096 European and 1,743 African ancestry individuals were included in the IOP analyses. 2) The DiscovEHR study population (GHS), consisting of a total of about 145,000 sequenced individuals from the MyCode Community Health Initiative of 15 Geisinger, from which 29,395 individuals with IOP measurements and were not diagnosed with glaucoma, 8,154 glaucoma cases and 116,557 controls were included. 3) The Malmö diet and cancer study (MDCS), based in Sweden, includes about 29,000 participants recruited to study the effects of diet on cancer. 1,708 cases of glaucoma and 26,222 controls from MDCS were included. 4) Mount Sinai's BioMe Personalized Medicine Cohort (MSSM) is an electronic health 20 record (EHR)-linked clinical care cohort consisting of about 31,000 participants of diverse ancestries characterized by a broad spectrum of biomedical traits. 424 cases and 8,774 controls of European, and 1,349 cases and 11,258 controls of African ancestry were used for glaucoma analyses. 5) The Primary Open Angle African American Glaucoma Genetics (POAAGG) study is a 25 5-year, population-based project consisting of self-identified individuals of African descent 35 years of age or older recruited from the Scheie Eye Institute at the University of Pennsylvania and its research affiliates in Philadelphia. For IOP association analyses in POAAGG, 3,097 individuals with IOP measurements who also did not have a POAG diagnosis were included, and 2,474 POAG cases and 4,092 controls were included in the glaucoma association analyses.

Phenotype definitions

30 IOP in UKB was measured in each eye using the Ocular Response Analyzer (ORA, Reichert Corp., Buffalo, New York). Participants were excluded from this test if they reported having eye surgery in the preceding 4 weeks or having an eye infection. The ORA calculates two

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forms of IOP, a Goldmann-correlated IOP (IOPg) and a corneal compensated IOP (IOPcc). IOPg most closely approximates the IOP measured by the Goldmann applanation tonometer, which has been the gold standard for measuring IOP, while IOPcc provides a measure of IOP that is adjusted to remove the influence of corneal biomechanics. For this study, IOPg was focused on,
5 as this measurement was the most comparable to IOP measurements in other cohorts, and herein IOPg will be referred to as IOP. For association analyses of IOP, the following individuals were excluded: 1) with a glaucoma diagnosis (N=1,932), 2) with IOP measures that were more than 5 standard deviations away from the mean, and 3) with more than a 10-mmHg difference between both eyes. A mean IOP measure between both eyes was developed for each
10 individual. IOP of only one eye was used in instances where IOP measures for both eyes were not available. As for UKB, the mean IOP between left and right eyes for GHS (the most recent IOP measure in the EHR was used) and POAAGG were analyzed, applying the same exclusions and criteria outlined above.

Glaucoma ICD-based definitions of cases in UKB required one primary diagnosis or ≥2
15 secondary diagnoses of ICD10-H40 in the in-patient Health Episode Statistics (HES) records. ICD-based glaucoma case definition in GHS, MDCS and MSSM required an in-patient diagnosis or ≥2 outpatient diagnoses of ICD10-H40 in the EHR. ICD-based excludes had ≥1 primary or ≥2 secondary diagnoses in the code range (H40-H42). ICD-based controls for glaucoma were defined as individuals who were not cases or excluded.

20 For UKB, ICD-based and self-reported glaucoma were combined in the case definition where individuals were considered cases if they: identified 'glaucoma' from the eye problems or disorders list in the touchscreen questionnaire or, stated they had glaucoma in the verbal interview or, were a case for ICD10 H40 glaucoma. Normal controls for glaucoma in UKB were defined as individuals who did not report having glaucoma in the touchscreen or the verbal
25 interview, and were defined as controls for ICD-based glaucoma as described above (Van Hout, 2019, BioRxiv. <https://doi.org/10.1101/572347>).

A detailed description of criteria used to define glaucoma cases in POAAGG is provided
elsewhere (Charlson, Ophthalmology, 2015, 122, 711-20). In brief, POAG cases were defined as
30 having an open iridocorneal angle and characteristic glaucomatous optic nerve findings in one or both eyes, characteristic visual field defects and all secondary causes of glaucoma excluded. Controls in POAAGG defined as subjects older than 35, without high myopia (greater than -8.00 diopters) or presbyopia (+8.00 diopters), a family history of POAG, abnormal visual field, IOP

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greater than 21 mmHg, neuroretinal rim thinning, excavation, notching or nerve fiber layer defects, optic nerves asymmetry or a cup to disc ratio between eyes greater than 0.2. Additional controls for POAAGG were identified from the Penn Medicine Biobank as individuals without ICD9 diagnoses for glaucoma.

5 *Sample preparation, sequencing and genotyping*

Sample preparation and whole-exome sequencing for UKB, GHS, MDCS, MSSM, and POAAGG were performed as described (Dewey, Science, 2016, 354, 6319; and Van Hout, 2019, BioRxiv. <https://doi.org/10.1101/572347>). Details on DNA extraction and genotyping for UK Biobank participants are described in Bycroft (Bycroft, Nature, 2019, 562, 203-209).

10 *Statistical analysis*

Statistical analysis included burden test description, rare variant analysis, and meta-analysis methods.

Human trabecular meshwork (TM) cell culture and dexamethasone treatment

Human TM cells were obtained from the Stamer laboratory at Duke University, NC, and characterized using previously developed methodology. Human TM cells were cultured and maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen-Gibco Life Technologies, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Atlas Biologicals, Fort Collins, CO, USA), penicillin (100 units/mL), streptomycin (0.1 mg/ mL), and L-glutamine (0.292 mg/mL) (Thermo Fisher Scientific, Rockford, IL, USA). Human TM cells were cultured on six-well plates until confluent and then treated with vehicle control (0.1% ethanol) or dexamethasone (DEX, 100 nM) for another 72 hours.

IOP Measurements

Isoflurane anesthetized IOPs were measured as previously described. For IOP measurements, mice were anesthetized before IOP was measured in both eyes using a TonoLab rebound tonometer (Colonial Medical Supply, Franconia, NH). IOP measurements for both eyes were completed in 3-5 minutes. IOP in each eye was measured before start of Angptl7 injections and every day afterwards for six days.

Intravitreal Injection of ANGPTL7 protein

A 33-gauge needle with a glass microsyringe (5- μ L volume; Hamilton Company) was used. The eye was proptosed, and the needle was inserted through the equatorial sclera and inserted into the vitreous chamber at an angle of approximately 45 degrees, taking care to avoid touching the posterior part of the lens or the retina. ANGPTL7 protein (catalog# 4960-AN-

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025; R&D Systems, Minneapolis, MN) or PBS (1 μ L) was injected into the vitreous over the course of 1 minute. The needle was then left in place for a further 45 seconds (to facilitate mixing), before being rapidly withdrawn. Only one injection was administered at day 0.

Intracameral Injection of ANGPTL7 protein

5 A 33-gauge needle with a glass microsyringe (5- μ L volume) (Hamilton Company) was used. Before and during injection, mice were anesthetized with isoflurane (2.5%) containing oxygen (0.8 L/min). For topical anesthesia, both eyes received one to two drops of 0.5% proparacaine HCl (Akorn, Inc.). Each eye was proptosed and the needle was inserted through the cornea just above the limbal region and into the anterior chamber at an angle parallel to
10 the cornea, taking care to avoid touching the iris, anterior lens capsule epithelium, or corneal endothelium. Up to 1 μ L of ANGPTL7 protein (catalog# 4960-AN-025; R&D Systems, Minneapolis, MN) or PBS was injected slowly (over a 30-second period). The needle was then withdrawn. The procedure was performed on both eyes of each animal. Only one injection was administered at day 0.

15 *In situ hybridization using RNAScope*

The expression pattern of TM single cell cluster specific gene expression in the human donor eye was determined by *in situ* hybridization using RNAScope[®] according to manufacturer's specifications (Advanced Cell Diagnostics). Briefly, 10% NBF fixed and paraffin embedded human donor eye cups were cut into 5 to 10 μ m sections and mounted on
20 SUPERFROST[®] Plus glass slides. For RNAScope, slides were baked on slide warmer for 1 hour at 60°C and deparaffinized for 20 minutes. Tissue sections then underwent 10 minutes of Pretreat 1- RNAScope hydrogen peroxide treatment at room temperature, followed by 20 minutes of boiling at 90°C in Pretreat 2-target retrieval treatment in Oster Steamer (IHC World, LLC, Model 5709) and 30 minutes of Pretreat 3- RNAScope protease plus treatment at 40°C in a HybEZ
25 Oven. Tissue sections were then incubated with DNase I for 10 minutes at 40°C to reduce potential background from probes binding to genomic DNA. Tissue sections were then washed five times with water, hybridized with RNAScope probes for 2 hours at 40°C and the remainder of the manufacturer's assay protocol was implemented from Amplified 1 to Amplified 6. The slides were washed twice (two minutes each at room temperature) with RNAScope wash
30 buffer. Signal was detected by incubation with Red working solution (1:60 ratio of Red B to Red A) at room temperature for 10 minutes in the absence of light, followed by washing the slides

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in water several times and viewing under microscope. In some experiments, fluorescent signals were visualized and captured using an open-field Nikon Eclipse Ti-E microscope.

Cell Culture.

HEK293 cell line was cultured in DMEM media (4.5g/L D-Glucose, (+) L-Glutamine, 5 (-) Sodium Phosphate, (-) Sodium Pyruvate supplemented with 10% FBS and 1% Penicillin-Streptomycin-Glutamine (BRAND), at 37°C in a humidified atmosphere under 5% CO₂.

Transfection.

The day before transfection, HEK293 cells were seeded in OptiMEM supplemented with 10% FBS. After 24 hours, the cells were transfected with FuGENE 6, and 10ug of pcDNA 10 3.1(+) encoding the following proteins: ANGPTL7 wild type, Gln175His, and Arg177*. After 24 hours, the media was changed with 2% FBS OptiMEM. The following day, the cells were collected in RIPA buffer, supplemented with protease and phosphatase inhibitors (BRAND) or TRIzol reagent (Invitrogen) for protein and RNA analysis, respectively. The supernatants were transferred to an Eppendorf tube and immediately flash frozen for downstream protein 15 analysis.

RNA extraction and Taqman analysis.

Total RNA was extracted using TRIzol reagent (Invitrogen) and RNeasy kit (Qiagen) according to manufacturer's instructions and treated with RNase-free DNase I (Promega). cDNA was synthesized using Superscript VILO cDNA synthesis kit (Invitrogen). Taqman analysis 20 was performed using TaqMan Fast Advanced Master Mix (Applied Biosystems) in a QuantStudio 6 Flex (Applied Biosystems) and commercially available primers and probes for ANGPTL (Hs00221727 - Applied Biosystem) and GAPDH (Hs02786624_g1 - Applied Biosystem).

Western Blot.

Western blot analysis was performed using a rabbit polyclonal antibody against 25 ANGPTL7 at 1:1,000 dilution (10396-1-AP ProteinTech), using standard procedures.

ELISA assay.

ANGPTL7 was quantified by ELISA according to manufacturer's instructions (LS-F50425 Life Sciences). The cell lysates were diluted 1:1,000. The supernatants were diluted 1:10,000. The ELISA plate was read at 450nm via SpectraMax M4 plate reader (Molecular Devices).

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Results

Coding variants in ANGPTL7 are associated with IOP and glaucoma

The effect of rare coding variation on IOP was studied across two large cohorts, UK Biobank (UKB) and Geisinger DiscovEHR (GHS) (Figure 1), on 120,145 individuals of European descent after exclusion of cases with a glaucoma diagnosis. 1,368,641 protein-altering variants (including splice variants) with a minor allele frequency (MAF) <1% for association with IOP were examined. Two rare coding variants were significantly associated (p-value < 5E-08) with decreased IOP (Figure 1): a missense variant (p.Pro191Arg; MAF = about 1.0%) in son of sevenless 2 (SOS2) associated with reduced IOP ($\beta_{allelic} = -0.11$ standard deviations (SD); p-value = 3.39E-08), and a missense variant (p.Gln175His, MAF = about 0.7%) in Angiopoietin-like 7 (ANGPTL7) also associated with reduced IOP ($\beta_{allelic} = -0.21$ SD, p-value = 3.2E-19, Figure 2A).

A sub-threshold association of a rare, predicted loss-of-function (pLOF) variant (Arg177*, AAF = about 0.03%) in ANGPTL7 with reduced IOP ($\beta_{allelic} = -0.31$ SD, p-value=4.0E-03, Figure 2B) was also noted. Heterozygous and homozygous carriers of Gln175His in ANGPTL7 have a 5.1% (0.8 mmHg) and 26.5% (4.1 mmHg) reduction in median IOP, respectively (Figure 2C), and the Arg177* variant conferred a median IOP decrease of 9% (1.4 mmHg) in heterozygous carriers (Figure 2D). To understand the biological significance of the decrease in IOP, the effect of ANGPTL7 variants on glaucoma risk in UKB, GHS and two additional series collected at Mount Sinai School of Medicine (MSSM, n = 31,203) and a Malmö (MDCS, n = 29,483) were examined. Meta-analysis across these cohorts showed a significant reduction in glaucoma risk in Gln175His carriers (odds ratio (OR_{allelic})=0.74, p-value=1.9E-05, Figure 2E), and a subthreshold but consistent reduction in risk in carriers of the rarer Arg177* variant (OR_{allelic}=0.79, p-value=3.6E-01, Figure 2F). Taken together, the associations of missense and pLOF variants in ANGPTL7 with reduced IOP and reduced glaucoma risk support the hypothesis that loss or reduced function of ANGPTL7 results in lower IOP, and protection from glaucoma.

Gene burden tests were performed to assess whether ultra-rare variants in ANGPTL7 had, in aggregate, an effect on IOP. The association between IOP and a set of 30 pLOF and missense variants predicted deleterious by five algorithms, excluding Gln175His and Arg177* was examined. A burden test showed a sub-threshold association with reduced IOP ($\beta = -0.31$, p-value = 8.40E-03) suggesting that additional variants in ANGPTL7 could confer protection from glaucoma by lowering IOP. However, at the current sample sizes these

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associations do not reach statistical significance. Figure 3 shows the distribution of IOP in carriers of Gln175His, Arg177* and other ultra-rare variants with at least 4 carriers.

ANGPTL7 variants in individuals of African descent

The association between IOP (and glaucoma) and ANGPTL7 variants in individuals of African ancestry in UKB, MSSM, and the Primary Open Angle African American Glaucoma Genetics (POAAGG) study was also analyzed. A pLOF variant (Trp188*) in ANGPTL7 was identified, more prevalent in individuals of African ancestry (MAF=about 0.27%) compared to Europeans (MAF = about 0.0013%), which trends towards a decrease in IOP (betaallelic = -0.13, p-value = 5.3E-01; Figure 7A), and decrease in risk for glaucoma (ORallelic = 0.71, p-value = 9.9E-02; Figure 7B) in a meta-analysis across two cohorts. A meta-analysis including both Arg177* and Trp188* pLOF variants decreased the p-value for association with glaucoma from 1.9E-01 (Arg177* alone) and 9.8E-02 (Trp188* alone) to 6.9E-02 (Figure 7D). Similar results were obtained in regard to IOP (Figure 7C).

ANGPTL7 expression in ocular tissues across species

To identify expression of ANGPTL7 in ocular tissues across different species, transcriptome profiles from different parts of eye were generated. High ANGPTL7 expression was observed in cornea, trabecular meshwork (TM), and sclera in human and African green monkey eyes (Figures 4A and 4B). High Angptl7 expression was also observed in cornea, TM, sclera, optic nerve, and choroid/RPE in eyes of C57BL/6J mice (Figure 4C). In situ hybridization on human donor and mouse eyes using RNAScope probes for human ANGPTL7 and mouse Angptl7 showed ANGPTL7/ Angptl7 expression in TM, cornea stroma, and sclera (Figures 4D and 4E).

Gene expression changes in human TM cells upon dexamethasone treatment

Dexamethasone (DEX) treatment is known to lead to many biochemical changes at the gene expression level in the TM, including upregulation ANGPTL7. To further characterize these previous findings, quantitative PCR (qPCR) was performed on three human TM primary cell lines from three independent human eyes treated with vehicle (0.1% ethanol) or DEX (100 nM) for 72 hours. qPCR analysis revealed increased expression of ANGPTL7 expression in two out of three (Figure 5), suggesting some degree of variability in the DEX-induced upregulation of ANGPTL7, consistent with the observed variation in response to steroid treatment in the general population.

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Angptl7 increases IOP in mouse eyes

Previous studies showed that overexpression of ANGPTL7 in TM cells leads to changes in extracellular matrix deposition and reorganization (Comes et al., Genes to Cells: Devoted to Molecular & Cellular Mechanisms, 2011, 16, 243-259; and Kuchtey, Invest. Ophthalmol. &

5 Visual Sci., 2008, 49, 3438-48) and that ANGPTL7 is increased in aqueous humor of glaucoma patients (Kuchtey, Invest. Ophthalmol. & Visual Sci., 2008, 49, 3438-48), however, the role of ANGPTL7 in IOP regulation is not clear. To investigate the role of ANGPTL7 in IOP regulation, ANGPTL7 protein was injected in mice via intravitreal and intracameral routes and measured IOP over time. Intravitreal injection of ANGPTL7 protein in mice led to an initial drop in IOP and 10 then, starting on day 4, to an elevation of IOP of 4-5 mmHg (22-25% compared to baseline) that lasted until the end of the experiment on day 7 (Figure 6A). Similarly, intracameral injection of ANGPTL7 protein in mice led to an initial drop and subsequent elevation (by 2-5 mmHg) of IOP, starting on day 3 until the end of the experiment on day 7 (Figure 6B). Vehicle-injected mice did not show an increase in IOP in either route of administration.

15 *ANGPTL7 Gln175His and Arg177Stop exogenous expression in HEK 293 whole cell lysates*

Studies were conducted to show the expression of two variants of ANGPTL7 (Gln175His and Arg177Stop) in HEK 293 whole cell lysates (Figure 8A and Figure 8B). A drastic decrease of the Gln175His variant was observed in the cell supernatant compared to the wild type ANGPTL7 (Figure 8C and Figure 8D). In addition, a study was performed to determine

20 whether the Arg177Stop variant was able to be secreted in the supernatant (Figure 8E).

Exogenous expression of ANGPTL7 wild type and Gln175His variant in HEK293 showed a comparable intracellular protein level, but a drastic decrease of secreted Gln175His compared to the wild type ANGPTL7. Expression of Arg177Stop in HEK293 cells showed reduced intracellular protein level. The Arg177Stop variant was not able to be secreted.

25 *Expression analysis of ANGPTL7 Gln175His and ANGPTL7 Arg177* in a HEK293 cell line*

In vitro experiments were conducted to assess the expression and secretion of two variants of ANGPTL7 (Gln175His and Arg177Stop) that were identified in genetic association analyses, in HEK293T cells. Plasmids carrying either the 'wild type' (non-mutant) ANGPTL7 coding region or the variations that lead to Gln175His and Arg177Stop mutant forms were

30 introduced into HEK293T. The levels of mRNA of each the wild type, Gln175His and Arg177Stop ANGPTL7 were measured, and it was observed that the Gln175His and Arg177Stop mRNAs were reduced compared to the wild type (Figure 9A). Whole cell lysate (Figure 9B) and the cell

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supernatant (Figure 9D) was probed with an anti-ANGPTL7 polyclonal antibody to determine the levels of the wild type ANGPTL7 and the two mutant proteins. An ELISA assay was performed to quantify the levels of each protein in the whole cell lysate (Figure 9C) and the supernatant (Figures 9E). The results indicate that the levels of wild type, Gln175His and 5 Arg177Stop proteins are not significantly different in the whole cell lysate (Figures 9B and 9C), however, there is a drastic reduction in the amount of Gln175His and Arg177Stop in the supernatant of the cells when compared to the wild type protein (Figures 9D and 9E). These data suggest that the Gln175His and Arg177Stop mutations cause ANGPTL7 to be secreted 10 inefficiently in this in vitro system, and are consistent with the genetic hypothesis that loss or reduction of ANGPTL7 function results in reduced intraocular pressure, and protection from glaucoma.

In this study, genetic and functional evidence highlighting inhibition of ANGPTL7 as a potential strategy for glaucoma therapy are demonstrated. Through genetic association analyses in Europeans, a rare, missense variant, Gln175His (rs28991009), in ANGPTL7 was 15 identified that associated with a decrease in IOP, and with decreased risk for glaucoma. A pLOF variant in ANGPTL7, Arg177* (rs143435072), was also identified that also associated with a decrease in IOP, suggesting that Gln175His carriers are protected from glaucoma through a loss or reduction in ANGPTL7 activity. Consistent with this hypothesis, several ultra-rare variants in ANGPTL7 were associated, in aggregate, with decreased IOP, and an additional ANGPTL7 pLOF 20 variant, Trp188*, was enriched in individuals of African descent, who also showed a trend towards protection from glaucoma. Taken together, the genetic data strongly imply a causal relationship between downregulation of ANGPTL7 and protection from glaucoma. The RNA sequencing and *in situ* hybridization data in ocular tissues across mice, humans and the African Green monkey showed strongest expression of ANGPTL7 in the cornea and trabecular 25 meshwork.

Various modifications of the described subject matter, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference (including, but not limited to, journal articles, U.S. and non-U.S. patents, patent application 30 publications, international patent application publications, gene bank accession numbers, and the like) cited in the present application is incorporated herein by reference in its entirety and for all purposes.

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What is Claimed is:

1. A method of treating a patient having increased IOP, the method comprising administering an angiopoietin like 7 (ANGPTL7) inhibitor to the patient.
2. A method of treating a patient having glaucoma, the method comprising administering 5 an ANGPTL7 inhibitor to the patient.
3. The method according to claim 1 or claim 2, wherein the ANGPTL7 inhibitor comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to an ANGPTL7 mRNA.
4. The method according to claim 1 or claim 2, wherein the ANGPTL7 inhibitor comprises 10 a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within an ANGPTL7 genomic nucleic acid molecule.
5. The method according to claim 4, wherein the Cas protein is Cas9 or Cpf1.
6. The method according to claim 4 or claim 5, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 4,291 according to SEQ ID 15 NO:1, position 4,287 according to SEQ ID NO:1, position 4,243 according to SEQ ID NO:1, position 4,325 according to SEQ ID NO:1, or position 4,336 according to SEQ ID NO:1.
7. The method according to any one of claims 4 to 6, wherein the gRNA recognition sequence is located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to: position 4,291 according to SEQ ID NO:1, 20 position 4,287 according to SEQ ID NO:1, position 4,243 according to SEQ ID NO:1, position 4,325 according to SEQ ID NO:1, or position 4,336 according to SEQ ID NO:1.
8. The method according to any one of claims 4 to 7, wherein a Protospacer Adjacent Motif (PAM) sequence is about 2 to 6 nucleotides downstream of the gRNA recognition sequence.
- 25 9. The method according to any one of claims 4 to 8, wherein the gRNA comprises from about 17 to about 23 nucleotides.
10. The method according to any one of claims 4 to 8, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOS:13-131 and 144-165.
- 30 11. The method according to any one of claims 1 to 10, further comprising detecting the presence or absence of an ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide in a biological sample from the patient.

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12. The method according to claim 11, wherein when the patient is ANGPTL7 reference, the patient is also administered a therapeutic agent that treats or inhibits an ophthalmic condition in a standard dosage amount.

13. The method according to claim 11, wherein when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, the patient is also administered a therapeutic agent that treats or inhibits an ophthalmic condition in a dosage amount that is the same as or lower than the standard dosage amount.

14. The method according to any one of claims 11 to 13, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is a nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys.

15. The method according to any one of claims 11 to 13, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is a nucleic acid molecule encoding ANGPTL7 Gln175His, Trp188Stop, Lys192Gln, Phe161Ile, or Arg177Stop.

16. The method according to claim 15, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

17. The method according to claim 15, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

18. The method according to claim 15, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an mRNA molecule having a nucleotide sequence comprising an adenine at a position

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corresponding to position 481 according to SEQ ID NO:135; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

19. The method according to claim 15, wherein the ANGPTL7 predicted loss-of-function

5 variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

10 20. The method according to claim 15, wherein the ANGPTL7 predicted loss-of-function

variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; an mRNA molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

15 21. The method according to any one of claims 11 to 20, wherein the detecting step is carried out *in vitro*.

20 22. The method according to any one of claims 11 to 16 and 21, wherein the detecting

step comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the

25 biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; and/or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic

30 acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid

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molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA

5 molecule in the biological sample comprises a thymine at a position corresponding to position 529 according to SEQ ID NO:8, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

23. The method according to any one of claims 11 to 15, 17, and 21, wherein the detecting step comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7

10 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion

comprises a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; and/or the nucleotide

15 sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic

acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, then the ANGPTL7 genomic nucleic acid molecule in

20 the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological

sample comprises a uracil at a position corresponding to position 525 according to SEQ ID NO:6, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA

25 molecule in the biological sample comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

24. The method according to any one of claims 11 to 15, 18, and 21, wherein the detecting step comprises sequencing at least a portion of: the nucleotide sequence of the

30 ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,243 according to SEQ ID NO:132; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the

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sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:135; and/or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:138; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132 then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135 , then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:138, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

15. 25. The method according to any one of claims 11 to 15, 19, and 21, wherein the detecting step comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; and/or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to

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position 563 according to SEQ ID NO:139, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

26. The method according to any one of claims 11 to 15, 20, and 21, wherein the detecting step comprises sequencing at least a portion of: the nucleotide sequence of the

5 ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,336 according to SEQ ID NO:134; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:137; and/or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological
10 sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:140; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134 then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid
15 molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a cytosine at a position
20 corresponding to position 574 according to SEQ ID NO:140, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

27. The method according to any one of claims 11 to 16, 21, and 22, wherein the detecting step comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a

25 position corresponding to position 4,291 according to SEQ ID NO:2; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:5; and/or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:8; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule corresponding to
30 position 4,291 according to SEQ ID NO:2; the ANGPTL7 mRNA molecule corresponding to position 529 according to SEQ ID NO:5; and/or the ANGPTL7 cDNA molecule corresponding to position 529 according to SEQ ID NO:8; and c) determining whether the extension product of

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the primer comprises: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; a uracil at a position corresponding to position 529 according to SEQ ID NO:5; and/or a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

28. The method according to any one of claims 11 to 15, 17, 21, and 23, wherein the

5 detecting step comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,287 according to SEQ ID NO:3; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:6; and/or the ANGPTL7 cDNA molecule that is proximate to a position 10 corresponding to position 525 according to SEQ ID NO:9; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,287 according to SEQ ID NO:3; the ANGPTL7 mRNA molecule corresponding to position 525 according to SEQ ID NO:6; and/or the ANGPTL7 cDNA molecule corresponding to position 525 according to SEQ ID NO:9; and c) determining whether 15 the extension product of the primer comprises: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; a uracil at a position corresponding to position 525 according to SEQ ID NO:6; and/or a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

29. The method according to any one of claims 11 to 15, 18, 21, and 24, wherein the

20 detecting step comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; and/or the ANGPTL7 cDNA molecule that is proximate to a 25 position corresponding to position 481 according to SEQ ID NO:138; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; and/or the ANGPTL7 cDNA molecule that is proximate to a 30 position corresponding to position 481 according to SEQ ID NO:138; c) determining whether the extension product of the primer comprises: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an adenine at a position corresponding to position 481

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according to SEQ ID NO:135; and/or an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

30. The method according to any one of claims 11 to 15, 19, 21, and 25, wherein the detecting step comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID NO:133; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; and/or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID NO:133; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; and/or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; c) determining whether the extension product of the primer comprises: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an adenine at a position corresponding to position 563 according to SEQ ID NO:136; and/or an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

31. The method according to any one of claims 11 to 15, 20, 21, and 26, wherein the detecting step comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,336 according to SEQ ID NO:134; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:137; and/or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:140; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,336 according to SEQ ID NO:134; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:137; and/or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 574 according to SEQ ID NO:140; c) determining whether the extension product of the primer comprises: a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; a cytosine at a position corresponding to position 574

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according to SEQ ID NO:137; and/or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

32. The method according to any one of claims 22 to 31, wherein the detecting step comprises sequencing the entire nucleic acid molecule.

5 33. The method according to any one of claims 11 to 16, 21, 22, 27, and 32, wherein the detecting step comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the 10 complement thereof; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the 15 amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and d) detecting the detectable label.

20 34. The method according to any one of claims 11 to 15, 17, 21, 23, 28, and 32, wherein the detecting step comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the 25 complement thereof; or a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the 30 amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or a

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thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and d) detecting the detectable label.

35. The method according to any one of claims 11 to 15, 18, 21, 24, 29, and 32, wherein the detecting step comprises: a) amplifying at least a portion of the nucleic acid molecule that

5 encodes the human ANGPTL7 polypeptide, wherein the portion comprises: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or an adenine at a position corresponding to position 481 according to SEQ ID NO:138; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe

10 comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; or an adenine at a position corresponding to position 481 according to SEQ ID NO:138; and d)

15 detecting the detectable label.

36. The method according to any one of claims 11 to 15, 19, 21, 25, 30, and 32, wherein the detecting step comprises: a) amplifying at least a portion of the nucleic acid molecule that

20 encodes the human ANGPTL7 polypeptide, wherein the portion comprises: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe

25 comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139; and d)

30 detecting the detectable label.

37. The method according to any one of claims 11 to 15, 20, 21, 26, 31, and 32, wherein the detecting step comprises: a) amplifying at least a portion of the nucleic acid molecule that

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encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or a cytosine at a position

corresponding to position 574 according to SEQ ID NO:140; b) labeling the amplified nucleic

5 acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe

comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic

acid sequence of the amplified nucleic acid molecule comprising: a cytosine at a position

corresponding to position 4,336 according to SEQ ID NO:134; a cytosine at a position

10 corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140; and d)

detecting the detectable label.

38. The method according any one of the claims 33 to 37, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the

15 amplifying step.

39. The method according to any one of claims 11 to 16, and 21, wherein the detecting step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of

20 the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and detecting the detectable label.

25 40. The method according to any one of claims 11 to 15, 17, and 21, wherein the detecting step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position

30 corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or a

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thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and detecting the detectable label.

41. The method according to any one of claims 11 to 15, 18, and 21, wherein the detecting step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-

5 specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; or an adenine at a position

10 corresponding to position 481 according to SEQ ID NO:138; and detecting the detectable label.

42. The method according to any one of claims 11 to 15, 19, and 21, wherein the detecting step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-

specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence

15 of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139; and detecting the detectable label.

43. The method according to any one of claims 11 to 15, 20, and 21, wherein the detecting

20 step comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; a cytosine at a position corresponding to position

25 574 according to SEQ ID NO:137, or the complement thereof; or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140; and detecting the detectable label.

44. A method of treating a patient with a therapeutic agent that treats or inhibits an

ophthalmic condition, wherein the patient is suffering from an ophthalmic condition, the method comprising the steps of:

30 determining whether the patient has an angiopoietin like 7 (ANGPTL7) predicted loss-of-function variant nucleic acid molecule encoding a human ANGPTL7 polypeptide by:

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obtaining or having obtained a biological sample from the patient;

and

5 performing or having performed a genotyping assay on the biological sample to determine if the patient has a genotype comprising the ANGPTL7 predicted loss-of-function variant nucleic acid molecule; and

when the patient is ANGPTL7 reference, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor; and

10 when the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, then administering or continuing to administer to the patient the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and administering to the patient an ANGPTL7 inhibitor;

wherein the presence of a genotype having the ANGPTL7 predicted loss-of-function variant nucleic acid molecule encoding the human ANGPTL7 polypeptide indicates the patient

15 has a reduced risk of developing the ophthalmic condition.

45. The method according to claim 44, wherein the patient is ANGPTL7 reference, and the patient is administered or continued to be administered the therapeutic agent that treats or inhibits the ophthalmic condition in a standard dosage amount, and is administered an ANGPTL7 inhibitor.

20 46. The method according to claim 44, wherein the patient is heterozygous for an ANGPTL7 predicted loss-of-function variant, and the patient is administered or continued to be administered the therapeutic agent that treats or inhibits the ophthalmic condition in an amount that is the same as or lower than a standard dosage amount, and is administered an ANGPTL7 inhibitor.

25 47. The method according to any one of claims 44 to 46, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is a nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile, Arg340His, Arg220His, Asn302Lys, or Arg220Cys.

48. The method according to any one of claims 44 to 46, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is a nucleic acid molecule encoding ANGPTL7 Gln175His, Arg177Stop, Trp188Stop, Lys192Gln, Phe161Ile.

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49. The method according to any one of claims 44 to 48, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; an mRNA molecule having a nucleotide sequence comprising a uracil

5 at a position corresponding to position 529 according to SEQ ID NO:5; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

50. The method according to any one of claims 44 to 48, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a

10 nucleotide sequence comprising a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3; an mRNA molecule having a nucleotide sequence comprising a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

15 51. The method according to any one of claims 44 to 48, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or a cDNA 20 molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

25 52. The method according to any one of claims 44 to 48, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an mRNA molecule having a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising an adenine at a position corresponding to position 563 according to SEQ 30 ID NO:139.

53. The method according to any one of claims 44 to 48, wherein the ANGPTL7 predicted loss-of-function variant nucleic acid molecule is: a genomic nucleic acid molecule having a

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nucleotide sequence comprising a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134; an mRNA molecule having a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:137; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence comprising a cytosine at a position corresponding to position 574 according to SEQ ID NO:140.

5 54. The method according to any one of claims 44 to 49, wherein the genotyping assay comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or the nucleotide sequence of the ANGPTL7 cDNA molecule produced from an mRNA molecule in the biological sample, wherein the sequenced portion

10 15 comprises a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 529 according to SEQ ID NO:5, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position

20 25 529 according to SEQ ID NO:8, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

55. The method according to any one of claims 44 to 48, and 50, wherein the genotyping assay comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to

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position 525 according to SEQ ID NO:6, or the complement thereof; or the nucleotide sequence of the ANGPTL7 cDNA molecule produced from an mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; wherein: when the sequenced portion of the

5 ANGPTL7 genomic nucleic acid molecule in the biological sample comprises a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises a uracil at a position corresponding to position 525

10 according to SEQ ID NO:6, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a thymine at a position corresponding to position 525 according to SEQ ID NO:9, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

15 56. The method according to any one of claims 44 to 48, and 51, wherein the genotyping assay comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,243 according to SEQ ID NO:132; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the

20 sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:135; or the nucleotide sequence of the ANGPTL7 cDNA molecule produced from an mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 481 according to SEQ ID NO:138; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID NO:135, then the ANGPTL7 mRNA

25 molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 481 according to SEQ ID

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NO:138, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

57. The method according to any one of claims 44 to 48, and 52, wherein the genotyping assay comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7

5 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or the nucleotide

10 sequence of the ANGPTL7 cDNA molecule produced from an mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid molecule in the biological sample comprises an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, then the ANGPTL7

15 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:136, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the

20 sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises an adenine at a position corresponding to position 563 according to SEQ ID NO:139, then the ANGPTL7 cDNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

58. The method according to any one of claims 44 to 48, and 53, wherein the genotyping

25 assay comprises sequencing at least a portion of: the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 4,336 according to SEQ ID NO:134; the nucleotide sequence of the ANGPTL7 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID

30 NO:137; or the nucleotide sequence of the ANGPTL7 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 574 according to SEQ ID NO:140; wherein: when the sequenced portion of the ANGPTL7 genomic nucleic acid

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molecule in the biological sample comprises a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, then the ANGPTL7 genomic nucleic acid molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant genomic nucleic acid molecule; when the sequenced portion of the ANGPTL7 mRNA molecule in the biological

5 sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, then the ANGPTL7 mRNA molecule in the biological sample is an ANGPTL7 predicted loss-of-function variant mRNA molecule; and when the sequenced portion of the ANGPTL7 cDNA molecule in the biological sample comprises a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, then the ANGPTL7 cDNA molecule

10 in the biological sample is an ANGPTL7 predicted loss-of-function variant cDNA molecule.

59. The method according to any one of claims 44 to 49, and 54, wherein the genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,291 according to SEQ ID NO:2; the ANGPTL7 mRNA

15 molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:5; or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 529 according to SEQ ID NO:8; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule corresponding to position 4,291 according to SEQ ID NO:2; the ANGPTL7 mRNA molecule corresponding to position 529 according to SEQ ID NO:5; or the ANGPTL7 cDNA molecule corresponding to position 529 according to SEQ ID NO:8; and c) determining whether the extension product of the primer comprises: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2; a uracil at a position corresponding to position 529 according to SEQ ID NO:5; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8.

25 60. The method according to any one of claims 44 to 48, 50, and 55, wherein the genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,287 according to SEQ ID NO:3; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:6; or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 525 according to SEQ ID NO:9; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid

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molecule corresponding to position 4,287 according to SEQ ID NO:3; the ANGPTL7 mRNA molecule corresponding to position 525 according to SEQ ID NO:6; or the ANGPTL7 cDNA molecule corresponding to position 525 according to SEQ ID NO:9; and c) determining whether the extension product of the primer comprises: a thymine at a position corresponding to 5 position 4,287 according to SEQ ID NO:3; a uracil at a position corresponding to position 525 according to SEQ ID NO:6; or a thymine at a position corresponding to position 525 according to SEQ ID NO:9.

61. The method according to any one of claims 44 to 48, 51, and 56, wherein the genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to a

10 portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481

according to SEQ ID NO:135; or the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:138; b) extending the primer at least

15 through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,243 according to SEQ ID NO:132; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 481 according to SEQ ID NO:135; or the ANGPTL7 cDNA molecule that is proximate to a position

corresponding to position 481 according to SEQ ID NO:138; c) determining whether the

20 extension product of the primer comprises: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132; an adenine at a position corresponding to position 481 according to SEQ ID NO:135; or an adenine at a position corresponding to position 481 according to SEQ ID NO:138.

62. The method according to any one of claims 44 to 48, 52, and 57, wherein the

25 genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID NO:133; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563

according to SEQ ID NO:136; or the ANGPTL7 cDNA molecule that is proximate to a position

30 corresponding to position 563 according to SEQ ID NO:139; b) extending the primer at least through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid molecule that is proximate to a position corresponding to position 4,325 according to SEQ ID

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NO:133; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:136; or the position of nucleotide sequence of the ANGPTL7 cDNA molecule that is proximate to a position corresponding to position 563 according to SEQ ID NO:139; c) determining whether the extension product of the primer comprises: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133; an adenine at a position corresponding to position 563 according to SEQ ID NO:136; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139.

63. The method according to any one of claims 44 to 48, 53, and 58, wherein the

genotyping assay comprises: a) contacting the biological sample with a primer hybridizing to a

portion of the nucleotide sequence of the ANGPTL7 genomic nucleic acid molecule that is

proximate to a position corresponding to position 4,336 according to SEQ ID NO:134; the

ANGPTL7 mRNA molecule that is proximate to a position corresponding to position 574

according to SEQ ID NO:137; or the ANGPTL7 cDNA molecule that is proximate to a position

corresponding to position 574 according to SEQ ID NO:140; b) extending the primer at least

15 through the position of the nucleotide sequence of: the ANGPTL7 genomic nucleic acid

molecule that is proximate to a position corresponding to position 4,336 according to SEQ ID

NO:134; the ANGPTL7 mRNA molecule that is proximate to a position corresponding to position

574 according to SEQ ID NO:137; or the ANGPTL7 cDNA molecule that is proximate to a position

corresponding to position 574 according to SEQ ID NO:140; c) determining whether the

20 extension product of the primer comprises: a cytosine at a position corresponding to position

4,336 according to SEQ ID NO:134; a cytosine at a position corresponding to position 574

according to SEQ ID NO:137; or a cytosine at a position corresponding to position 574 according

to SEQ ID NO:140.

64. The method according to any one of claims 59 to 63, wherein the detecting step

25 comprises sequencing the entire nucleic acid molecule.

65. The method according to any one of claims 44 to 49, 54, 59, and 64 wherein the

genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that

encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a thymine at a

position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof;

30 a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the

complement thereof; or a thymine at a position corresponding to position 529 according to SEQ

ID NO:8, or the complement thereof; b) labeling the amplified nucleic acid molecule with a

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detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 5, 4,291 according to SEQ ID NO:2, or the complement thereof; a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and d) detecting the detectable label.

66. The method according to any one of claims 44 to 48, 50, 55, 60, and 64, wherein the 10 genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or a thymine at a position corresponding to position 525 according to SEQ 15 ID NO:9, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 20 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and d) detecting the detectable label.

67. The method according to any one of claims 44 to 48, 51, 56, 61, and 64, wherein the 25 genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; or an adenine at a position corresponding to position 481 according 30 to SEQ ID NO:138, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a

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nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement

5 thereof; or an adenine at a position corresponding to position 481 according to SEQ ID NO:138, or the complement thereof; and d) detecting the detectable label.

68. The method according to any one of claims 44 to 48, 52, 57, 62, and 64, wherein the genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: an adenine at a

10 position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support

15 comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement

20 thereof; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139, or the complement thereof; and d) detecting the detectable label.

69. The method according to any one of claims 44 to 48, 53, 58, 63, and 64, wherein the genotyping assay comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human ANGPTL7 polypeptide, wherein the portion comprises: a cytosine at a

25 position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: a cytosine at a position corresponding to position

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4,336 according to SEQ ID NO:134, or the complement thereof; a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140, or the complement thereof; and d) detecting the detectable label.

5 70. The method according to any one of claims 65 to 69, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the amplifying step.

71. The method according to any one of claims 44 to 49, wherein the genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,291 according to SEQ ID NO:2, or the complement thereof; a uracil at a position corresponding to position 529 according to SEQ ID NO:5, or the complement thereof; or a thymine at a position corresponding to position 529 according to SEQ ID NO:8, or the complement thereof; and detecting the detectable label.

72. The method according to any one of claims 44 to 48, and 50, wherein the genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: a thymine at a position corresponding to position 4,287 according to SEQ ID NO:3, or the complement thereof; a uracil at a position corresponding to position 525 according to SEQ ID NO:6, or the complement thereof; or a thymine at a position corresponding to position 525 according to SEQ ID NO:9, or the complement thereof; and detecting the detectable label.

73. The method according to any one of claims 44 to 48, and 51, wherein the genotyping assay comprises the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,243 according to SEQ ID NO:132, or the complement thereof; an adenine at a position corresponding to position 481 according to SEQ ID NO:135, or the complement thereof; or an adenine at a position corresponding to position 481 according to SEQ ID NO:138; and detecting the detectable label.

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74. The method according to any one of claims 44 to 48, and 52, wherein the genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: an adenine at a position corresponding to position 4,325 according to SEQ ID NO:133, or the complement thereof; an adenine at a position corresponding to position 563 according to SEQ ID NO:136, or the complement thereof; or an adenine at a position corresponding to position 563 according to SEQ ID NO:139; and detecting the detectable label.

10 75. The method according to any one of claims 44 to 48, and 53, wherein the genotyping assay comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: a cytosine at a position corresponding to position 4,336 according to SEQ ID NO:134, or the complement thereof; a cytosine at a position corresponding to position 574 according to SEQ ID NO:137, or the complement thereof; or a cytosine at a position corresponding to position 574 according to SEQ ID NO:140; and detecting the detectable label.

15 76. The method according to any one of claims 44 to 75, wherein the nucleic acid molecule is present within a cell obtained from the human subject.

77. The method according to any one of claims 44 to 76, wherein the ANGPTL7 inhibitor comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to an ANGPTL7 mRNA.

20 78. The method according to any one of claims 44 to 76, wherein the ANGPTL7 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within an ANGPTL7 genomic nucleic acid molecule.

79. The method according to claim 78, wherein the Cas protein is Cas9 or Cpf1.

80. The method according to claim 78 or claim 79, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 4,291 according to SEQ ID NO:1, position 4,287 according to SEQ ID NO:1, position 4,243 according to SEQ ID NO:1, position 4,325 according to SEQ ID NO:1, or position 4,336 according to SEQ ID NO:1.

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81. The method according to any one of claims 78 to 80, wherein the gRNA recognition sequence is located from about 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of a position corresponding to: position 4,291 according to SEQ ID NO:1, position 4,287 according to SEQ ID NO:1, position 4,243 according to SEQ ID NO:1, position 5 4,325 according to SEQ ID NO:1, or position 4,336 according to SEQ ID NO:1.

82. The method according to any one of claims 78 to 81, wherein a Protospacer Adjacent Motif (PAM) sequence is about 2 to 6 nucleotides downstream of the gRNA recognition sequence.

83. The method according to any one of claims 78 to 82, wherein the gRNA comprises 10 from about 17 to about 23 nucleotides.

84. The method according to any one of claims 78 to 83, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOS:13-131 and 144-165.

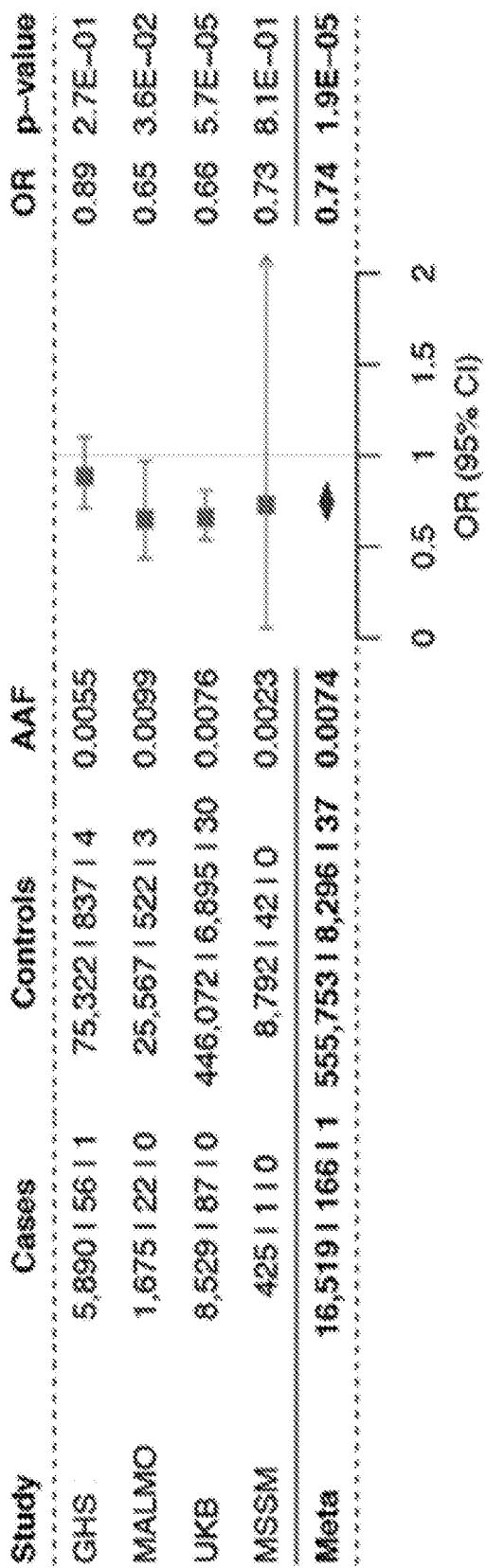


Figure 2E

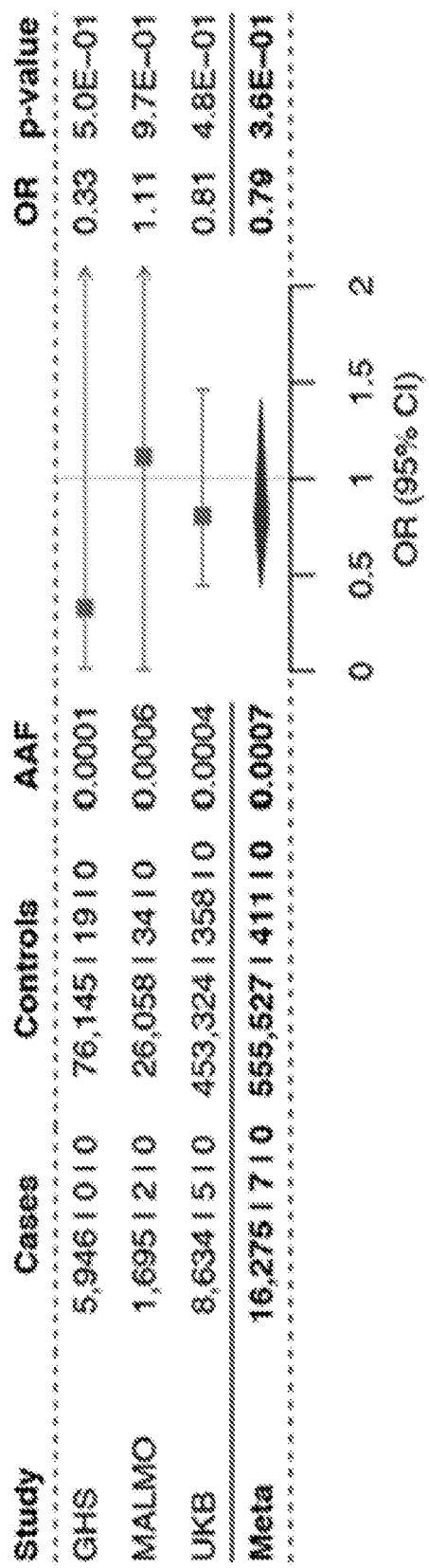


Figure 2F

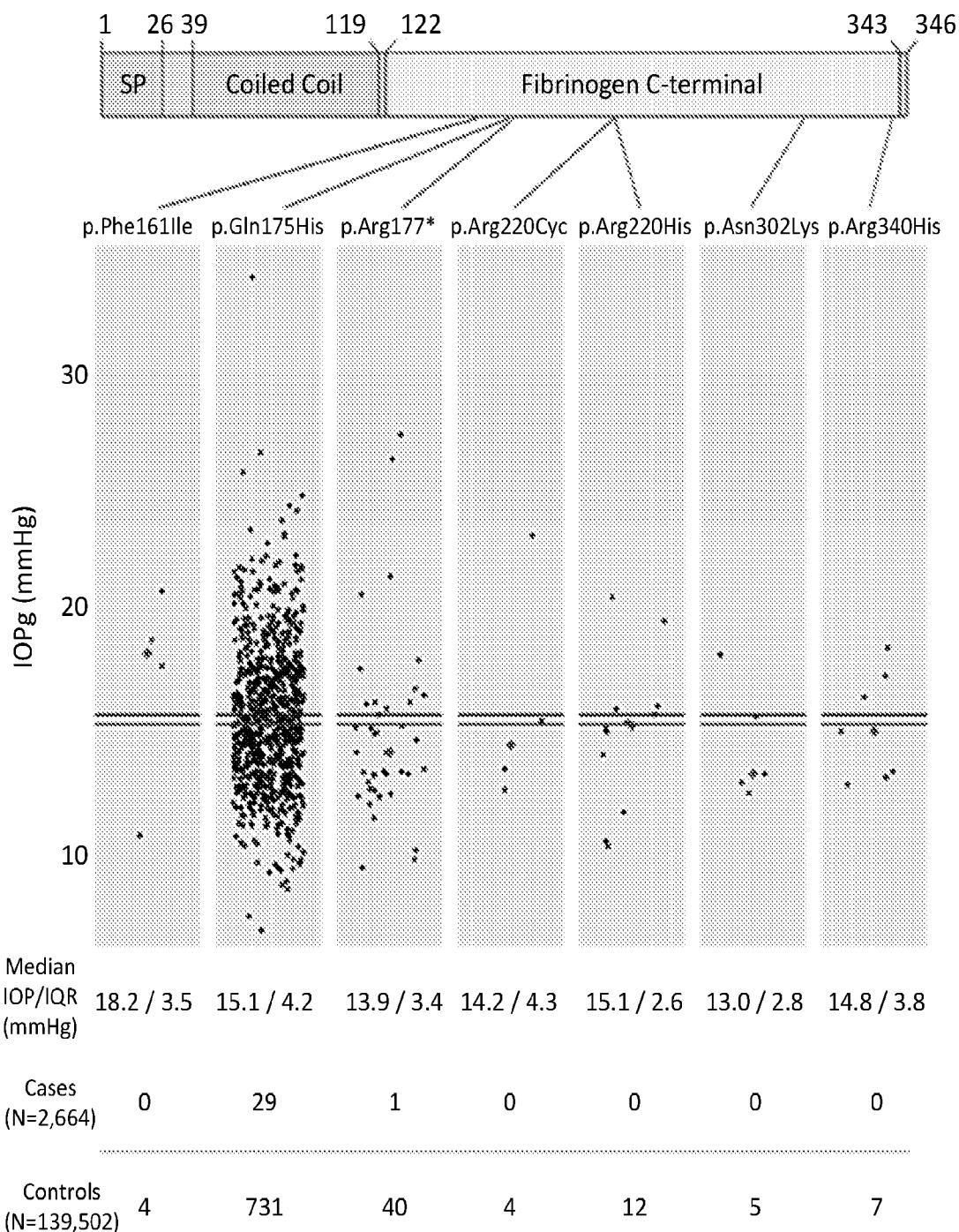


Figure 3

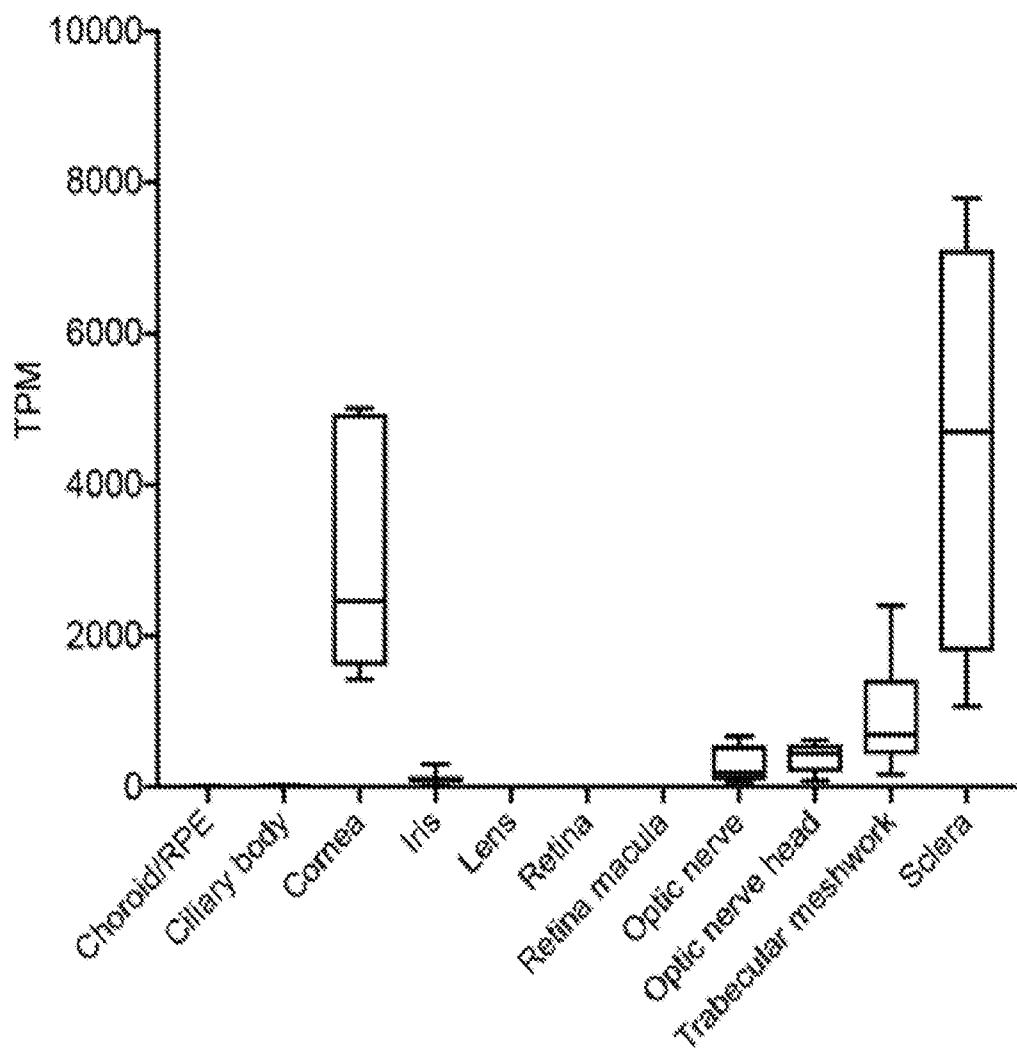


Figure 4A

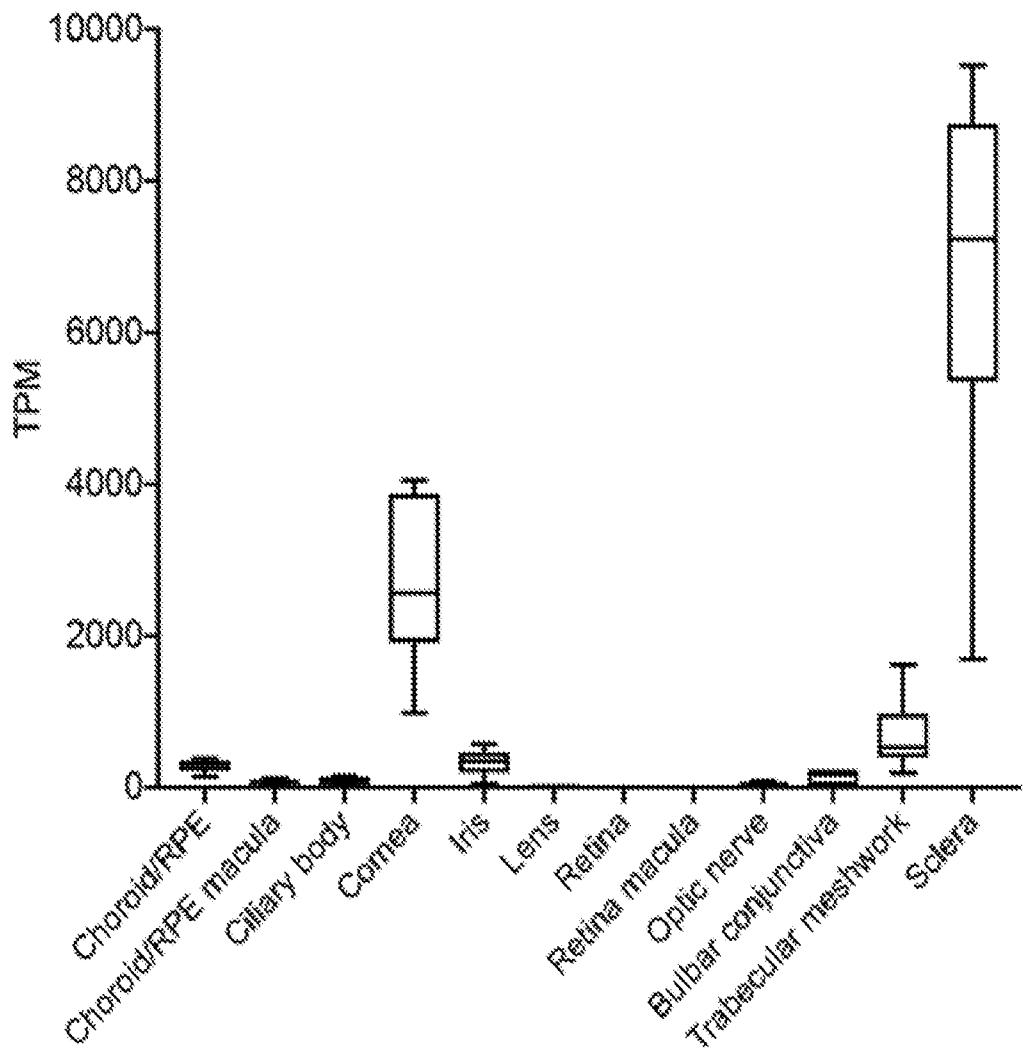


Figure 4B

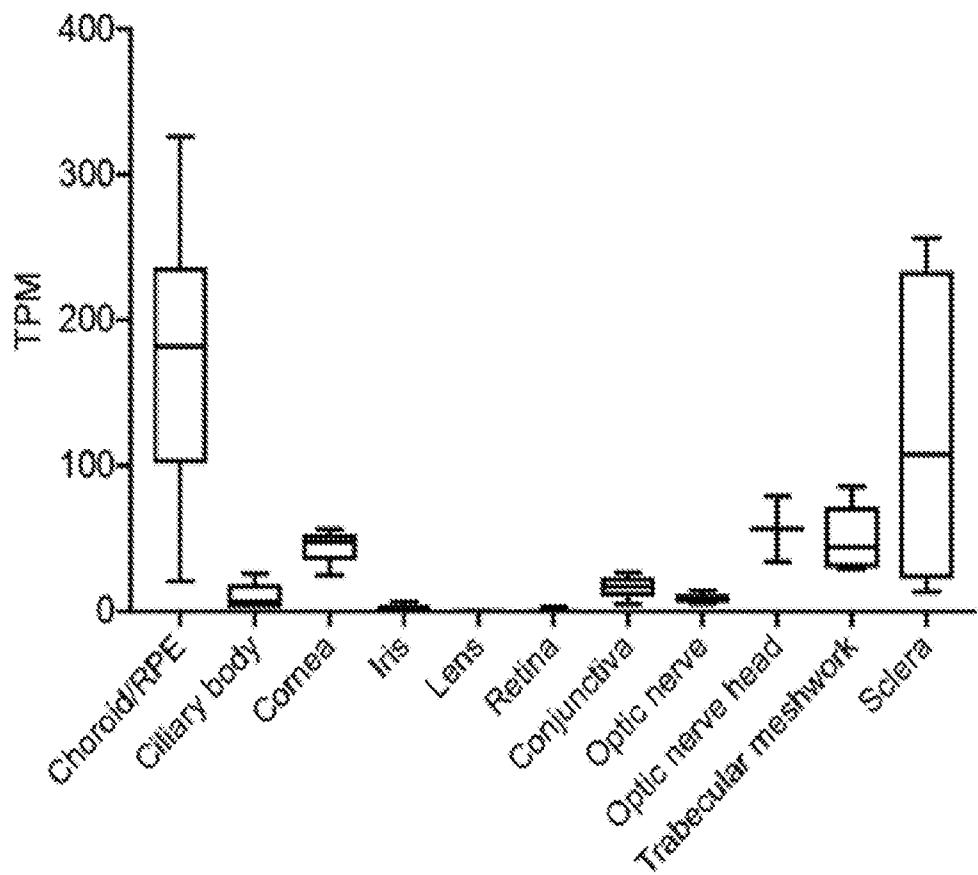


Figure 4C

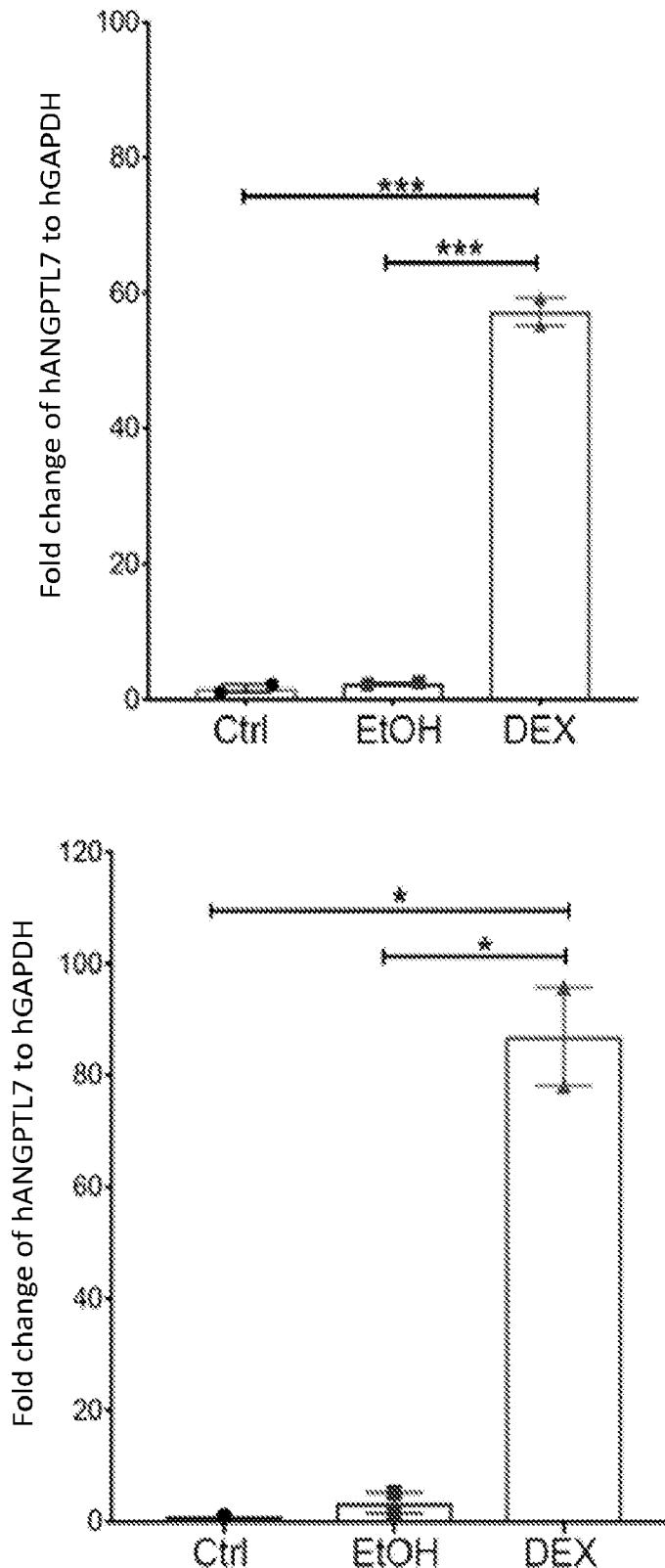


Figure 5

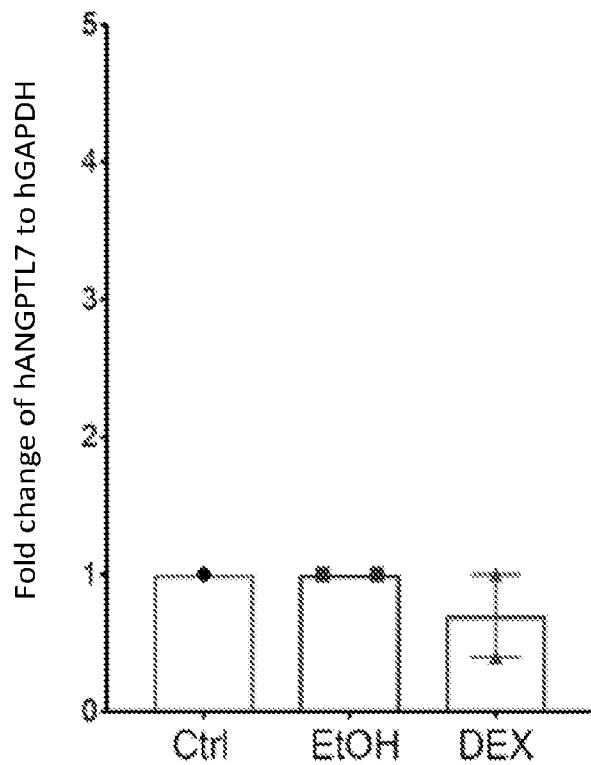


Figure 5 (cont.)

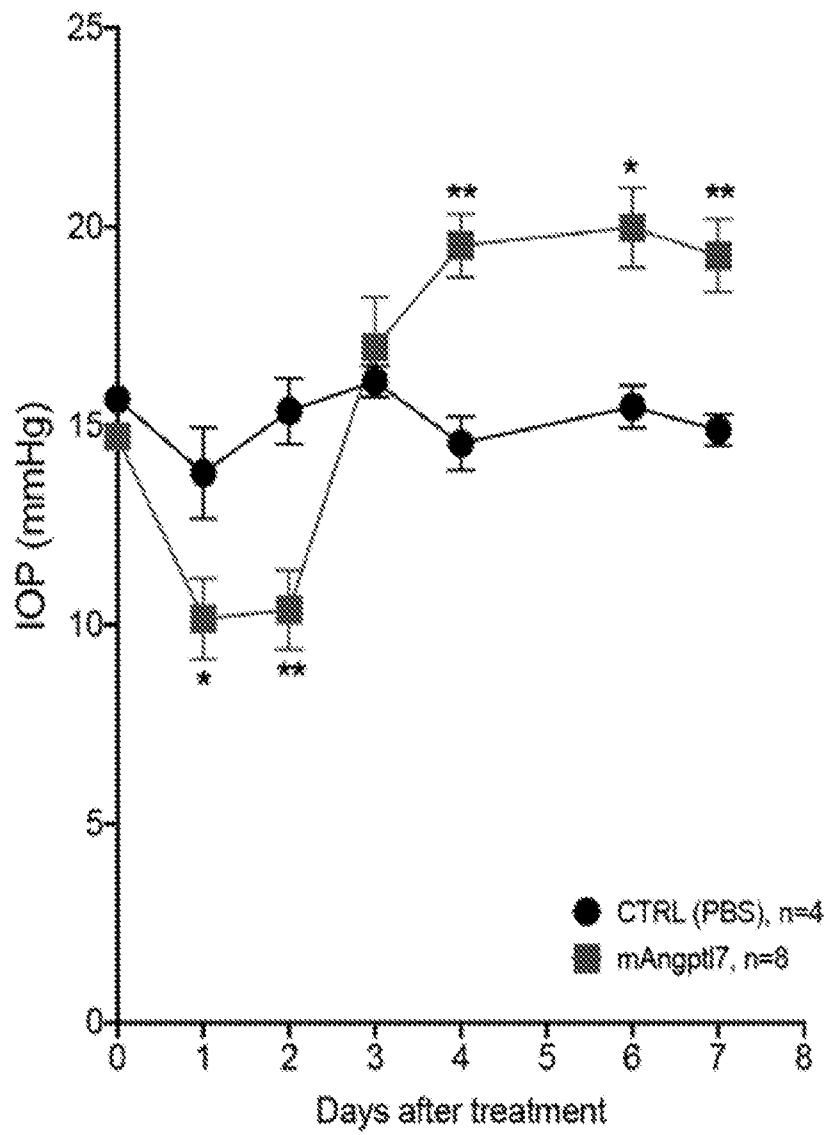


Figure 6A

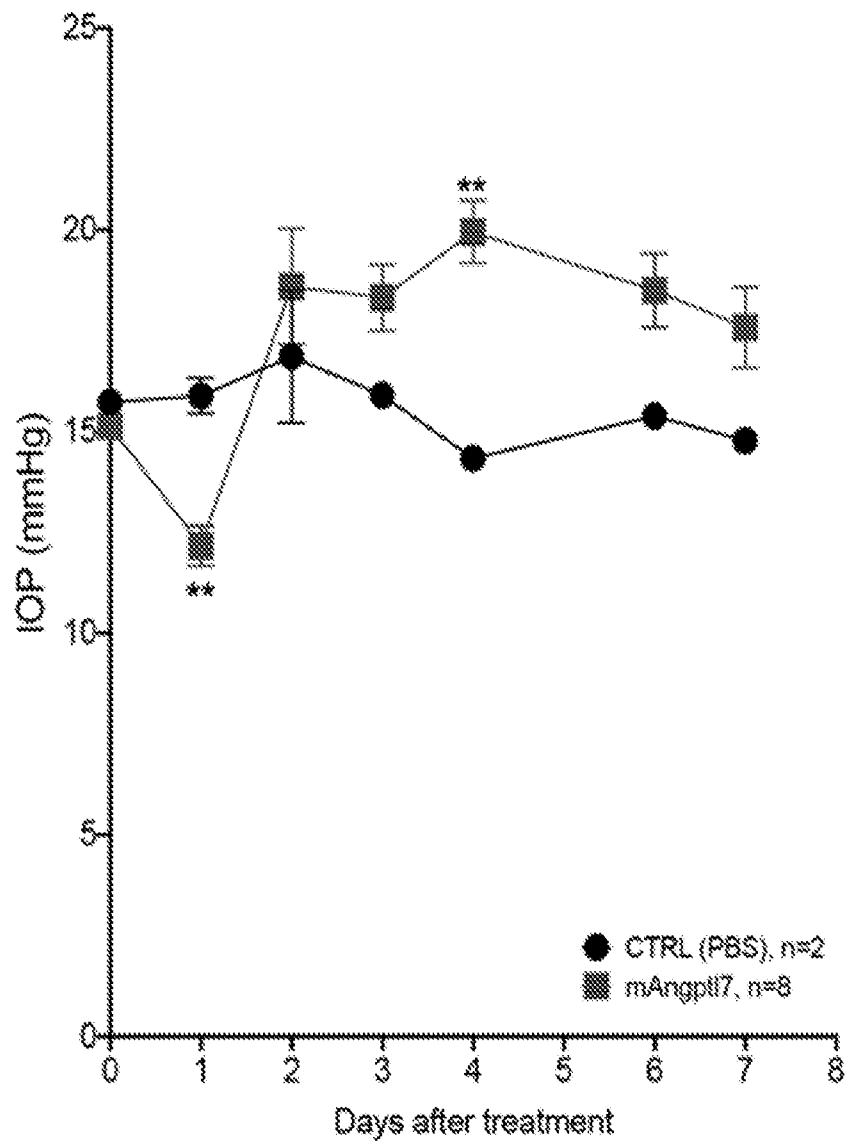


Figure 6B

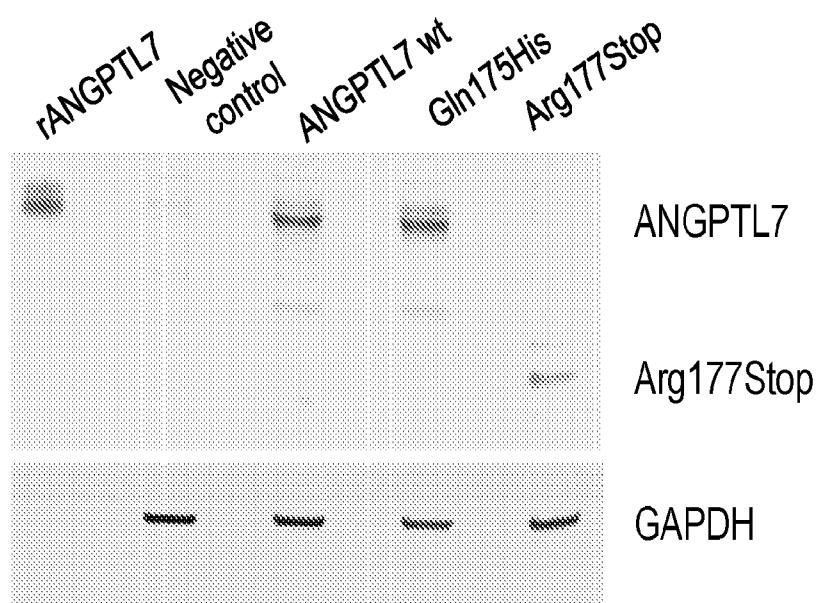
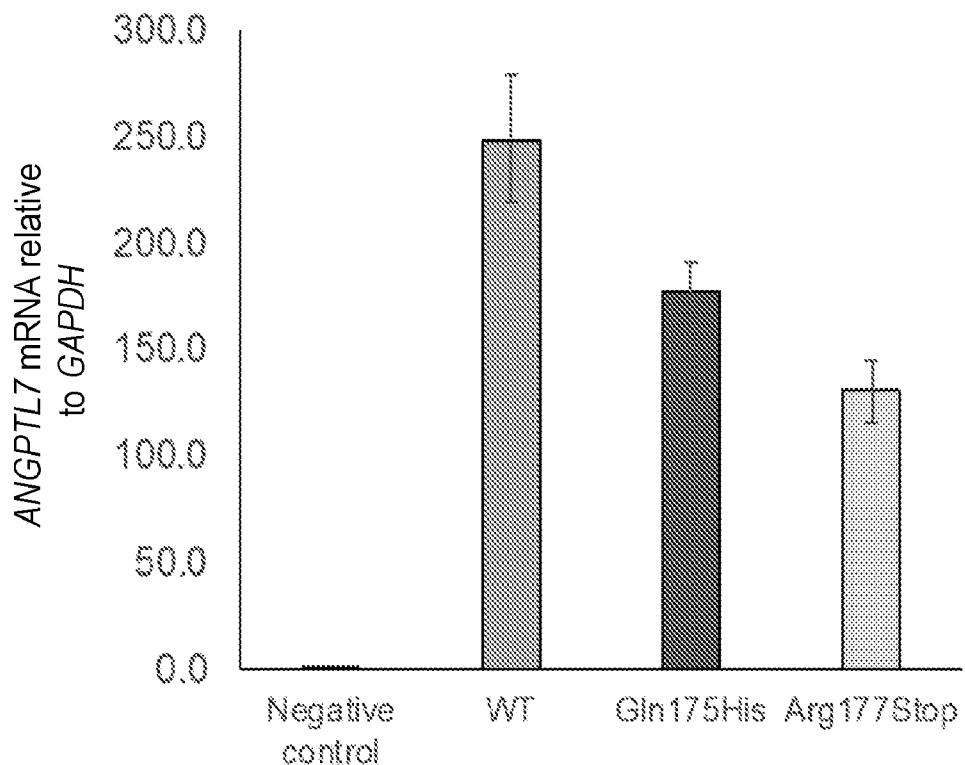


Figure 8A

Western blotting quantification

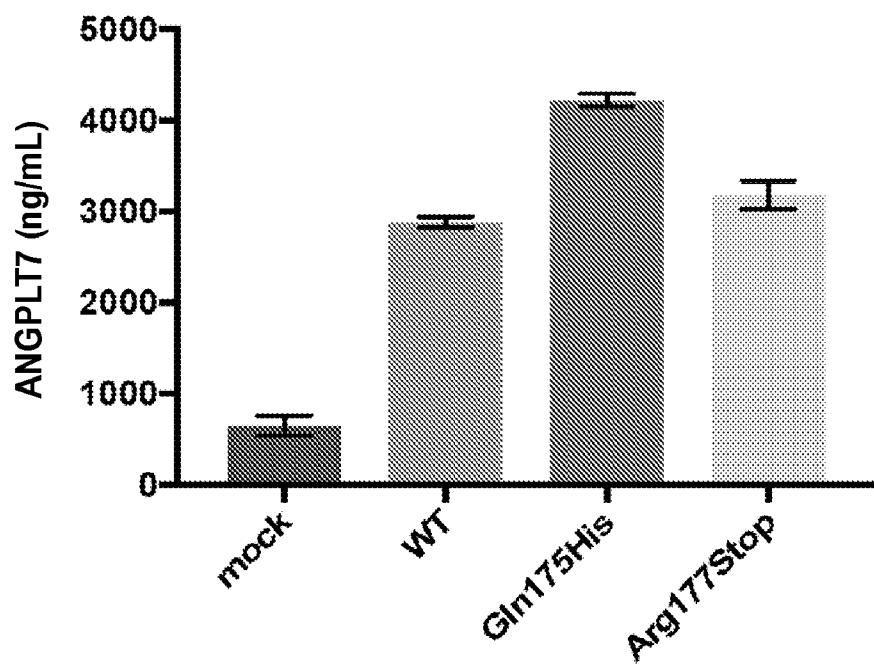
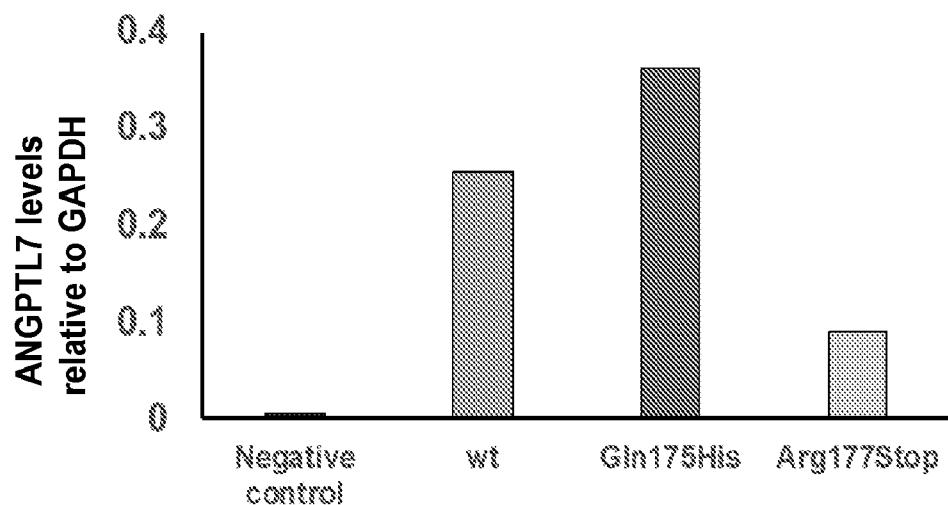


Figure 8B

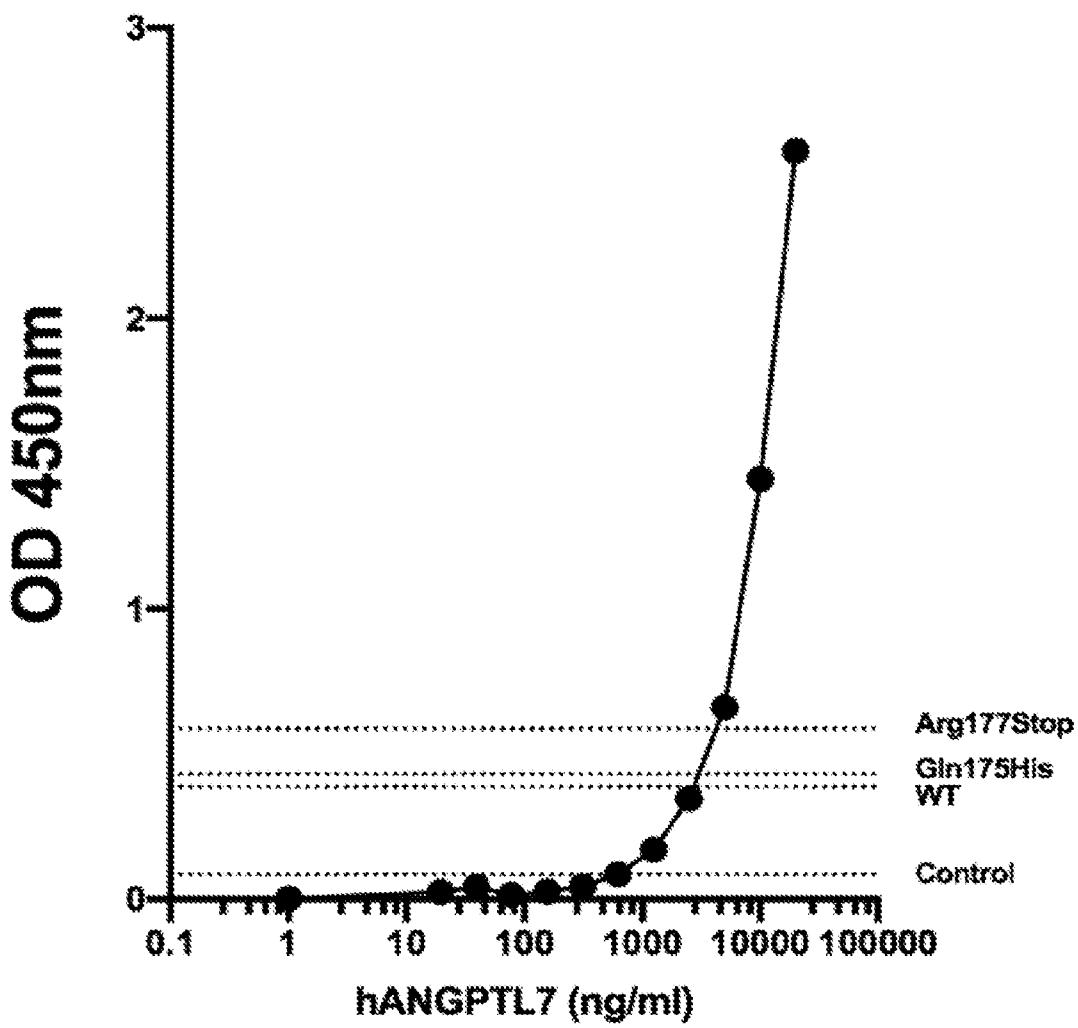


Figure 8B (cont.)

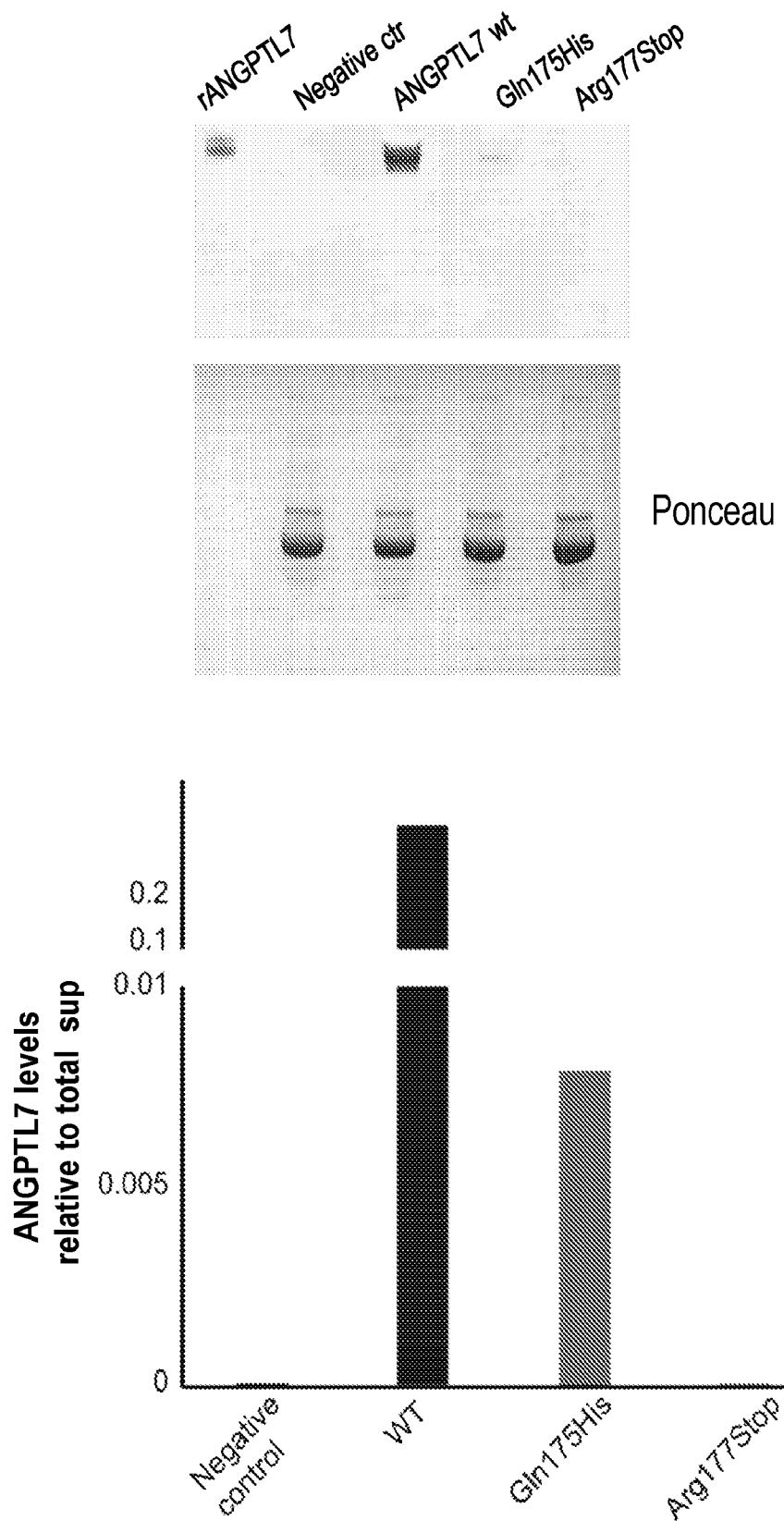


Figure 8C

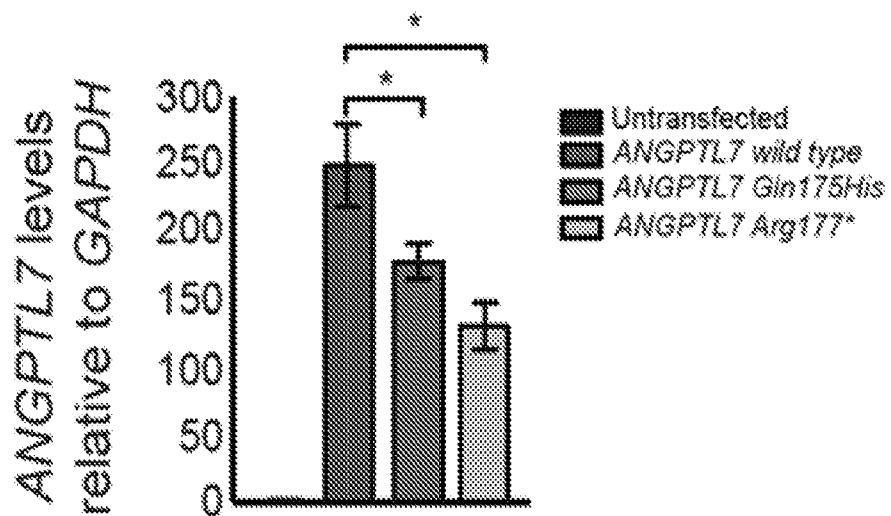


Figure 9A

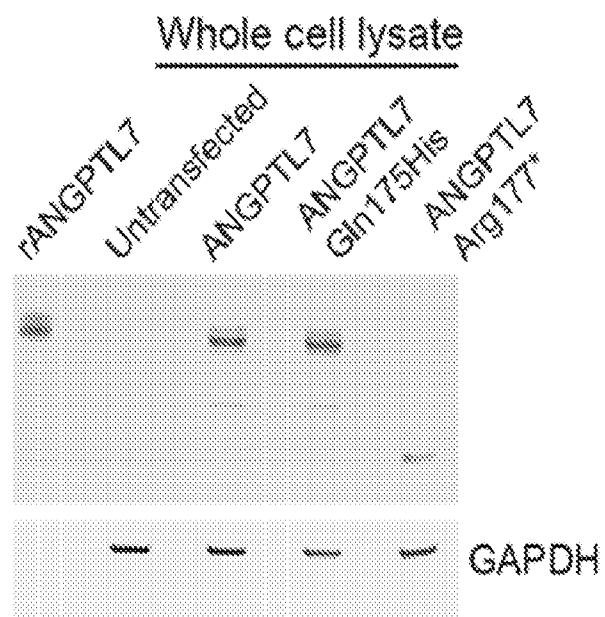


Figure 9B

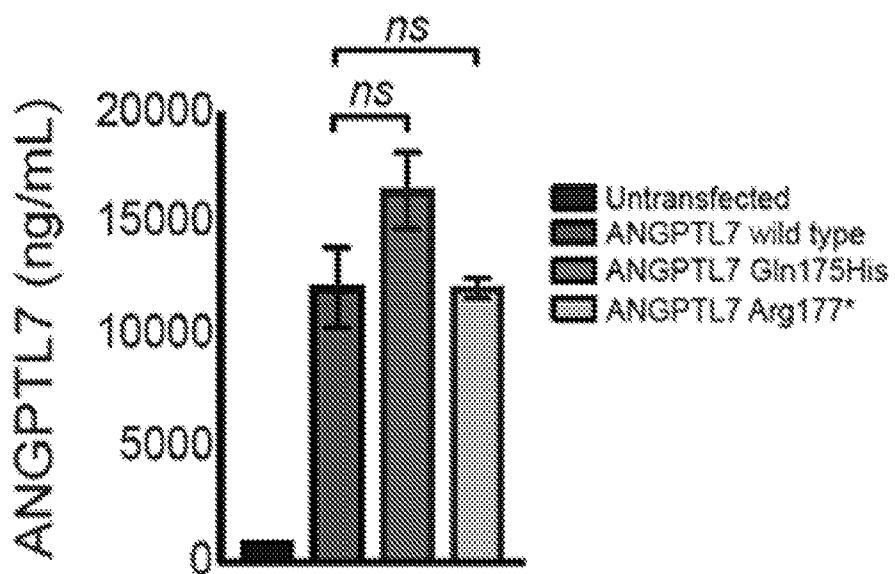


Figure 9C

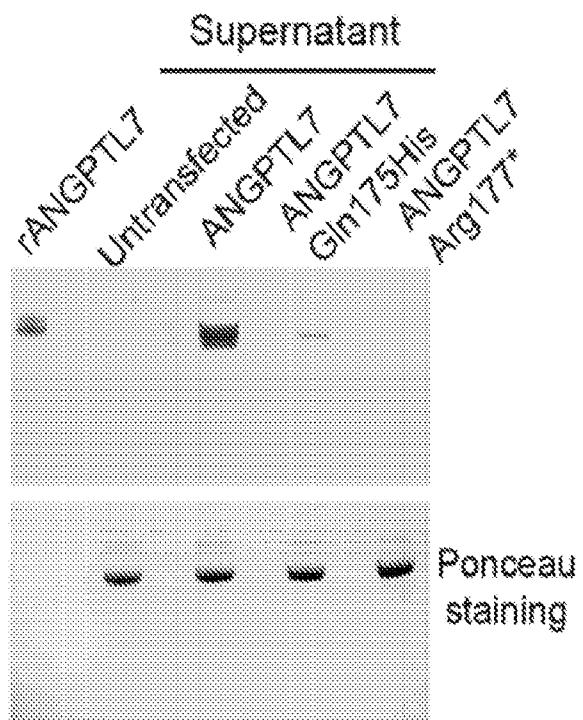


Figure 9D

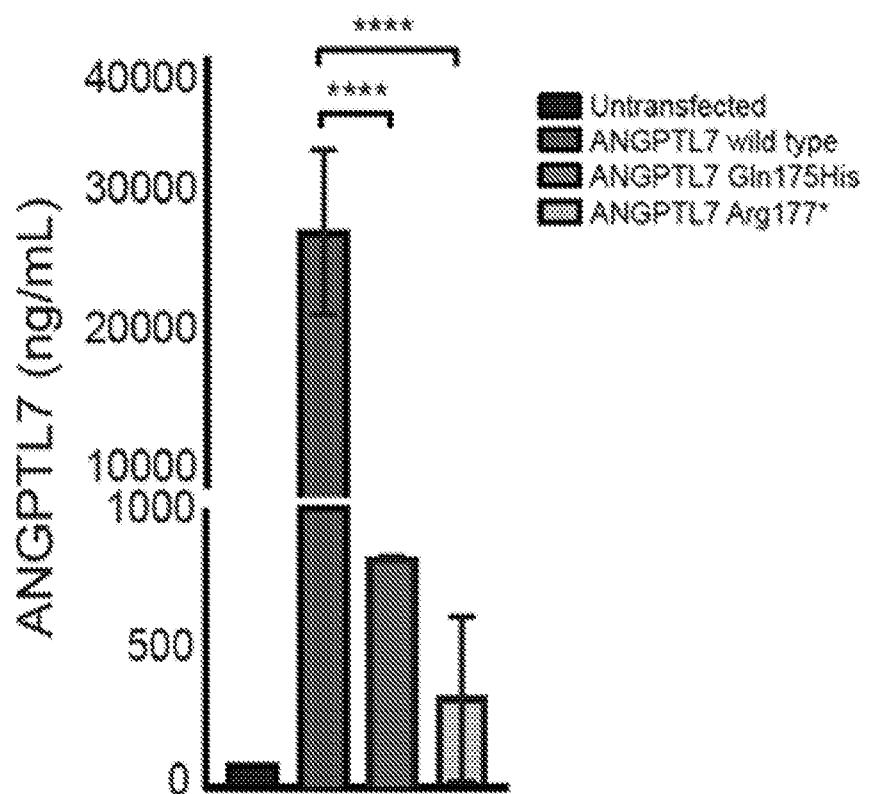


Figure 9E