(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 June 2017 (22.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/106370 A1

(51) International Patent Classification:
C12N 15/113 (2010.01) *C12Q 1/68* (2006.01)
C12N 15/11 (2006.01)

(21) International Application Number:
PCT/US2016/066691

(22) International Filing Date:
14 December 2016 (14.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/267,259 14 December 2015 (14.12.2015) US
62/318,958 6 April 2016 (06.04.2016) US

(71) Applicants: **COLD SPRING HARBOR LABORATORY** [US/US]; One Bungtown Road, Nicholas Building, P.O. Box 100, Cold Spring Harbor, New York 11724 (US). **STOKE THERAPEUTICS, INC.** [US/US]; 3 Preston Court, Bedford, Massachusetts 01730 (US).

(72) Inventors: **AZNAREZ, Isabel**; 55 Magazine Street, Apt. 12A, Cambridge, Massachusetts 02139 (US). **NASH, Huw M.**; 4 Washington Street, Lexington, Massachusetts 02421 (US).

(74) Agents: **ROHATGI, Kyanne** et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

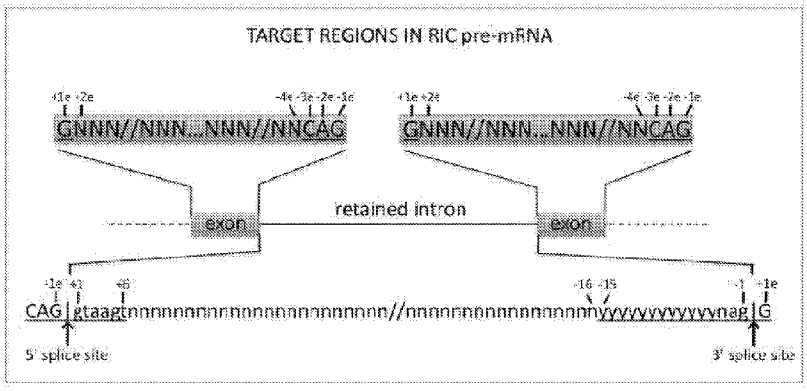
— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: COMPOSITIONS AND METHODS FOR TREATMENT OF EYE DISEASES

FIG. 1



(57) **Abstract**: Provided herein are methods and compositions for increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA, and for treating a subject in need thereof, e.g., a subject with deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein expression.

WO 2017/106370 A1

COMPOSITIONS AND METHODS FOR TREATMENT OF EYE DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/267,259, filed on December 14, 2015, and U.S. Provisional Application No. 62/318,958, filed on April 6, 2016, which are incorporated by reference herein in their entirety.

REFERENCE TO A SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 12, 2016, is named 47991-713_601_SL.txt and is 15,418,644 bytes in size.

BACKGROUND OF THE INVENTION

[0003] Certain diseases affecting eye function are associated with a deficiency in the expression of a gene, and in turn, a deficiency in the gene product. Examples of gene products for which increased expression can provide benefit in eye diseases or conditions include ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 and IDUA.

SUMMARY OF THE INVENTION

[0004] Disclosed herein, in some embodiments, are methods of treating an eye disease in a subject in need thereof by increasing the expression of a target protein or functional RNA by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site, an exon flanking the 3' splice site, and wherein the RIC pre-mRNA encodes the target protein or functional RNA, the method comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding the target protein or functional RNA, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding the target protein or functional RNA, thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of the target protein or functional RNA in the cells of the subject. In some embodiments, the eye disease is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital

amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome.

[0005] Also disclosed herein are methods of increasing expression of a target protein, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA, by cells having a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising contacting the cells with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, thereby increasing the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT,

RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the cells, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA.

[0006] In some embodiments of any of the aforementioned methods, the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA. In some embodiments, the target protein or the functional RNA is a compensating protein or a compensating functional RNA that functionally augments or replaces a target protein or functional RNA that is deficient in amount or activity in the subject. In some embodiments, the cells are in or from a subject having a condition caused by a deficient amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein.

[0007] In some embodiments of any of the aforementioned methods, the deficient amount of the target protein is caused by haploinsufficiency of the target protein, wherein the subject has a first allele encoding a functional target protein, and a second allele from which the target protein is not produced, or a second allele encoding a nonfunctional target protein, and wherein the antisense oligomer binds to a targeted portion of a RIC pre-mRNA transcribed from the first allele. In some embodiments, the subject has a condition caused by a disorder resulting from a deficiency in the amount or function of the target protein, wherein the subject has (a) a first mutant allele from which (i) the target protein is produced at a reduced level compared to production from a wild-type allele, (ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or (iii) the target protein is not produced, and (b) a second mutant allele from which (i) the target protein is produced at a reduced level compared to production from a wild-type allele, (ii) the target protein is produced in a form having reduced function compared to an equivalent wild type protein, or (iii) the target protein is not produced, and wherein when the subject has a first mutant allele a(iii), the second mutant allele is b(i) or b(ii), and wherein when the subject has a second mutant allele b(iii), the

first mutant allele is a(i) or a(ii), and wherein the RIC pre-mRNA is transcribed from either the first mutant allele that is a(i) or a(ii), and/or the second allele that is b(i) or b(ii). In some embodiments, the target protein is produced in a form having reduced function compared to the equivalent wild-type protein. In some embodiments, the target protein is produced in a form that is fully-functional compared to the equivalent wild-type protein.

[0008] In some embodiments of any of the aforementioned methods, the targeted portion of the RIC pre-mRNA is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron. In some embodiments, the targeted portion of the RIC pre-mRNA is in the retained intron within the region +69 relative to the 5' splice site of the retained intron to –79 relative to the 3' splice site of the retained intron.

[0009] In some embodiments of any of the aforementioned methods, the target protein is (a) ABCA4, (b) RPE65, (c) MYOC, (d) CNGA3, (e) MFSD8, (f) IDUA, (g) LRAT, (h) OPTN, (i) RGR, (j) TEAD1, (k) PAX6, (l) ROM1, (m) RDH5, (n) RDH12, (o) NR2E3, (p) RLBP1, (q) CTNS, (r) PER1, (s) FSCN2, (t) TCF4, (u) RDH8, (v) NXNL1, or (w) CRX. In some embodiments, the targeted portion of the RIC pre-mRNA comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to (a) any one of SEQ ID NOs 84-1126, (b) any one of SEQ ID NOs 1127-1528, (c) any one of SEQ ID NOs 1529-2318, (d) any one of SEQ ID NOs 2319-2770, (e) any one of SEQ ID NOs 2771-3631, (f) any one of SEQ ID NOs 3632-4443, (g) any one of SEQ ID NOs 4444-6647, (h) any one of SEQ ID NOs 6648-7579, (i) any one of SEQ ID NOs 7580-8958, (j) any one of SEQ ID NOs 8959-9163, (k) any one of SEQ ID NOs 9164-15179, (l) any one of SEQ ID NOs 15180-15486, (m) any one of SEQ ID NOs 15487-16202, (n) any one of SEQ ID NOs 16203-16458, (o) any one of SEQ ID NOs 16459-18209, (p) any one of SEQ ID NOs 18210-18638, (q) any one of SEQ ID NOs 18639-19534, (r) any one of SEQ ID NOs 19535-19845, (s) any one of SEQ ID NOs 19846-20849, (t) any one of SEQ ID NOs 20850-24737, (u) any one of SEQ ID NOs 24738-24873, (v) any one of SEQ ID NOs 24874-25231, or (w) any one of SEQ ID NOs 25232-26654. In some embodiments, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of (a) SEQ ID NO 26674, SEQ ID NO 26706, SEQ ID NO 26656, SEQ ID NO 26681, or SEQ ID NO 26664, (b) SEQ ID NO 26691 or SEQ ID NO 26671, (c) SEQ ID NO 26669 or SEQ ID NO 26696, (d) SEQ ID NO 26711, (e) SEQ ID NO 26703 or SEQ ID NO 26708, (f) SEQ ID NO 26668, SEQ ID NO 26679, SEQ ID NO 26700, SEQ ID NO 26655, or SEQ ID NO 26663, (g) SEQ ID NO 26685, (h) SEQ ID NO 26714, (i) SEQ ID NO 26657, SEQ ID NO 26687, or SEQ ID NO 26683, (j) SEQ ID NO 26672, (k) SEQ ID NO 26697, SEQ ID NO

26677, SEQ ID NO 26707, SEQ ID NO 26678, SEQ ID NO 26713, SEQ ID NO 26694, or SEQ ID NO 26659, (l) SEQ ID NO 26665, (m) SEQ ID NO 26704, SEQ ID NO 26666, SEQ ID NO 26709, or SEQ ID NO 26684, (n) SEQ ID NO 26693, (o) SEQ ID NO 26702, SEQ ID NO 26660, SEQ ID NO 26705, SEQ ID NO 26698, SEQ ID NO 26658, SEQ ID NO 26676, SEQ ID NO 26712 SEQ ID NO 26701, (p) SEQ ID NO 26673 or SEQ ID NO 26667, (q) SEQ ID NO 26690 or SEQ ID NO 26692, (r) SEQ ID NO 26682 or SEQ ID NO 26710, (s) SEQ ID NO 26670, SEQ ID NO 26662, or SEQ ID NO 26661, (t) SEQ ID NO 26688 or SEQ ID NO 26689, (u) SEQ ID NO 26680, (v) SEQ ID NO 26699, or (w) SEQ ID NO 26695 or SEQ ID NO 26686. In some embodiments, the ASO comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to (a) any one of SEQ ID NOs 84-1126, (b) any one of SEQ ID NOs 1127-1528, (c) any one of SEQ ID NOs 1529-2318, (d) any one of SEQ ID NOs 2319-2770, (e) any one of SEQ ID NOs 2771-3631, (f) any one of SEQ ID NOs 3632-4443, (g) any one of SEQ ID NOs 4444-6647, (h) any one of SEQ ID NOs 6648-7579, (i) any one of SEQ ID NOs 7580-8958, (j) any one of SEQ ID NOs 8959-9163, (k) any one of SEQ ID NOs 9164-15179, (l) any one of SEQ ID NOs 15180-15486, (m) any one of SEQ ID NOs 15487-16202, (n) any one of SEQ ID NOs 16203-16458, (o) any one of SEQ ID NOs 16459-18209, (p) any one of SEQ ID NOs 18210-18638, (q) any one of SEQ ID NOs 18639-19534, (r) any one of SEQ ID NOs 19535-19845, (s) any one of SEQ ID NOs 19846-20849, (t) any one of SEQ ID NOs 20850-24737, (u) any one of SEQ ID NOs 24738-24873, (v) any one of SEQ ID NOs 24874-25231, or (w) any one of SEQ ID NOs 25232-26654. In some embodiments, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to (a) SEQ ID NO 24, (b) SEQ ID NO 25, (c) SEQ ID NO 26, (d) SEQ ID NO 27 or SEQ ID NO 28, (e) SEQ ID NO 29, (f) SEQ ID NO 30 or SEQ ID NO 31, (g) SEQ ID NO 32 or SEQ ID NO 33, (h) SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, or SEQ ID NO 37, (i) SEQ ID NO 38, SEQ ID NO 39, or SEQ ID NO 40, (j) SEQ ID NO 41, (k) SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, , SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, or SEQ ID NO 52, (l) SEQ ID NO 53, (m) SEQ ID NO 54 or SEQ ID NO 55, (n) SEQ ID NO 56, (o) SEQ ID NO 57 or SEQ ID NO 58, (p) SEQ ID NO 59, (q) SEQ ID NO 60 or SEQ ID NO 61, (r) SEQ ID NO 62, (s)SEQ ID NO 63 or SEQ ID NO 64, (t) SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74, SEQ ID NO 75, SEQ ID NO 76, SEQ ID NO 77, SEQ ID NO 78, SEQ ID NO 79, or SEQ ID NO 80, (u) SEQ ID NO 81, (v) SEQ ID NO 82, or (w) SEQ ID NO 83. In some embodiments, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) SEQ ID NO 1, (b) SEQ ID NO 2, (c) SEQ ID NO 3, (d) SEQ ID NO 4, (e) SEQ ID NO 5, (f) SEQ ID NO 6, (g) SEQ ID NO 7, (h) SEQ ID NO 8, (i) SEQ ID NO 9, (j) SEQ ID NO 10, (k) SEQ ID NO 11, (l) SEQ ID NO 12, (m) SEQ ID NO 13, (n) SEQ ID NO 14, (o) SEQ ID NO 15, (p) SEQ ID NO 16, (q) SEQ ID NO 17, (r) SEQ ID NO 18, (s) SEQ ID NO 19, (t) SEQ ID NO 20, (u) SEQ ID NO 21, (v) SEQ ID NO 22, (w) SEQ ID NO 23.

[0010] In some embodiments of any of the aforementioned methods, the targeted portion of the RIC pre-mRNA is in the retained intron within: (a) the region +6 to +100 relative to the 5' splice site of the retained intron; or (b) the region -16 to -100 relative to the 3' splice site of the retained intron. In some embodiments, the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron. In some embodiments, the targeted portion of the RIC pre-mRNA is within: (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.

[0011] In some embodiments of any of the aforementioned methods, the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating alternative splicing of pre-mRNA transcribed from a gene encoding the functional RNA or target protein. In some embodiments, the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or the functional RNA. In some embodiments, the RIC pre-mRNA was produced by partial splicing of a full-length pre-mRNA or partial splicing of a wild-type pre-mRNA. In some embodiments, the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA. In some embodiments, the target protein produced is full-length protein, or wild-type protein. In some embodiments, the total amount of the mRNA encoding the target protein or functional RNA produced in the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of the mRNA encoding the

target protein or functional RNA produced in a control cell. In some embodiments, the total amount of target protein produced by the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of target protein produced by a control cell.

[0012] In some embodiments, of any of the aforementioned methods, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some embodiments, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some embodiments, the antisense oligomer comprises at least one modified sugar moiety. In some embodiments, each sugar moiety is a modified sugar moiety. In some embodiments, the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. In some embodiments, the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted portion of the RIC pre-mRNA encoding the protein.

[0013] In some embodiments of any of the aforementioned methods, the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the most abundant retained intron in the population of RIC pre-mRNAs. In some embodiments, the binding of the antisense oligomer to

the most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA. In some embodiments, the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the second most abundant retained intron in the population of RIC pre-mRNAs. In some embodiments, the binding of the antisense oligomer to the second most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA. In some embodiments, the condition is a disease or disorder. In some embodiments, the disease or disorder is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome. In some embodiments, the target protein and the RIC pre-mRNA are encoded by the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene. In some embodiments, the method further comprises assessing protein expression. In some embodiments, the antisense oligomer binds to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human animal. In some embodiments, the subject is a fetus, an embryo, or a child. In some embodiments, the cells are ex vivo. In some embodiments, the antisense oligomer is administered by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject.

In some embodiments, the 9 nucleotides at -3e to -1e of the exon flanking the 5' splice site and +1 to +6 of the retained intron, are identical to the corresponding wild-type sequence. In some embodiments, the 16 nucleotides at -15 to -1 of the retained intron and +1e of the exon flanking the 3' splice site are identical to the corresponding wild-type sequence.

[0014] Disclosed herein, in some embodiments, are antisense oligomers as used in the methods described herein. In some embodiments, the antisense oligomer comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs 84-26654.

[0015] Also disclosed herein, in some embodiments, are pharmaceutical compositions comprising any of the aforementioned antisense oligomers and an excipient.

[0016] Disclosed herein, in some embodiments, are methods of treating a subject in need thereof by administering any of the aforementioned pharmaceutical compositions by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0017] Disclosed herein, in some embodiments, are compositions comprising an antisense oligomer for use in a method of increasing expression of a target protein or a functional RNA by cells to treat Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome in a subject in need thereof associated with a deficient protein or deficient functional RNA, wherein the deficient protein or deficient functional RNA is deficient in amount or activity in the subject, wherein the antisense oligomer enhances constitutive splicing of a retained intron-containing pre-mRNA (RIC pre-mRNA) encoding the target protein or the functional RNA, wherein the target protein is: (a) the deficient protein; or (b) a compensating protein which functionally augments or replaces the deficient protein or in the subject; and wherein the

functional RNA is: (a) he deficient RNA; or (b) a compensating functional RNA which functionally augments or replaces the deficient functional RNA in the subject; wherein the RIC pre-mRNA comprises a retained intron, an exon flanking the 5' splice site and an exon flanking the 3' splice site, and wherein the retained intron is spliced from the RIC pre-mRNA encoding the target protein or the functional RNA, thereby increasing production or activity of the target protein or the functional RNA in the subject.

[0018] Disclosed herein, in some embodiments, are compositions comprising an antisense oligomer for use in a method of treating a condition associated with ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in a subject in need thereof, the method comprising the step of increasing expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA) comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising contacting the cells with the antisense oligomer, whereby the retained intron is constitutively spliced from the RIC pre-mRNA transcripts encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, in the cells of the subject. In some embodiments, the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA. In some embodiments, the condition is a disease or disorder. In some embodiments, the disease or disorder is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod

dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome. In some embodiments, the target protein and RIC pre-mRNA are encoded by the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene. In some embodiments, the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron. In some embodiments, the targeted portion of the RIC pre-mRNA is in the retained intron within the region +69 relative to the 5' splice site of the retained intron to –79relative to the 3' splice site of the retained intron. In some embodiments, the target protein is (a) ABCA4, (b) RPE65, (c) MYOC, (d) CNGA3, (e) MFSD8, (f) IDUA, (g) LRAT, (h) OPTN, (i) RGR, (j) TEAD1, (k) PAX6, (l) ROM1, (m) RDH5, (n) RDH12, (o) NR2E3, (p) RLBP1, (q) CTNS, (r) PER1, (s) FSCN2, (t) TCF4, (u) RDH8, (v) NXNL1, or (w) CRX. In some embodiments, the targeted portion of the RIC pre-mRNA comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to to (a) any one of SEQ ID NOs 84-1126, (b) any one of SEQ ID NOs 1127-1528, (c) any one of SEQ ID NOs 1529-2318, (d) any one of SEQ ID NOs 2319-2770, (e) any one of SEQ ID NOs 2771-3631, (f) any one of SEQ ID NOs 3632-4443, (g) any one of SEQ ID NOs 4444-6647, (h) any one of SEQ ID NOs 6648-7579, (i) any one of SEQ ID NOs 7580-8958, (j) any one of SEQ ID NOs 8959-9163, (k) any one of SEQ ID NOs 9164-15179, (l) any one of SEQ ID NOs 15180-15486, (m) any one of SEQ ID NOs 15487-16202, (n) any one of SEQ ID NOs 16203-16458, (o) any one of SEQ ID NOs 16459-18209, (p) any one of SEQ ID NOs 18210-18638, (q) any one of SEQ ID NOs 18639-19534, (r) any one of SEQ ID NOs 19535-19845, (s) any one of SEQ ID NOs 19846-20849, (t) any one of SEQ ID NOs 20850-24737, (u) any one of SEQ ID NOs 24738-24873, (v) any one of SEQ ID NOs 24874-25231, or (w) any one of SEQ ID NOs 25232-26654. In some embodiments, the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of (a) SEQ ID NO 26674, SEQ ID NO 26706, SEQ ID NO

26656, SEQ ID NO 26681, or SEQ ID NO 26664, (b) SEQ ID NO 26691 or SEQ ID NO 26671, (c) SEQ ID NO 26669 or SEQ ID NO 26696, (d) SEQ ID NO 26711, (e) SEQ ID NO 26703 or SEQ ID NO 26708, (f) SEQ ID NO 26668, SEQ ID NO 26679, SEQ ID NO 26700, SEQ ID NO 26655, or SEQ ID NO 26663, (g) SEQ ID NO 26685, (h) SEQ ID NO 26714, (i) SEQ ID NO 26657, SEQ ID NO 26687, or SEQ ID NO 26683, (j) SEQ ID NO 26672, (k) SEQ ID NO 26697, SEQ ID NO 26677, SEQ ID NO 26707, SEQ ID NO 26678, SEQ ID NO 26713, SEQ ID NO 26694, or SEQ ID NO 26659, (l) SEQ ID NO 26665, (m) SEQ ID NO 26704, SEQ ID NO 26666, SEQ ID NO 26709, or SEQ ID NO 26684, (n) SEQ ID NO 26693, (o) SEQ ID NO 26702, SEQ ID NO 26660, SEQ ID NO 26705, SEQ ID NO 26698, SEQ ID NO 26658, SEQ ID NO 26676, SEQ ID NO 26712 SEQ ID NO 26701, (p) SEQ ID NO 26673 or SEQ ID NO 26667, (q) SEQ ID NO 26690 or SEQ ID NO 26692, (r) SEQ ID NO 26682 or SEQ ID NO 26710, (s) SEQ ID NO 26670, SEQ ID NO 26662, or SEQ ID NO 26661, (t) SEQ ID NO 26688 or SEQ ID NO 26689, (u) SEQ ID NO 26680, (v) SEQ ID NO 26699, or (w) SEQ ID NO 26695 or SEQ ID NO 26686. In some embodiments, the ASO comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to (a) any one of SEQ ID NOs 84-1126, (b) any one of SEQ ID NOs 1127-1528, (c) any one of SEQ ID NOs 1529-2318, (d) any one of SEQ ID NOs 2319-2770, (e) any one of SEQ ID NOs 2771-3631, (f) any one of SEQ ID NOs 3632-4443, (g) any one of SEQ ID NOs 4444-6647, (h) any one of SEQ ID NOs 6648-7579, (i) any one of SEQ ID NOs 7580-8958, (j) any one of SEQ ID NOs 8959-9163, (k) any one of SEQ ID NOs 9164-15179, (l) any one of SEQ ID NOs 15180-15486, (m) any one of SEQ ID NOs 15487-16202, (n) any one of SEQ ID NOs 16203-16458, (o) any one of SEQ ID NOs 16459-18209, (p) any one of SEQ ID NOs 18210-18638, (q) any one of SEQ ID NOs 18639-19534, (r) any one of SEQ ID NOs 19535-19845, (s) any one of SEQ ID NOs 19846-20849, (t) any one of SEQ ID NOs 20850-24737, (u) any one of SEQ ID NOs 24738-24873, (v) any one of SEQ ID NOs 24874-25231, or (w) any one of SEQ ID NOs 25232-26654. In some embodiments, the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to (a) SEQ ID NO 24, (b) SEQ ID NO 25, (c) SEQ ID NO 26, (d) SEQ ID NO 27 or SEQ ID NO 28, (e) SEQ ID NO 29, (f) SEQ ID NO 30 or SEQ ID NO 31, (g) SEQ ID NO 32 or SEQ ID NO 33, (h) SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, or SEQ ID NO 37, (i) SEQ ID NO 38, SEQ ID NO 39, or SEQ ID NO 40, (j) SEQ ID NO 41, (k) SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, , SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, or SEQ ID NO 52, (l) SEQ ID NO 53, (m) SEQ ID NO 54 or SEQ ID NO 55, (n) SEQ ID NO 56, (o) SEQ ID NO 57 or SEQ ID NO 58, (p) SEQ ID NO 59, (q) SEQ ID NO 60 or SEQ ID NO 61, (r) SEQ ID NO 62, (s)SEQ ID NO 63 or SEQ ID NO 64, (t) SEQ

ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74, SEQ ID NO 75, SEQ ID NO 76, SEQ ID NO 77, SEQ ID NO 78, SEQ ID NO 79, or SEQ ID NO 80, (u) SEQ ID NO 81, (v) SEQ ID NO 82, or (w) SEQ ID NO 83. In some embodiments, the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to (a) SEQ ID NO 1, (b) SEQ ID NO 2, (c) SEQ ID NO 3, (d) SEQ ID NO 4, (e) SEQ ID NO 5, (f) SEQ ID NO 6, (g) SEQ ID NO 7, (h) SEQ ID NO 8, (i) SEQ ID NO 9, (j) SEQ ID NO 10, (k) SEQ ID NO 11, (l) SEQ ID NO 12, (m) SEQ ID NO 13, (n) SEQ ID NO 14, (o) SEQ ID NO 15, (p) SEQ ID NO 16, (q) SEQ ID NO 17, (r) SEQ ID NO 18, (s) SEQ ID NO 19, (t) SEQ ID NO 20, (u) SEQ ID NO 21, (v) SEQ ID NO 22, (w) SEQ ID NO 23. In some embodiments, the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within: (a) the region +6 to +100 relative to the 5' splice site of the retained intron; or (b) the region -16 to -100 relative to the 3' splice site of the retained intron. In some embodiments, the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron. In some embodiments, the targeted portion of the RIC pre-mRNA is within: (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.

[0019] Disclosed herein, in some embodiments, the antisense oligomer does not increase the amount of target protein or functional RNA by modulating alternative splicing of the pre-mRNA transcribed from a gene encoding the target protein or functional RNA. In some embodiments, the antisense oligomer does not increase the amount of the functional RNA or functional protein by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or functional RNA. In some embodiments, the RIC pre-mRNA was produced by partial splicing from a full-length pre-mRNA or a wild-type pre-mRNA. In some embodiments, the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA. In some embodiments, the target protein produced is full-length protein, or wild-type protein. In some embodiments, the retained intron is a rate-limiting intron. In some embodiments, the retained intron is the most abundant retained intron in the RIC pre-mRNA. In some embodiments, the retained intron is the second most abundant retained intron in the RIC pre-mRNA.

[0020] In some embodiments of any of the aforementioned compositions, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a

phosphorodiamidate linkage. In some embodiments, the antisense oligomer is an antisense oligonucleotide. In some embodiments, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some embodiments, the antisense oligomer comprises at least one modified sugar moiety. In some embodiments, each sugar moiety is a modified sugar moiety. In some embodiments, the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. In some embodiments, the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to the targeted portion of the RIC pre-mRNA encoding the protein. In some embodiments, the antisense oligomer binds to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA.

[0021] Disclosed herein, in some embodiments, are pharmaceutical compositions comprising the antisense oligomer of any of the aforementioned compositions and an excipient.

[0022] Disclosed herein, in some embodiments, are methods of treating a subject in need thereof by administering any of the aforementioned pharmaceutical compositions by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0023] Diclsoed herein, in some embodiments, are pharmaceutical compositions comprising: an antisense oligomer that hybridizes to a target sequence of a deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript comprises a retained intron, wherein the antisense oligomer induces splicing out of the retained intron from the deficient ROM1, TEAD1,

RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript; and a pharmaceutical acceptable excipient. In some embodiments, the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript. In some embodiments, the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is in the retained intron within the region +500 relative to the 5' splice site of the retained intron to -500 relative to the 3' spliced site of the retained intron. In some embodiments, the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 1-23. In some embodiments, the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 24-83. In some embodiments, the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some embodiments, the antisense oligomer is an antisense oligonucleotide. In some embodiments, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some embodiments, the antisense oligomer comprises at least one modified sugar moiety. In some embodiments, the antisense oligomer comprises from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. In some embodiments, the antisense oligomer is at least 80%, at least 85%, at least

90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript. In some embodiments, the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is within a sequence selected from SEQ ID NOs: 26655-26714. In some embodiments, the antisense oligomer comprises a nucleotide sequence that is at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 84-26654. In some embodiments, the antisense oligomer comprises a nucleotide sequence selected from SEQ ID NOs: 84-26654. In some embodiments, the pharmaceutical composition is formulated for intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

[0024] Disclosed herein, in some embodiments, are methods of inducing processing of a deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript to facilitate removal of a retained intron to produce a fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript that encodes a functional form of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising: (a) contacting an antisense oligomer to a target cell of a subject; (b) hybridizing the antisense oligomer to the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript is capable of encoding the functional form of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein and comprises at least one retained intron; (c) removing the at least one retained intron from the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4,

MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript to produce the fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript that encodes the functional form of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein; and (d) translating the functional form of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein from the fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript. In some embodiments, the retained intron is an entire retained intron. In some embodiments, the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript is a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript.

[0025] Disclosed herein, in some embodiments, are methods of treating a subject having a condition caused by a deficient amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein comprising administering to the subject an antisense oligomer comprising a nucleotide sequence with at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 84-26654.

INCORPORATION BY REFERENCE

[0026] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained

by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings.

[0028] FIG. 1 depicts a schematic representation of an exemplary retained-intron-containing (RIC) pre-mRNA transcript. The 5' splice site consensus sequence is indicated with underlined letters (letters are nucleotides; upper case: exonic portion and lower case: intronic portion) from -3e to -1e and +1 to +6 (numbers labeled "e" are exonic and unlabeled numbers are intronic). The 3' splice site consensus sequence is indicated with underlined letters (letters are nucleotides; upper case: exonic portion and lower case: intronic portion) from -15 to -1 and +1e (numbers labeled "e" are exonic and unlabeled numbers are intronic). Intronic target regions for ASO screening comprise nucleotides +6 relative to the 5' splice site of the retained intron (arrow at left) to -16 relative to the 3' splice site of the retained intron (arrow at right). In embodiments, intronic target regions for ASO screening comprise nucleotides +6 to +100 relative to the 5' splice site of the retained intron and -16 to -100 relative to the 3' splice site of the retained intron. Exonic target regions comprise nucleotides +2e to -4e in the exon flanking the 5' splice site of the retained intron and +2e to -4e in the exon flanking the 3' splice site of the retained intron. "n" or "N" denote any nucleotide, "y" denotes pyrimidine. The sequences shown represent consensus sequences for mammalian splice sites and individual introns and exons need not match the consensus sequences at every position.

[0029] FIG. 2A depicts an exemplary schematic representations of the Targeted Augmentation of Nuclear Gene Output (TANGO) approach. FIG. 2A shows a cell divided into nuclear and cytoplasmic compartments. In the nucleus, a pre-mRNA transcript of a target gene consisting of exons (rectangles) and introns (connecting lines) undergoes splicing to generate an mRNA, and this mRNA is exported to the cytoplasm and translated into target protein. For this target gene, the splicing of intron 1 is inefficient and a retained intron-containing (RIC) pre-mRNA accumulates primarily in the nucleus, and if exported to the cytoplasm, is degraded, leading to no target protein production.

[0030] FIG. 2B depicts an exemplary schematic representation of the Targeted Augmentation of Nuclear Gene Output (TANGO) approach. FIG. 2B shows an example of the same cell as in FIG. 2A divided into nuclear and cytoplasmic compartments. Treatment with an antisense oligomer (ASO) promotes the splicing of intron 1 and results in an increase in mRNA, which is in turn translated into higher levels of target protein.

[0031] FIG. 3 depicts a schematic of the RefSeq Genes for FSCN2 corresponding to NM_012418 and NM_001077182. The Percent Intron Retention (PIR) of the circled intron is shown.

[0032] **FIG. 4** depicts an exemplary graph showing the fold change in expression levels of FSCN2 mRNA without intron 1 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0033] **FIG. 5** depicts a schematic of the RefSeq Genes for FSCN2 corresponding to NM_012418 and NM_001077182. The Percent Intron Retention (PIR) of the circled intron is shown.

[0034] **FIG. 6** depicts an exemplary graph showing the fold change in expression levels of FSCN2 mRNA without intron 3 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0035] **FIG. 7** depicts an exemplary graph showing the fold change in expression levels of FSCN2 mRNA without intron 3 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0036] **FIG. 8** depicts a schematic of the RefSeq Genes for MFSD8 corresponding to NM_152778. The Percent Intron Retention (PIR) of the circled intron is shown.

[0037] **FIG. 9** depicts a schematic of the RefSeq Genes for MFSD8 corresponding to NM_152778. The Percent Intron Retention (PIR) of the circled intron is shown.

[0038] **FIG. 10** depicts an exemplary graph showing the fold change in expression levels of MFSD8 mRNA without intron 12 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0039] **FIG. 11** depicts a schematic of the RefSeq Genes for OPTN corresponding to NM_001008211, NM_00100212, NM_001008213, and NM_021980. The Percent Intron Retention (PIR) of the circled intron is shown.

[0040] **FIG. 12** depicts an exemplary graph showing the fold change in expression levels of OPTN mRNA without intron 7 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0041] **FIG. 13** depicts a schematic of the RefSeq Genes for RDH5 corresponding to NM_002905 and NM_001199771. The Percent Intron Retention (PIR) of the circled intron is shown.

[0042] **FIG. 14** depicts an exemplary graph showing the fold change in expression levels of RDH5 mRNA without intron 1 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0043] **FIG. 15** depicts a schematic of the RefSeq Genes for RDH5 corresponding to NM_002905 and NM_001199771. The Percent Intron Retention (PIR) of the circled intron is shown.

[0044] **FIG. 16** depicts a schematic of the RefSeq Genes for RLBP1 corresponding to NM_000326. The Percent Intron Retention (PIR) of the circled intron is shown.

[0045] **FIG. 17** depicts an exemplary graph showing the fold change in expression levels of RLBP1 mRNA without intron 2 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0046] **FIG. 18** depicts a schematic of the RefSeq Genes for TCF4 corresponding to NM_001243236, NM_00123235, NM_001243234, NM_001243233, NM_001243232, NM_001243231, NM_003199, NM_001306207, NM_ 001306208, NM_001243227, NM_001243228, NM_001243230, NM_001243226, NM_001083962, NM_001330605, and NM_001330604. The Percent Intron Retention (PIR) of the circled intron is shown.

[0047] **FIG. 19** depicts a schematic of the RefSeq Genes for ROM1 corresponding to NM_000327. The Percent Intron Retention (PIR) of the circled intron is shown.

[0048] **FIG. 20** depicts a schematic of the RefSeq Genes for CNGA3 corresponding to NM_001298 and NM_001079878. The Percent Intron Retention (PIR) of the circled intron is shown.

[0049] **FIG. 21** depicts a schematic of the RefSeq Genes for RGR corresponding to NM_002921, NM_001012722, and NM_001012720. The Percent Intron Retention (PIR) of the circled intron is shown.

[0050] **FIG. 22** depicts a schematic of the RefSeq Genes for RGR corresponding to NM_002921, NM_001012722, and NM_001012720. The Percent Intron Retention (PIR) of the circled intron is shown.

[0051] **FIG. 23** depicts a schematic of the RefSeq Genes for RPE65 corresponding to NM_000329. The Percent Intron Retention (PIR) of the circled intron is shown.

[0052] **FIG. 24** depicts a schematic of the RefSeq Genes for RPE65 corresponding to NM_000329. The Percent Intron Retention (PIR) of the circled intron is shown.

[0053] **FIG. 25** depicts a schematic of the RefSeq Genes for RDH8 corresponding to NM_015725. The Percent Intron Retention (PIR) of the circled intron is shown.

[0054] **FIG. 26** depicts a schematic of the RefSeq Genes for NXNL1 corresponding to NM_138454. The Percent Intron Retention (PIR) of the circled intron is shown.

[0055] **FIG. 27** depicts a schematic of the RefSeq Genes for ABCA4 corresponding to NM_000350. The Percent Intron Retention (PIR) of the circled intron is shown.

[0056] **FIG. 28** depicts a schematic of the RefSeq Genes for ABCA4 corresponding to NM_000350. The Percent Intron Retention (PIR) of the circled intron is shown.

[0057] **FIG. 29** depicts an exemplary graph showing the fold change in expression levels of ABCA4 mRNA without intron 38 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0058] **FIG. 30** depicts a schematic of the RefSeq Genes for ABCA4 corresponding to NM_000350. The Percent Intron Retention (PIR) of the circled intron is shown.

[0059] **FIG. 31** depicts a schematic of the RefSeq Genes for ABCA4 corresponding to NM_000350. The Percent Intron Retention (PIR) of the circled intron is shown.

[0060] **FIG. 32** depicts an exemplary graph showing the fold change in expression levels of ABCA4 mRNA without intron 40 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0061] **FIG. 33** depicts a schematic of the RefSeq Genes for ABCA4 corresponding to NM_000350. The Percent Intron Retention (PIR) of the circled intron is shown

[0062] **FIG. 34** depicts a schematic of the RefSeq Genes for RDH12 corresponding to NM_152443. The Percent Intron Retention (PIR) of the circled intron is shown.

[0063] **FIG. 35** depicts a schematic of the RefSeq Genes for IDUA corresponding to NM_000203 and NR_110313. The Percent Intron Retention (PIR) of the circled intron is shown.

[0064] **FIG. 36** depicts an exemplary graph showing the fold change in expression levels of IDUA mRNA without intron 3 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

[0065] **FIG. 37** depicts a schematic of the RefSeq Genes for IDUA corresponding to NM_000203 and NR_110313. The Percent Intron Retention (PIR) of the circled intron is shown.

[0066] **FIG. 38** depicts a schematic of the RefSeq Genes for IDUA corresponding to NM_000203 and NR_110313. The Percent Intron Retention (PIR) of the circled intron is shown.

[0067] **FIG. 39** depicts a schematic of the RefSeq Genes for IDUA corresponding to NM_000203 and NR_110313. The Percent Intron Retention (PIR) of the circled intron is shown.

[0068] **FIG. 40** depicts a schematic of the RefSeq Genes for IDUA corresponding to NM_000203 and NR_110313. The Percent Intron Retention (PIR) of the circled intron is shown.

[0069] **FIG. 41** depicts a schematic of the RefSeq Genes for CTNS corresponding to NM_004937 and NM_001031681. The Percent Intron Retention (PIR) of the circled intron is shown.

[0070] **FIG. 42** depicts a schematic of the RefSeq Genes for CTNS corresponding to NM_004937 and NM_001031681. The Percent Intron Retention (PIR) of the circled intron is shown.

[0071] **FIG. 43** depicts an exemplary graph showing the fold change in expression levels of CTNS mRNA without intron 10 in ARPE-19 cells treated for 24 hrs with 80 nM of the indicated ASOs over mock treated cells. Data is normalized to RPL32 expression.

DETAILED DESCRIPTION OF THE INVENTION

[0072] Individual introns in primary transcripts of protein-coding genes having more than one intron are spliced from the primary transcript with different efficiencies. In most cases only the fully spliced mRNA is exported through nuclear pores for subsequent translation in the cytoplasm. Unspliced and partially spliced transcripts are detectable in the nucleus. It is generally thought that nuclear accumulation of transcripts that are not fully spliced is a mechanism to prevent the accumulation of potentially deleterious mRNAs in the cytoplasm that may be translated to protein. For some genes, splicing of the least efficient intron is a rate-limiting post-transcriptional step in gene expression, prior to translation in the cytoplasm.

[0073] Substantial levels of partially-spliced transcripts encoding the: ROM1 protein, deficient in Retinitis pigmentosa-7; TEAD1 protein, deficient in Sveinsson chorioretinal atrophy; RDH5 protein, deficient in Fundus Albipunctatus; NR2E3 protein, deficient in Retinitis pigmentosa 37; PAX6 protein, deficient in Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia; CRX protein, deficient in Cone-rod dystrophy-2, Leber congenital amaurosis-7; FSCN2 protein, deficient in Retinitis Pigmentosa 30; ABCA4 protein, deficient in Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3; MYOC protein, deficient in Primary open angle glaucoma; TCF4 protein, deficient in Fuchs endothelial corneal dystrophy-3; MFSD8 protein, deficient Macular dystrophy with central cone involvement; CTNS protein, deficient in Ocular nonnephropathic cystinosis; NXNL1 protein, in Leber congenital amaurosis and Bardet-biedl syndrome; OPTN protein deficient in primary open angle glucoma and amyotrophic lateral sclerosis 12; RLBP1 protein deficient in bothnia retinal dystrophy, fundus albipunctatus and retinitis punctata albescens; RPE65 protein deficient in leber congenital amaurosis 2 and retinitis pigmentosa 20; LRAT protein deficient in leber congenital amaurosis 14 and retinitis pigmentosa; RDH8 protein in eye diseases with slow clearance or accumulation of all trans retinal; RDH12 protein deficient in leber congenital amaurosis 13 and retinitis pigmentosa; RGR protein deficient in retinitis pigmentosa 44; CNGA3 protein deficient in achromatopsia 2; PER1 protein in jet lag, ALMS1 protein deficient in Alstrom syndrome and IDUA protein deficient in attenuated MPS 1 (hurler-scheie syndrome and scheie syndrome) have been discovered in the nucleus of human cells. These ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR,

CNGA3, ALMS1, PER1 and IDUA pre-mRNA species comprise at least one retained intron. The present invention provides compositions and methods for upregulating splicing of one or more retained ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA introns that are rate-limiting for the nuclear stages of gene expression to increase steady-state production of fully-spliced, mature mRNA, and thus, translated ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein levels. These compositions and methods can utilize antisense oligomers (ASOs) that promote constitutive splicing at intron splice sites of a retained-intron-containing ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA (RIC pre-mRNA) that accumulates in the nucleus. Thus, in embodiments, ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein can be increased using the methods of the invention to treat a condition caused by ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, OPTN, RLBP1, RPE65, LRAT, RDH12, RGR, CNGA3, ALMS1 or IDUA deficiency. In embodiments, the condition is not caused by a deficiency of the target protein but is nonetheless treated by increasing production of the target protein using the present methods. In certain embodiments, wherein the condition that is not caused by a deficiency of the target protein but is nonetheless treated by increasing production of the target protein using the present methods, the target protein is RDH8, NXNL1, or PER1. In related embodiments, the condition treated is an in eye diseases with slow clearance or accumulation of all trans retinal and the target protein is RDH8, or the condition is jet lag, and the target protein is PER1.

[0074] In other embodiments, the methods of the invention can be used to increase ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA production to treat a condition in a subject in need thereof. In embodiments, the subject has a condition in which ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA is not necessarily deficient relative to wild-type, but where an increase in ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3,

ALMS1, PER1 or IDUA mitigates the condition nonetheless. In embodiments, the condition can be caused by a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA haploinsufficiency.

ROM1

[0075] ROM1 (retinal outer segment membrane protein 1) encodes Rod outer segment membrane protein 1. This gene is a member of a photoreceptor-specific gene family and encodes an integral membrane protein found in the photoreceptor disk rim of the eye. This protein can form homodimers or can heterodimerize with another photoreceptor, retinal degeneration slow (RDS). ROM1 is essential for disk morphogenesis, and may also function as an adhesion molecule involved in the stabilization and compaction of outer segment disks or in the maintenance of the curvature of the rim. Certain defects in this gene have been associated with the degenerative eye disease retinitis pigmentosa.

Retinitis pigmentosa-7 (RP7)

[0076] Retinitis pigmentosa 7 (RP7) is retinal dystrophy belonging to the group of pigmentary retinopathies. Retinitis pigmentosa is characterized by retinal pigment deposits visible on fundus examination and primary loss of rod photoreceptor cells followed by secondary loss of cone photoreceptors. Patients typically have night vision blindness and loss of midperipheral visual field. As their condition progresses, affected individuals lose their far peripheral visual field and eventually central vision as well. The disease may be caused by mutations affecting distinct genetic loci, including ROM1. A digenic form of retinitis pigmentosa 7 results from a mutation in the PRPH2 gene and a null mutation of the ROM1 gene has been reported.

TEAD1

[0077] *TEAD1* encodes Transcriptional enhancer factor TEF-1. Transcriptional enhancer factor TEF-1 is a transcription factor which plays a key role in the Hippo signaling pathway, a pathway involved in organ size control and tumor suppression by restricting proliferation and promoting apoptosis. The core of this pathway is composed of a kinase cascade wherein MST1/MST2, in complex with its regulatory protein SAV1, phosphorylates and activates LATS1/2 in complex with its regulatory protein MOB1, which in turn phosphorylates and inactivates YAP1 oncoprotein and WWTR1/TAZ. TEAD1 acts by mediating gene expression of YAP1 and WWTR1/TAZ, thereby regulating cell proliferation, migration and epithelial mesenchymal transition (EMT) induction. TEAD1 binds specifically and cooperatively to the SPH and GT-IIC 'enhansons' (5'-GTGGAATGT-3') and activates transcription in vivo in a cell-specific manner. The activation function appears to be mediated by a limiting cell-specific transcriptional

intermediary factor (TIF). TEAD1 is also involved in cardiac development, and binds to the M-CAT motif.

Sveinsson chorioretinal atrophy

[0078] Sveinsson chorioretinal atrophy is caused by a mutation in the TEA domain family member-1 gene TEAD1. Sveinsson's chorioretinal atrophy (SCRA), also referred to as helicoid peripapillary chorioretinal degeneration or atrophia areata, is an autosomal dominant eye disease, characterized by symmetrical lesions radiating from the optic disc involving the retina and the choroid.

RDH5

[0079] RDH5 encodes 11-cis retinol dehydrogenase. This enzyme belongs to the short-chain dehydrogenases/reductases (SDR) family. This retinol dehydrogenase functions to catalyze the final step in the biosynthesis of 11-cis retinaldehyde, which is the universal chromophore of visual pigments. Mutations in this gene cause autosomal recessive fundus albipunctatus, a rare form of night blindness that is characterized by a delay in the regeneration of cone and rod photopigments. Alternative splicing results in multiple transcript variants. Read-through transcription also exists between this gene and the neighboring upstream BLOC1S1 (biogenesis of lysosomal organelles complex-1, subunit 1) gene.

Fundus Albipunctatus

[0080] Fundus Albipuctatus is a rare form of night blindness that is characterized by a delay in the regeneration of cone and rod photopigments. This form of fleck retina disease is characterized by discrete uniform white dots over the entire fundus with greatest density in the midperiphery and no macular involvement. Night blindness occurs. Both autosomal dominant and autosomal recessive inheritance has been suggested.

NR2E3

[0081] NR2E3 encodes photoreceptor cell-specific nuclear receptor (PNR), also known as NR2E3 (nuclear receptor subfamily 2, group E, member 3). NR2E3 is a nuclear receptor of retinal photoreceptor cells. NR2E3 is a transcriptional factor that is an activator of rod development and repressor of cone development. NR2E3 binds the promoter region of a number of rod- and cone-specific genes, including rhodopsin, M- and S-opsin and rod-specific phosphodiesterase beta subunit. NR2E3 enhances rhodopsin expression and represses M- and S-cone opsin expression.

Retinitis pigmentosa 37

[0082] Retinitis pigmentosa 37 is caused by homozygous or heterozygous mutation in the NR2E3 gene. Retinitis pigmentosa 37 (RP37) is a retinal dystrophy belonging to the group of

pigmentary retinopathies. Retinitis pigmentosa is an inherited, degenerative eye disease that causes severe vision impairment due to the progressive degeneration of the rod photoreceptor cells in the retina. This form of retinal dystrophy manifests initial symptoms independent of age; thus, Retinitis pigmentosa diagnosis occurs anywhere from early infancy to late adulthood. Patients in the early stages of Retinitis pigmentosa first notice compromised peripheral and dim light vision due to the decline of the rod photoreceptors. The progressive rod degeneration is later followed by abnormalities in the adjacent retinal pigment epithelium (RPE) and the deterioration of cone photoreceptor cells. As peripheral vision becomes increasingly compromised, patients experience progressive "tunnel vision" and eventual blindness. Affected individuals may additionally experience defective light-dark adaptations, nyctalopia (night blindness), and the accumulation of bone spicules in the fundus.

PAX6

[0083] *PAX6* encodes Paired box protein Pax-6 also known as aniridia type II protein (AN2) or oculorhombin. PAX6, a member of the paired box gene family, and encodes a transcriptional regulator involved in oculogenesis and other developmental processes. Pax6 is a transcription factor present during embryonic development. The encoded protein contains two different binding sites that are known to bind DNA and function as regulators of gene transcription. PAX6 is a key regulatory gene of eye and brain development. Within the brain, the protein is involved in development of the specialized cells that process smell. As a transcription factor, Pax6 activates and/or deactivates gene expression patterns to ensure for proper development of the tissue.

Aniridia

[0084] Aniridia is caused by heterozygous mutation in the PAX6 gene on chromosome 11p13. More than 280 mutations in the *PAX6* gene have been found to cause aniridia, which is an absence of the iris. Most of these mutations lead to the production of an abnormally short, nonfunctional PAX6 protein. As a result, there is less PAX6 protein to regulate the activity of other genes.

[0085] The majority of mutations that cause aniridia occur within the PAX6 gene, however, some disease-causing mutations occur in neighboring regions of DNA that normally regulate the expression of the *PAX6* gene, known as regulatory regions. Mutations in PAX6 gene regulatory regions reduce the expression of the PAX6 gene. These mutations lead to a shortage of functional PAX6 protein, which disrupts the formation of the eyes during development.

[0086] Aniridia is an eye disorder characterized by a complete or partial absence of the colored part of the iris. These iris abnormalities may cause the pupils to be abnormal or misshapen.

Aniridia can cause reduction in visual acuity and increased sensitivity to light (photophobia). Individuals with aniridia can also have other eye problems. Increased pressure in the eye (glaucoma) typically appears in late childhood or early adolescence. Clouding of the lens of the eye (cataracts), occur in 50 percent to 85 percent of people with aniridia. In about 10 percent of affected people, the optic nerves are underdeveloped. Individuals with aniridia may also have involuntary eye movements (nystagmus) or underdevelopment of the region at the back of the eye responsible for sharp central vision (foveal hypoplasia). Many of these eye problems contribute to progressive vision loss in affected individuals. The severity of symptoms is typically the same in both eyes. Rarely, people with aniridia have behavioral problems, developmental delay, and problems detecting odors. Aniridia can be inherited in an autosomal dominant pattern. In approximately two-thirds of cases, an affected person inherits the mutation from one affected parent. The remaining one-third of cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Coloboma of the optic nerve

[0087] Coloboma of the optic nerve is caused by mutation in the PAX6 gene. Coloboma of the optic nerve is a congenital anomaly of the optic disc in which there is a defect of the inferior aspect of the optic nerve. Vision in the affected eye is impaired, the degree of which depends on the size of the defect, and typically affects the visual field more than visual acuity. Additionally, there is an increased risk of serous retinal detachment, manifesting in 1/3 of patients. If retinal detachment does occur, it is usually not correctable and all sight is lost in the affected area of the eye, which may or may not involve the macula.

Ocular coloboma

[0088] Ocular coloboma is caused by heterozygous mutation in the PAX6 gene on chromosome 11p13. Coloboma is an ocular birth defect resulting from abnormal development of the eye during embryogenesis. It is defined as a congenital defect in any ocular tissue, typically presenting as absent tissue or a gap, at a site consistent with aberrant closure of the optic fissure. Failure of fusion can lead to coloboma of one or multiple regions of the inferior portion of the eye affecting any part of the globe traversed by the fissure, from the iris to the optic nerve, including the ciliary body, retina, and choroid. Coloboma is also frequently associated with small (microphthalmic) or absent (anophthalmic) eyes as part of an interrelated spectrum of developmental eye anomalies, and can affect either one or both eyes.

Foveal hypoplasia-1

[0089] Foveal hypoplasia-1 with or without anterior segment anomalies and/or cataract (FVH1) is caused by heterozygous mutation in the PAX6 gene on chromosome 11p13. Foveal hypoplasia

is defined as the lack of foveal depression with continuity of all neurosensory retinal layers in the presumed foveal area. Foveal hypoplasia as an isolated entity is a rare phenomenon; it is usually described in association with other ocular disorders, such as aniridia, microphthalmia, albinism, or achromatopsia. All reported cases of foveal hypoplasia have been accompanied by decreased visual acuity and nystagmus.

Bilateral optic nerve hypoplasia

[0090] Bilateral optic nerve hypoplasia can be caused by mutations in the PAX6 gene. Optic nerve hypoplasia is a medical condition arising from the underdevelopment of the optic nerve(s). This condition is the most common congenital optic nerve anomaly. The optic disc appears abnormally small, because not all the optic nerve axons have developed properly. It is often associated with endocrinopathies (hormone deficiencies), developmental delay, and brain malformations. The optic nerve, which is responsible for transmitting visual signals from the retina to the brain, has approximately 1.2 million nerve fibers in the average person. In those diagnosed with Optic nerve hypoplasia, however, there are noticeably fewer nerves. Optic nerve hypoplasia can be unilateral (in one eye) or bilateral (in both eyes), although it presents most often bilaterally (80%). Because the unilateral cases tend to have better vision, they are typically diagnosed at a later age than those with bilateral Optic nerve hypoplasia. Visual acuity can range from no light perception to near-normal vision.

CRX

[0091] CRX encodes Cone-rod homeobox protein. Cone-rod homeobox protein is a photoreceptor-specific transcription factor which plays a role in the differentiation of photoreceptor cells. This homeodomain protein is necessary for the maintenance of normal cone and rod function. Cone-rod homeobox protein is a transcription factor that binds and transactivates the sequence 5'-TAATC[CA]-3' which is found upstream of several photoreceptor-specific genes, including the opsin genes. CRX acts synergistically with other transcription factors, such as NRL, RORB and RAX, to regulate photoreceptor cell-specific gene transcription and is essential for the maintenance of mammalian photoreceptors.

Cone-rod dystrophy-2 (CORD2)

[0092] Cone-rod dystrophy-2 (CORD2) is caused by heterozygous mutation in the CRX gene on chromosome 19q13. Cone-rod dystrophy 2 (CORD2) is an inherited retinal dystrophy characterized by retinal pigment deposits visible on fundus examination, predominantly in the macular region, and initial loss of cone photoreceptors followed by rod degeneration. This leads to decreased visual acuity and sensitivity in the central visual field, followed by loss of peripheral vision. Severe loss of vision occurs earlier than in retinitis pigmentosa.

Leber congenital amaurosis-7

[0093] Leber congenital amaurosis-7 can be caused by heterozygous or homozygous mutation in the CRX gene on chromosome 19q13. Leber congenital amaurosis comprises a group of early-onset childhood retinal dystrophies characterized by vision loss, nystagmus, and severe retinal dysfunction. Patients usually present at birth with profound vision loss and pendular nystagmus. Electroretinogram (ERG) responses are usually nonrecordable. Other clinical findings may include high hypermetropia, photodysphoria, oculodigital sign, keratoconus, cataracts, and a variable appearance to the fundus

FSCN2

[0094] FSCN2 encodes Fascin-2. This gene encodes a member of the fascin protein family. Fascins crosslink actin into filamentous bundles within dynamic cell extensions. This family member is proposed to play a role in photoreceptor disk morphogenesis. A mutation in this gene results in one form of autosomal dominant retinitis pigmentosa and macular degeneration. Multiple transcript variants encoding different isoforms have also been found.

Retinitis pigmentosa 30

[0095] Petinitis pigmentosa 30 is caused by mutation in the retinal fascin gene (FSCN2) on chromosome 17q25.Retinitis pigmentosa 30 (RP30) is a retinal dystrophy belonging to the group of pigmentary retinopathies. Retinitis pigmentosa is characterized by retinal pigment deposits visible on fundus examination and primary loss of rod photoreceptor cells followed by secondary loss of cone photoreceptors. Patients typically have night vision blindness and loss of midperipheral visual field. As their condition progresses, they lose their far peripheral visual field and eventually central vision as well.

ABCA4

[0096] *ABCA4* encodes ATP-binding cassette, sub-family A (ABC1), member 4, also known as ABCA4 or ABCR. ABCA4 is a member of the ATP-binding cassette transporter gene sub-family A (ABC1) found exclusively in multicellular eukaryotes. The ABCA4 protein is produced in photoreceptors. The ABCA4 protein is active following phototransduction, the process by which light entering the eye is converted into electrical signals that are transmitted to the brain. Phototransduction leads to the formation of potentially toxic substances. The ABCA4 protein removes one of these substances, called N-retinylidene-PE, from photoreceptor cells.

Stargardt disease-1 (STGD1)

[0097] Stargardt disease-1 (STGD1) is caused by homozygous or compound heterozygous mutation in the ABCA4 gene (601691) on chromosome 1p22. Stargardt macular degeneration is a genetic eye disorder that causes progressive vision loss. This disorder affects the retina.

Specifically, Stargardt macular degeneration affects a small area near the center of the retina called the macula. The macula is responsible for sharp central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. In most people with Stargardt macular degeneration, a fatty yellow pigment (lipofuscin) builds up in cells underlying the macula. Over time, the abnormal accumulation of this substance can damage cells that are critical for clear central vision. In addition to central vision loss, people with Stargardt macular degeneration have problems with night vision that can make it difficult to navigate in low light. Some affected individuals also have impaired color vision. The signs and symptoms of Stargardt macular degeneration typically appear in late childhood to early adulthood and worsen over time.

[0098] More than 500 mutations in the *ABCA4* gene have been found to cause Stargardt macular degeneration. Most of these mutations change single amino acids in the ABCA4 protein. A malfunctioning ABCA4 protein cannot remove N-retinylidene-PE from photoreceptor cells. As a result, N-retinylidene-PE combines with another substance to produce a fatty yellow pigment called lipofuscin, which builds up in retinal cells. The buildup of lipofuscin is toxic to the cells of the retina and causes progressive vision loss in people with Stargardt macular degeneration. In most cases, Stargardt macular degeneration is caused by mutations in the *ABCA4* gene.

Retinitis pigmentosa-19 (RP19)

[0099] Retinitis Pigmentosa-19 (RP19) can be caused by homozygous or compound heterozygous mutation in the ABCR gene (ABCA4) on chromosome 1p22. Retinitis pigmentosa is an inherited eye disorder characterized by progressive loss of peripheral vision and night vision difficulties that can cause central vision loss. There are a large number of genes linked to retinitis pigmentosa. Type 19 is linked to a genetic defect on chromosome 1p21-p13. Retinitis Pigmentosa-19 is characterized by night-blindness, peripheral loss of vision, progressive retinal degeneration, tunnel vision, progressive vision loss, decreased vision at night or in low light, loss of central vision in advanced phases, and retinal pigment epithelium mottling.

Age-related macular degeneration-2 (ARMD2)

[00100] Age-related macular degeneration-2 (ARMD2) is conferred by variation in the ABCA4 gene on chromosome 1p22. Age-related macular degeneration is an eye disease that is a leading cause of vision loss in older people in developed countries. The vision loss usually becomes noticeable in a person's sixties or seventies and tends to worsen over time. Age-related macular degeneration mainly affects central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. The vision loss in this condition results from a gradual deterioration of light-sensing cells in the tissue at the back of the eye that detects light and color (the retina). Specifically, age-related macular degeneration affects a small area near the center of

the retina, called the macula, which is responsible for central vision. Side (peripheral) vision and night vision are generally not affected. Researchers have described two major types of age-related macular degeneration, known as the dry form and the wet form. The dry form is much more common, accounting for 85 to 90 percent of all cases of age-related macular degeneration. It is characterized by a buildup of yellowish deposits called drusen beneath the retina and slowly progressive vision loss. The condition typically affects vision in both eyes, although vision loss often occurs in one eye before the other. The wet form of age-related macular degeneration is associated with severe vision loss that can worsen rapidly. This form of the condition is characterized by the growth of abnormal, fragile blood vessels underneath the macula. These vessels leak blood and fluid, which damages the macula and makes central vision appear blurry and distorted.

Cone-rod dystrophy-3 (CORD3)

[00101] Cone-rod dystrophy-3 (CORD3) is caused by homozygous or compound heterozygous mutation in the ABCA4 on chromosome 1p22. Cone rod dystrophies are inherited retinal dystrophies that belong to the group of pigmentary retinopathies. The prevalence of Cone rod dystrophie is estimated at 1 in 40,000. Cone rod dystrophies are characterized by retinal pigment deposits, visible on fundus examination, predominantly localized to the macular region. In contrast to typical retinitis pigmentosa (RP), also called the rod cone dystrophies (RCDs), resulting from the primary loss in rod photoreceptors and later followed by the secondary loss in cone photoreceptors, Cone rod dystrophies reflect the opposite sequence of events. Cone rod dystrophy is characterized by primary cone involvement or, sometimes, by concomitant loss of both cones and rods, explaining the predominant symptoms of Cone rod dystrophies: decreased visual acuity, color vision defects, photoaversion and decreased sensitivity in the central visual field, later followed by progressive loss in peripheral vision and night blindness. The clinical course of Cone rod dystrophies is generally more severe and rapid than that of RCDs, leading to earlier legal blindness and disability. At end stage, however, Cone rod dystrophies do not differ from RCDs. Cone rod dystrophies are most frequently nonsyndromic, but they may also be part of several syndromes, such as Bardet-Biedl syndrome and Spinocerebellar Ataxia Type 7 (SCA7). Nonsyndromic Cone rod dystrophies are genetically heterogeneous (ten cloned genes and three loci have been identified so far). The four major causative genes involved in the pathogenesis of Cone rod dystrophies are ABCA4 (which causes Stargardt disease and also 30 to 60% of autosomal recessive Cone rod dystrophies), CRX and GUCY2D (which are responsible for many reported cases of autosomal dominant Cone rod dystrophies), and RPGR (which causes about 2/3 of X-linked RP and also an undetermined percentage of X-linked Cone rod

dystrophies). It is likely that highly deleterious mutations in genes that otherwise cause RP or macular dystrophy may also lead to Cone rod dystrophies. The diagnosis of Cone rod dystrophies is based on clinical history, fundus examination and electroretinogram. Moleculardiagnosis can be made for some genes, genetic counseling is always advised. Currently, there is no therapy that stops the evolution of the disease or restores the vision, and the visual prognosis is poor. Management aims at slowing down the degenerative process, treating the complications and helping patients to cope with the social and psychological impact of blindness.

MYOC

[00102] The *MYOC* gene encodes myocilin. Myocilin is found in the trabecular meshwork and the ciliary body, that regulate intraocular pressure. It is also found in various types of muscle. Myocilin's function is not well understood, but it may help to control the intraocular pressure through its action in the muscle tissue of the ciliary body. Researchers believe that myocilin functions together with other proteins as part of a protein complex. Myocilin may interact with a number of other proteins including a form of the cytochrome P450 protein, the product of the *CYP1B1* gene.

Primary open angle glaucoma

[00103] Primary open angle glaucoma (POAG), designated GLC1A, is caused by heterozygous mutation in the MYOC gene on chromosome 1q. There are no symptoms associated with POAG. The pressure in the eye slowly rises and the cornea adapts without swelling. If the cornea were to swell, which is usually a signal that something is wrong, symptoms would be present. But as this is not the case, this disease often goes undetected. It is painless, and the patient often does not realize that he or she is slowly losing vision until the later stages of the disease. However, by the time the vision is impaired, the damage is irreversible. Glaucoma is a group of eye disorders in which the optic nerves connecting the eyes and the brain are progressively damaged. This damage can lead to reduction in side (peripheral) vision and eventual blindness. Other signs and symptoms may include bulging eyes, excessive tearing, and abnormal sensitivity to light (photophobia). The term "early-onset glaucoma" may be used when the disorder appears before the age of 40. In most people with glaucoma, the damage to the optic nerves is caused by increased pressure within the eyes (intraocular pressure). Intraocular pressure depends on a balance between fluid entering and leaving the eyes. Usually glaucoma develops in older adults, in whom the risk of developing the disorder may be affected by a variety of medical conditions including high blood pressure (hypertension) and diabetes mellitus, as well as family history. The risk of early-onset glaucoma depends mainly on heredity. Structural abnormalities that impede fluid drainage in the eye may be present at birth and usually become apparent during

the first year of life. Such abnormalities may be part of a genetic disorder that affects many body systems, called a syndrome. If glaucoma appears before the age of 5 without other associated abnormalities, it is called primary congenital glaucoma. Other individuals experience early onset of primary open-angle glaucoma, the most common adult form of glaucoma. If primary open-angle glaucoma develops during childhood or early adulthood, it is called juvenile open-angle glaucoma.

TCF4

[00104] TCF4 encodes TCF4, or sometimes referred to as immunoglobulin transcription factor 2. TCF4 is a broadly expressed basic helix-loop-helix (bHLH) protein that functions as a homodimer or as a heterodimer with other bHLH proteins. These dimers bind DNA at Ephrussi (E) box sequences. Alternative splicing produces numerous N-terminally distinct TCF4 isoforms that differ in their subcellular localization and transactivational capacity. TCF4 proteins act as transcription factors which will bind to the immunoglobulin enhancer mu-E5/kappa-E2 motif. TCF4 activates transcription by binding to the E-box (5'-CANNTG-3') found usually on SSTR2-INR, or somatostatin receptor 2 initiator element. TCF4 is primarily involved in neurological development of the fetus during pregnancy by initiating neural differentiation by binding to DNA. It is found in the central nervous system, somites, and gonadal ridge during early development. Later in development it will be found in the thyroid, thymus, and kidneys while in adulthood TCF4 it will be found in lymphocytes, muscles, and gastrointestinal system.

Fuchs endothelial corneal dystrophy-3 (FECD3)

[00105] Fuchs endothelial corneal dystrophy-3 (FECD3) is caused by heterozygous intronic trinucleotide repeat expansion (CTG)n in the TCF4 gene on chromosome 18q22. Late-onset Fuchs endothelial corneal dystrophy (FECD) is a degenerative disorder affecting roughly 4% of the population older than 40 years. It is distinguished from other corneal disorders by the progressive formation of guttae, which are microscopic refractile excrescences of the Descemet membrane, a collagen-rich basal lamina secreted by the corneal endothelium. From onset, it usually takes 2 decades for FECD to impair endothelial cell function seriously, leading to stromal edema and impaired vision. The first symptom of this condition is typically blurred vision in the morning that usually clears during the day. Over time, affected individuals lose visual acuity. People with Fuchs endothelial dystrophy also become sensitive to bright lights. Fuchs endothelial dystrophy specifically affects the front surface of the eye called the cornea. Deposits called guttae, which are detectable during an eye exam, form in the middle of the cornea and eventually spread. These guttae contribute to the loss of cells in the cornea, leading to vision problems. Tiny blisters may develop on the cornea, which can burst and cause eye pain. The signs and symptoms

of Fuchs endothelial dystrophy usually begin in a person's forties or fifties. A very rare early-onset variant of this condition starts to affect vision in a person's twenties.

MFSD8

[00106] MFSD8 encodes Major facilitator superfamily domain containing 8 also known as MFSD8. The MFSD8 protein is found in cell lysosomes. The MFSD8 protein belongs to a large group of related proteins called the major facilitator superfamily of secondary active transporter proteins. Proteins in this family move certain molecules between structures in cells or in and out of cells. While it is likely that the MFSD8 protein transports molecules, the specific molecules it moves are unknown. The MFSD8 protein probably transports substances across the membranes of lysosomes.

Macular dystrophy with central cone involvement (CCMD)

[00107] Macular dystrophy with central cone involvement (CCMD) is caused by compound heterozygous mutation in the MFSD8 gene on chromosome 4q28. This is primarily a cone dystrophy but there is evidence of some rod damage in older patients. A mild decrease in central acuity is noted by individuals in the third to sixth decades. Slight pigmentary changes and color vision abnormalities can be documented with the onset of these symptoms and a bull's eye maculopathy and severe atrophy of the central fovea may be present. An enlarging central scotoma with normal periphery can sometimes be identified. Other patients have an atrophic appearance to the peripapillary area with a pale optic disc. Compound heterozygosity for a missense mutation and a nonsense mutation in the MFSD8 gene (4q28.2) has been found among members of a Dutch sibship suggesting autosomal recessive inheritance.

CTNS

[00108] The CTNS gene encodes called cystinosin. This protein is located in the membrane of lysosomes, which are compartments in the cell that digest and recycle materials. Proteins digested inside lysosomes are broken down into smaller amino acids. The amino acids are then moved out of lysosomes by transport proteins. Cystinosin is a transport protein that specifically moves the amino acid cystine out of the lysosome.

Ocular nonnephropathic cystinosis

[00109] Ocular nonnephropathic cystinosis is caused by mutation in the gene encoding cystinosin (CTNS) which maps to chromosome 17p13. Ocular nonnephropathic cystinosis, a variant of the classic nephropathic type of cystinosis, is an autosomal recessive lysosomal storage disorder characterized by photophobia due to corneal cystine crystals but absence of renal disease. More than 80 different mutations that are responsible for causing cystinosis have been identified in the CTNS gene. The most common mutation is a deletion of a large part of the

CTNS gene (sometimes referred to as the 57-kb deletion), resulting in the complete loss of cystinosin. This deletion is responsible for approximately 50 percent of cystinosis cases in people of European descent. Other mutations result in the production of an abnormally short protein that cannot carry out its normal transport function. Mutations that change very small regions of the CTNS gene may allow the transporter protein to retain some of its usual activity, resulting in a milder form of cystinosis.

NXNL1

[00110] NXNL1 encodes Nucleoredoxin-Like 1 (NXNL1). NXNL1 may play a role in cone cell viability, slowing down cone degeneration. NXNL1 does not seem to play a role in degenerating rods. Diseases associated with NXNL1 include leber congenital amaurosis and bardet-biedl syndrome. Leber congenital amaurosis is an eye disorder that primarily affects the retina. Individuals with this condition typically have severe visual impairment beginning in infancy. Other features include photophobia, involuntary movements of the eyes (nystagmus), and extreme farsightedness. The pupils also do not react normally to light. Additionally, the cornea may be cone-shaped and abnormally thin (keratoconus). Franceschetti's oculo-digital sign is characteristic of leber congenital amaurosis. This sign consists of poking, pressing, and rubbing the eyes with a knuckle or finger. At least 13 types of this condition have been described, which are distinguished by their genetic cause, patterns of vision loss, and related eye abnormalities.

[00111] Bardet-biedl syndrome is an inherited condition that affects many parts of the body. Individuals with this condition have progressive visual impairment due to cone-rod dystrophy, extra fingers or toes (polydactyly), truncal obesity, decreased function of the male gonads (hypogonadism), kidney abnormalities, and learning difficulties. At least 14 genes are known to be associated with bardet-biedl syndrome. This condition is usually inherited in an autosomal recessive pattern.

OPTN

[00112] The OPTN gene encodes the coiled-coil containing protein optineurin. Optineurin may play a role in normal-tension glaucoma and adult-onset primary open angle glaucoma. Optineurin interacts with adenovirus E3-14.7K protein and may utilize tumor necrosis factor-alpha or Fas-ligand pathways to mediate apoptosis, inflammation or vasoconstriction. Optineurin may also function in cellular morphogenesis and membrane trafficking, vesicle trafficking, and transcription activation through its interactions with the RAB8, huntingtin, and transcription factor IIIA proteins. Alternative splicing results in multiple transcript variants encoding the same protein.

[00113] Optineurin plays an important role in the maintenance of the Golgi complex, in membrane trafficking, in exocytosis, through its interaction with myosin VI and Rab8. Optineurin links myosin VI to the Golgi complex and plays an important role in Golgi ribbon formation. Optineurin negatively regulates the induction of IFNB in response to RNA virus infection. Optineurin plays a neuroprotective role in the eye and optic nerve. Optineurin is indicated as part of the TNF-alpha signaling pathway that can shift the equilibrium toward induction of cell death. Optineurin may act by regulating membrane trafficking and cellular morphogenesis via a complex that contains Rab8 and hungtingtin (HD). Optineurin mediates the interaction of Rab8 with the probable GTPase-activating protein TBC1D17 during Rab8-mediated endocytic trafficking, such as of transferrin receptor (TFRC/TfR); regulates Rab8 recruitment to tubules emanating from the endocytic recycling compartment. Autophagy receptor that interacts directly with both the cargo to become degraded and an autophagy modifier of the MAP1 LC3 family; targets ubiquitin-coated bacteria (xenophagy), such as cytoplasmic Salmonella enterica, and appears to function in the same pathway as SQSTM1 and CALCOCO2/NDP52. Optineurin may constitute a cellular target for adenovirus E3 14.7, an inhibitor of TNF-alpha functions, thereby affecting cell death.

Primary Open Angle Glaucoma;

[00114] Primary open angle glaucoma (POAG) is characterized by a specific pattern of optic nerve and visual field defects. The angle of the anterior chamber of the eye is open, and usually the intraocular pressure is increased. However, glaucoma can occur at any intraocular pressure. The disease is generally asymptomatic until the late stages, by which time significant and irreversible optic nerve damage has already taken place. The disease is caused by mutations affecting the OPTN gene

Amyotrophic Lateral Sclerosis 12

[00115] Amyotrophic lateral sclerosis 12 (ALS12) is a neurodegenerative disorder affecting upper motor neurons in the brain and lower motor neurons in the brain stem and spinal cord, resulting in fatal paralysis. Sensory abnormalities are absent. The pathologic hallmarks of the disease include pallor of the corticospinal tract due to loss of motor neurons, presence of ubiquitin-positive inclusions within surviving motor neurons, and deposition of pathologic aggregates. The etiology of amyotrophic lateral sclerosis is likely to be multifactorial, involving both genetic and environmental factors. The disease is inherited in 5-10% of the cases.

[00116] In some cases, in a patient with amyotrophic lateral sclerosis 12, heterozygous mutations in the OPTN (G538EfsX27) and TBK1 (R117X) genes can be identified. In some cases, in a patient with amyotrophic lateral sclerosis 12, a deletion of exon 5 can be identified. In

some cases, in a patient with amyotrophic lateral sclerosis 12, a nonsense mutation (Q398X) can be identified. In some cases, in a patient with amyotrophic lateral sclerosis 12, heterozygosity for a missense mutation (E478G) within the OPTN ubiquitin-binding domain can be identified.

RLBP1

[00117] The RLBP1 gene encodes is a 36-kD water-soluble protein which carries 11-cis-retinaldehyde or 11-cis-retinal as physiologic ligands. The RLBP1 protein may be a functional component of the visual cycle. Mutations of this gene have been associated with severe rod-cone dystrophy, Bothnia dystrophy (nonsyndromic autosomal recessive retinitis pigmentosa) and retinitis punctata albescens.

Bothnia Retinal Dystrophy

[00118] Bothnia retinal dystrophy (BRD) is a type of retinitis punctata albescens. Affected individuals show night blindness from early childhood with features consistent with retinitis punctata albescens and macular degeneration. The disease is caused by mutations affecting the RLBP1 gene.

Fundus Albipunctatus

[00119] Fundus albipunctatus is a retinal disorder characterized by night blindness and delayed dark adaptation after exposure to bright light, which typically presents during early childhood. The fundi of affected individuals contain multiple small, white or pale yellow dots in the retinal pigment epithelium, which may or may not involve the macula. These dots can remain unchanged, become more prominent, or can fade during aging; new dots may also appear. The dark-adaptation curve of affected individuals features prolonged recovery of cone and rod sensitivity and electroretinogram cone and rod amplitudes are markedly reduced after 30-40 minutes of dark adaptation; however, they may come to normal or near-normal levels after many hours of adaptation showed that approximately 38% of individuals with fundus albipunctatus have extensive cone dysfunction. Mutations in the RLBP1 gene have also been reported in fundus albipunctatus patients.

Retinitis Punctata Albescens

[00120] Retinitis punctata albescens (RPA) is a form of fleck retina disease characterized by aggregation of white flecks posteriorly in the retina, causing night blindness and delayed dark adaptation. It differs from fundus albipunctatus in being progressive and evolving to generalized atrophy of the retina. The disease is caused by mutations affecting the RLBP1 gene.

RPE65

[00121] The RPE65 gene alos “retinal pigment epithelium-specific protein 65kDa.” The *RPE65* gene encodes the RPE65 protein that is essential for normal vision. The RPE65 protein is

produced in the retinal pigment epithelium (RPE). The RPE supports and nourishes the retina, which is the light-sensitive tissue that lines the back of the eye. The RPE65 protein is involved in a multi-step process called the visual cycle, which converts light entering the eye into electrical signals that are transmitted to the brain. When light hits photosensitive pigments in the retina, it changes 11-cis retinal (a form of vitamin A) to all-trans retinal. This conversion triggers a series of chemical reactions that create electrical signals. The RPE65 protein then helps convert all-trans retinal back to 11-cis retinal so the visual cycle can begin again

Leber CongenitalAamaurosis 2

[00122] Leber congenital amaurosis is an eye disorder that primarily affects the retina, which is the specialized tissue at the back of the eye that detects light and color. People with this disorder typically have severe visual impairment beginning in infancy. The visual impairment tends to be stable, although it may worsen very slowly over time.

[00123] Leber congenital amaurosis is also associated with other vision problems, including an increased sensitivity to light (photophobia), involuntary movements of the eyes (nystagmus), and extreme farsightedness (hyperopia). The pupils, which usually expand and contract in response to the amount of light entering the eye, do not react normally to light. Instead, they expand and contract more slowly than normal, or they may not respond to light at all. Additionally, the clear front covering of the eye (the cornea) may be cone-shaped and abnormally thin, a condition known as keratoconus.

[00124] A specific behavior called Franceschetti's oculo-digital sign is characteristic of Leber congenital amaurosis. This sign consists of poking, pressing, and rubbing the eyes with a knuckle or finger. Researchers suspect that this behavior may contribute to deep-set eyes and keratoconus in affected children.

[00125] In rare cases, delayed development and intellectual disability have been reported in people with the features of Leber congenital amaurosis. However, it is uncertain whether these individuals actually have Leber congenital amaurosis or another syndrome with similar signs and symptoms. At least 13 types of Leber congenital amaurosis have been described. The types are distinguished by their genetic cause, patterns of vision loss, and related eye abnormalities. Leber Congenital Aamaurosis 2 is distinguished by moderate visual impairment at infancy that progresses to total blindness by mid to late adulthood. One of the unique qualities of Leber Congenital Aamaurosis 2 is that, even with profound early visual impairment, retinal cells are relatively preserved.

[00126] In some cases, in patients with leber congenital amaurosis 2, compound heterozygosity for mutations in the RPE65 gene, a 1-bp deletion and/or a nonsense mutation can be identified.

Retinitis Pigmentosa 20

[00127] Retinitis pigmentosa 20 is retinal dystrophy belonging to the group of pigmentary retinopathies. Retinitis pigmentosa is characterized by retinal pigment deposits visible on fundus examination and primary loss of rod photoreceptor cells followed by secondary loss of cone photoreceptors. Patients typically have night vision blindness and loss of midperipheral visual field. As their condition progresses, they lose their far peripheral visual field and eventually central vision as well.

LRAT

[00128] LRAT gene, or lecithin retinol acyltransferase (phosphatidylcholine--retinol O-acyltransferase) encodes the LRAT protein that localized to the endoplasmic reticulum, where it catalyzes the esterification of all-trans-retinol into all-trans-retinyl ester. This reaction is an important step in vitamin A metabolism in the visual system. Mutations in this gene have been associated with early-onset severe retinal dystrophy and Leber congenital amaurosis 14. Alternative splicing results in multiple transcript variants. The LRAT protein transfers the acyl group from the sn-1 position of phosphatidylcholine to all-trans retinol, producing all-trans retinyl esters. Retinyl esters are storage forms of vitamin A. LRAT plays a critical role in vision. It provides the all-trans retinyl ester substrates for the isomerohydrolase which processes the esters into 11-cis-retinol in the retinal pigment epithelium; due to a membrane-associated alcohol dehydrogenase, 11 cis-retinol is oxidized and converted into 11-cis-retinaldehyde which is the chromophore for rhodopsin and the cone photopigments.

Leber congenital amaurosis 14;

[00129] Leber congenital amaurosis 14 (LCA14) is a severe dystrophy of the retina, typically becoming evident in the first years of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia and keratoconus. The disease is caused by mutations affecting the LRAT gene.

Retinitis pigmentosa

[00130] Retinitis pigmentosa is a group of related eye disorders that cause progressive vision loss. These disorders affect the retina, which is the layer of light-sensitive tissue at the back of the eye. In people with retinitis pigmentosa, vision loss occurs as the light-sensing cells of the retina gradually deteriorate. The first sign of retinitis pigmentosa is usually a loss of night vision, which becomes apparent in childhood. Problems with night vision can make it difficult to

navigate in low light. Later, the disease causes blind spots to develop in the side (peripheral) vision. Over time, these blind spots merge to produce tunnel vision. The disease progresses over years or decades to affect central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. In adulthood, many people with retinitis pigmentosa become legally blind.

[00131] The signs and symptoms of retinitis pigmentosa are most often limited to vision loss. When the disorder occurs by itself, it is described as nonsyndromic. Researchers have identified several major types of nonsyndromic retinitis pigmentosa, which are usually distinguished by their pattern of inheritance: autosomal dominant, autosomal recessive, or X-linked. Less commonly, retinitis pigmentosa occurs as part of syndromes that affect other organs and tissues in the body. These forms of the disease are described as syndromic. The most common form of syndromic retinitis pigmentosa is Usher syndrome, which is characterized by the combination of vision loss and hearing loss beginning early in life. Retinitis pigmentosa is also a feature of several other genetic syndromes, including Bardet-Biedl syndrome; Refsum disease; and neuropathy, ataxia, and retinitis pigmentosa (NARP).

RDH8

[00132] Retinol dehydrogenase 8 (all-trans) is an enzyme encoded by the *RDH8* gene. All-trans-retinol dehydrogenase (RDH8) is a visual cycle enzyme that reduces all-trans-retinal to all-trans-retinol in the presence of NADPH. It is a member of the short chain dehydrogenase/reductase family and is located in the outer segments of photoreceptors; hence it is also known as photoreceptor retinol dehydrogenase. It is important in the visual cycle by beginning the rhodopsin regeneration pathway by reducing all-trans-retinal, the product of bleached and hydrolyzed rhodopsin.

RDH12

[00133] The RDH12 gene, Retinol dehydrogenase 12 (all-trans/9-cis/11-cis), ecodes the RDH12 protein which is an NADPH-dependent retinal reductase whose highest activity is toward 9-cis and all-trans-retinol. The encoded enzyme also plays a role in the metabolism of short-chain aldehydes but does not exhibit steroid dehydrogenase activity. Defects in this gene are a cause of Leber congenital amaurosis type 13 and Retinitis Pigmentosa 53.

Leber Congenital Amaurosis13

[00134] Leber congenital amaurosis 13 (LCA13) is a severe dystrophy of the retina, typically becoming evident in the first years of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia and keratoconus. In some cases, leber congenital amaurosis-13 can be caused by

homozygous or compound heterozygous mutation in the photoreceptor-specific retinal dehydrogenase gene RDH12 on chromosome 14q23.3.

Retinitis Pigmentosa 53

[00135] Retinitis pigmentosa 53 (RP53) is a retinal dystrophy belonging to the group of pigmentary retinopathies. Retinitis pigmentosa is characterized by retinal pigment deposits visible on fundus examination and primary loss of rod photoreceptor cells followed by secondary loss of cone photoreceptors. Patients typically have night vision blindness and loss of midperipheral visual field. As their condition progresses, they lose their far peripheral visual field and eventually central vision as well.

RGR

[00136] The RGR gene encodes a putative retinal G-protein coupled receptor. The gene is a member of the opsin subfamily of the 7 transmembrane, G-protein coupled receptor 1 family. Like other opsins which bind retinaldehyde, it contains a conserved lysine residue in the seventh transmembrane domain. The protein acts as a photoisomerase to catalyze the conversion of all-trans-retinal to 11-cis-retinal. The reverse isomerization occurs with rhodopsin in retinal photoreceptor cells. The protein is exclusively expressed in tissue adjacent to retinal photoreceptor cells, the retinal pigment epithelium and Mueller cells. This gene may be associated with autosomal recessive and autosomal dominant retinitis pigmentosa (arRP and adRP, respectively). Alternative splicing results in multiple transcript variants encoding different isoforms. Retinal G protein-coupled receptor (RGR) is a rhodopsin homolog found exclusively in cells adjacent to the retinal photoreceptor cells (i.e., the retinal pigment epithelium and Muller cells). It preferentially binds all-trans retinal rather than 11-cis retinal, which is normally found in rhodopsin. In mammals, photons of light convert all-trans retinal within RGR to 11-cis retinal, whereas the reverse isomerization reaction occurs in rhodopsin in photoreceptor cells.

Retinitis Pigmentosa 44

[00137] Retinitis pigmentosa 44 (RP44) is a retinal dystrophy belonging to the group of pigmentary retinopathies. Retinitis pigmentosa is characterized by retinal pigment deposits visible on fundus examination and primary loss of rod photoreceptor cells followed by secondary loss of cone photoreceptors. Patients typically have night vision blindness and loss of midperipheral visual field. As their condition progresses, they lose their far peripheral visual field and eventually central vision as well. The disease is caused by mutations affecting the RGR gene.

CNGA3

[00138] The CNGA3 or cyclic nucleotide gated channel alpha 3 gene encodes one part (the alpha subunit) of the cone photoreceptor cyclic nucleotide-gated (CNG) channel. These

channels are found exclusively in cones, which are located in the retina. Cones provide vision in bright light (daylight vision), including color vision.

[00139] CNG channels are openings in the cell membrane that transport cations into cells. In cones, CNG channels remain open under dark conditions, allowing cations to flow in. When light enters the eye, it triggers the closure of these channels, stopping the inward flow of cations. This change in cation transport alters the cone's electrical charge, which ultimately causes phototransduction. More than 100 mutations in the *CNGA3* gene have been found to cause the vision disorder achromatopsia. These mutations underlie about 25 percent of cases of complete achromatopsia, a form of the disorder characterized by a total lack of color vision and other vision problems that are present from early infancy. *CNGA3* gene mutations have also been identified in a few individuals with incomplete achromatopsia, a milder form of the disorder associated with limited color vision.

[00140] The *CNGA3* gene mutations that underlie complete achromatopsia affect the production or function of the alpha subunit. In some cases, no protein is produced. In others, the protein is altered and does not function normally. CNG channels assembled without the alpha subunit or with an abnormal subunit are nonfunctional; they prevent cones from carrying out phototransduction. In some cases, defective channels allow a huge influx of cations into cones, which ultimately causes these cells to undergo apoptosis. A loss of cone function underlies the lack of color vision and other vision problems in people with complete achromatopsia.

[00141] A few mutations in the *CNGA3* gene reduce but do not eliminate the function of CNG channels in cones. These mutations cause incomplete achromatopsia because the partially functioning cones can transmit some visual information to the brain. Because these CNG channels are specific to cones, rods are generally unaffected by this disorder.

[00142] Mutations in the *CNGA3* gene have also been identified in a small percentage of cases of progressive cone dystrophy. However, unlike achromatopsia, progressive cone dystrophy is associated with cones that work normally at birth but begin to malfunction in childhood or adolescence. Over time, people with progressive cone dystrophy develop increasing blurriness and loss of color vision. It is unclear why some *CNGA3* gene mutations cause achromatopsia and others result in progressive cone dystrophy

Achromatopsia-2

[00143] Achromatopsia-2 is an autosomal recessive disorder and is total colorblindness, also referred to as rod monochromacy or complete achromatopsia, is a rare congenital autosomal recessive disorder characterized by photophobia, reduced visual acuity, nystagmus, and the complete inability to discriminate between colors. Electroretinographic recordings show that in

achromatopsia the rod photoreceptor function is normal, whereas cone photoreceptor responses are absent.

PER1

[00144] The PER1 gene encodes the period circadian protein homolog 1 protein in humans. PER1 is a master regulator of circadian rhythm and functions in the nucleus to repress expression of the central circadian clock genes (e.g., CLOCK). The periodicity of PER1 abundance, nuclear translocation, and transcriptional repression is regulated by PER1 phosphorylation, ubiquitination, and proteasomal degradation

[00145] .The PER1 protein is important to the maintenance of circadian rhythms in cells, and m ay also play a role in the development of cancer. This gene is a member of the period family of genes. It is expressed with a daily oscillating circadian rhythm, or an oscillation that cycles with a period of approximately 24 hours. PER1 is most notably expressed in the region of the brain called the suprachiasmatic nucleus (SCN), which is the primary circadian pacemaker in the mammalian brain. PER1 is also expressed throughout mammalian peripheral tissues. Genes in this family encode components of the circadian rhythms of locomotor activity, metabolism, and behavior. Circadian expression of PER1 in the suprachiasmatic nucleus will free-run in constant darkness, meaning that the 24-hour period of the cycle will persist without the aid of external light cues. Subsequently, a shift in the light/dark cycle evokes a proportional shift of gene expression in the suprachiasmatic nucleus. The time of gene expression is sensitive to light, as light during a mammal's subjective night results in a sudden increase in per expression and thus a shift in phase in the suprachiasmatic nucleus.Alternative splicing has been observed in this gene. In some cases, PER1 can be involved in the effects of Jet lag.

IDUA

[00146] The *IDUA* gene encodes an enzyme called alpha-L-iduronidase, which is essential for the breakdown of large sugar molecules, for example glycosaminoglycans (GAGs). Through hydrolysis, alpha-L-iduronidase uses water molecules to break down unsulfated alpha-L-iduronic acid, which is present in heparan sulfate and dermatan sulfate. Alpha-L-iduronidase can be located in lysosomes. More than 100 mutations in the *IDUA* gene have been found to cause mucopolysaccharidosis type I (MPS I). Most mutations that cause MPS I reduce or completely eliminate the function of alpha-L-iduronidase. It usually cannot be determined whether a certain mutation will cause severe or attenuated MPS I; however, people who do not produce any alpha-L-iduronidase have the severe form of this disorder.

[00147] The lack of alpha-L-iduronidase enzyme activity leads to the accumulation of heparan sulfate and dermatan sulfate within the lysosomes. The buildup of GAGs increases the

size of the lysosomes. The accumulated GAGs may also interfere with the functions of other proteins inside the lysosomes and disrupt the movement of molecules inside the cell.

Attenuated MPS-I

[00148] Mucopolysaccharidosis type I (MPS I) is a condition that affects many parts of the body. This disorder was once divided into three separate syndromes: Hurler syndrome (MPS I-H), Hurler-Scheie syndrome (MPS I-H/S), and Scheie syndrome (MPS I-S), listed from most to least severe. Because there is so much overlap between each of these three syndromes, MPS I is currently divided into the severe and attenuated types.

[00149] Children with MPS I often have no signs or symptoms of the condition at birth, although some have a soft out-pouching around the belly-button (umbilical hernia) or lower abdomen (inguinal hernia). People with severe MPS I generally begin to show other signs and symptoms of the disorder within the first year of life, while those with the attenuated form have milder features that develop later in childhood.

[00150] Individuals with MPS I may have a large head (macrocephaly), a buildup of fluid in the brain (hydrocephalus), heart valve abnormalities, distinctive-looking facial features that are described as "coarse," an enlarged liver and spleen (hepatosplenomegaly), and a large tongue (macroglossia). Vocal cords can also enlarge, resulting in a deep, hoarse voice. The airway may become narrow in some people with MPS I, causing frequent upper respiratory infections and short pauses in breathing during sleep (sleep apnea).

[00151] People with MPS I often develop clouding of the clear covering of the eye (cornea), which can cause significant vision loss. Affected individuals may also have hearing loss and recurrent ear infections.

[00152] Some individuals with MPS I have short stature and joint deformities (contractures) that affect mobility. Most people with the severe form of the disorder also have dysostosis multiplex, which refers to multiple skeletal abnormalities seen on x-ray. Carpal tunnel syndrome develops in many children with this disorder and is characterized by numbness, tingling, and weakness in the hand and fingers. Narrowing of the spinal canal (spinal stenosis) in the neck can compress and damage the spinal cord.

[00153] While both forms of MPS I can affect many different organs and tissues, people with severe MPS I experience a decline in intellectual function and a more rapid disease progression. Developmental delay is usually present by age 1, and severely affected individuals eventually lose basic functional skills (developmentally regress). Children with this form of the disorder usually have a shortened lifespan, sometimes living only into late childhood. Individuals with attenuated MPS I typically live into adulthood and may or may not have a shortened

lifespan. Some people with the attenuated type have learning disabilities, while others have no intellectual impairments. Heart disease and airway obstruction are major causes of death in people with both types of MPS I.

Hurler-Scheie Syndrome

[00154] Hurler-Scheie syndrome is the intermediate form of mucopolysaccharidosis type 1 (MPS1) between the two extremes Hurler syndrome and Scheie syndrome, it is a rare lysosomal storage disease, characterized by skeletal deformities and a delay in motor development. The prevalence of MPS I has been estimated at 1/100,000, with Hurler-Scheie syndrome accounting for 23% of cases or a prevalence of approximately 1/435,000. Patients with Hurler-Scheie syndrome have normal or almost normal intelligence but exhibit various degrees of physical impairment. Patients present in the first years of life with musculoskeletal alterations to different degrees including short stature, multiple dysostosis, thoracic-lumbar kyphosis, progressive coarsening of the facial features to different degrees, cardiomyopathy and valvular abnormalities, neurosensorial hearing loss, enlarged tonsils and adenoids, and nasal secretion. Hydrocephaly can occur after the age of two. Corneal opacity is seen between two and four years of age and requires keratoplasty to restore sight. Other manifestations may include organomegaly, hernias and hirsutism.

[00155] Hurler-Scheie syndrome is caused by mutations in the *IDUA* gene (4p16.3) leading to partial deficiency in the alpha-L-iduronidase enzyme and lysosomal accumulation of dermatan sulfate and heparan sulfate. Early diagnosis is difficult because the first clinical signs are not specific. Diagnosis can be based on detection of increased urinary secretion of heparan and dermatan sulfate through 1,9-dimethylmethylene blue (DMB) test and glycosaminoglycan (GAG) electrophoresis, and demonstration of enzymatic deficiency in leukocytes or fibroblasts. Genetic testing is available. Differential diagnoses include the milder and more severe forms of mucopolysaccharidosis type 1 (Scheie syndrome and Hurler syndrome respectively), mucopolysaccharidosis typeVI and mucopolysaccharidosis type II. Antenatal diagnosis is possible by measurement of enzymatic activity in cultivated chorionic villus or amniocytes and by genetic testing if the disease-causing mutation is known. Transmission is autosomal recessive. Bone marrow or umbilical cord blood transplant has been successful and can preserve neurocognition, improve some aspects of the somatic disease and increase survival. However it is associated with many risks and most of the positive effects occur only if the procedure is performed in the first two years of life.

[00156] The enzyme substitute (laronidase) obtained EU marketing authorization as an orphan drug in 2003. Given through weekly infusions it leads to improvement of lung function

and joint mobility. Enzyme replacement therapy (ERT) can be started at diagnosis and may be beneficial in patients awaiting hematopoietic stem cell transplantation (HSCT). Early treatment can slow the progression of the disease. In individual patients with MPS1 of intermediate severity, HSCT may be considered if there is a suitable donor. There are however no data on the efficacy of HSCT in patients with this form of the disease.

[00157] Life expectancy for Hurler-Scheie syndrome may be reduced, with death occurring before adolescence due to serious cardiovascular and respiratory complications.

[00158] In some cases, in a patient with hurler scheie syndrome, homozygosity for an arg619-to-gly (R619G) mutation due to a C-to-G transversion at nucleotide 1943 can be identified. In some cases, in a patient with hurler scheie syndrome, homozygosity for a thr364-to-met (T364M) mutation in the IDUA gene can be identified.

ALMS1

[00159] The *ALMS1* gene encodes the ALMS1 protein. *ALMS1* gene is located on the short (p) arm of chromosome 2 at position 13. The ALMS1 protein may play a role in hearing, vision, regulation of body weight, and functions of the heart, kidney, lungs, and liver. It may also affect how the pancreas regulates insulin, a hormone that helps control blood sugar levels.

[00160] The ALMS1 protein is present in most of the body's tissues, usually at low levels. Within cells, this protein is located in centrosomes. Centrosomes play a role in cell division and the assembly of microtubules. The ALMS1 protein is also found at the base of cilia. Based on its location within cells, the ALMS1 protein may be involved in the organization of microtubules, the transport of various materials, and the normal function of cilia.

Alstrom Syndrome

[00161] Alström syndrome is a rare condition that affects many body systems. Many of the signs and symptoms of this condition begin in infancy or early childhood, although some appear later in life. Alström syndrome is characterized by a progressive loss of vision and hearing, a form of heart disease that enlarges and weakens the heart muscle (dilated cardiomyopathy), obesity, type 2 diabetes mellitus and short stature. This disorder can also cause serious or life-threatening medical problems involving the liver, kidneys, bladder, and lungs. Some individuals with Alström syndrome have a skin condition called acanthosis nigricans, which causes the skin in body folds and creases to become thick, dark, and velvety. The signs and symptoms of Alström syndrome vary in severity, and not all affected individuals have all of the characteristic features of the disorder.

[00162] More than 80 mutations in the *ALMS1* gene have been identified in people with Alström syndrome. 32 mutations in exon 16, 19 mutations in exon 10, and 17 mutations in exon

8 were identified in Alstrom syndrome patients. The most common allele was a 1-bp deletion (10775delC) identified in 12% of mutated alleles. In some cases, in patients with Alstrom syndrome a homozygosity for insertion of a novel 333-bp Alu Ya5 SINE retrotransposon into exon 16 of the ALMS1 gene can be identified. In some cases, in patients with Alstrom syndrome an insertion of 19 bp in exon 16 of the ALMS1 gene, causing a frameshift resulting in early termination at codon 3530 can be identified. In some cases, in patients with Alstrom syndrome an 8383C-T transition in the ALMS1 gene in homozygous state, causing a nonsense change, glu2795 to ter (G2795X) can be identified. In some cases, in patients with Alstrom syndrome a 10775delC mutation in the ALMS1 gene can be identified. In some cases, in patients with Alstrom syndrome a deletion of 2 bp in exon 8 (2141delCT) can be identified. In some cases, in patients with Alstrom syndrome a compound heterozygosity for a 10775delC mutation and a trp3664-to-ter mutation in the ALMS1 gene can be identified. In some cases, in patients with Alstrom syndrome a homozygous 8164C-T transition in the ALMS1 gene, resulting in an arg2722-to-ter (R2722X) substitution can be identified. In some cases, in patients with Alstrom syndrome a homozygosity for insertion of a 333-bp Alu Ya5 element in exon 16 of the ALMS1 gene can be identified. In some cases, in patients with Alstrom syndrome 2 alleles carrying a 10945G-T transversion in exon 16 of the ALMS1 gene, resulting in a glu3649-to-ter (E3649X) substitution can be identified. In some cases, in patients with Alstrom syndrome a homozygosity for the E3649X mutation in the ALMS1 gene can be identified. Most of these mutations lead to the production of an abnormally small version of the ALMS1 protein that does not function properly. A lack of normally functioning ALMS1 protein in the brain can lead to overeating. A loss of this protein in the pancreas may cause insulin resistance. The combined effects of overeating and insulin resistance impair the body's ability to handle excess sugar, leading to diabetes and obesity (two common features of Alström syndrome).

Retained Intron Containing Pre-mRNA (RIC Pre-mRNA)

[00163] In embodiments, the methods of the present invention can exploit the presence of retained-intron-containing pre-mRNA (RIC pre-mRNA) transcribed from the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene and encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, in the cell nucleus. Splicing of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-

mRNA species to produce mature, fully-spliced, ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA, can be induced using ASOs that stimulate splicing out of the retained introns. The resulting mature ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA can be exported to the cytoplasm and translated, thereby increasing the amount of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the patient's cells and alleviating symptoms of the eye disease or conditions caused by deficiency in ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA. This method, described further below, is known as Targeted Augmentation of Nuclear Gene Output (TANGO).

Nuclear Transcripts

[00164] ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene can be analyzed for intron-retention events. RNA sequencing (RNAseq), can be visualized in the UCSC genome browser, and can show ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA transcripts expressed in ARPE-19 and localized in either the cytoplasmic or nuclear fraction. The retained-intron containing pre-mRNA transcripts are retained in the nucleus and are not exported out to the cytoplasm.

[00165] In embodiments, a retained intron is an intron that is identified as a retained intron based on a determination of at least about 5%, 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%, or at least about 50%, retention. In embodiments, a retained intron is an intron that is identified as a retained intron based on a determination of about 5% to about 100%, about 5% to about 95%, about 5% to about 90%, about 5% to about 85%, about 5% to about 80%, about 5% to about 75%, about 5% to about 70%, about 5% to about 65%, about 5% to about 60%, about 5% to about 65%, about 5% to about 60%, about 5% to about 55%, about 5% to about 50%, about 5% to about 45%, about 5% to about 40%, about 5% to about 35%, about 5% to about 30%, about 5% to about 25%, about 5% to about 20%, about 5% to about 15%, about 10% to

about 100%, about 10% to about 95%, about 10% to about 90%, about 10% to about 85%, about 10% to about 80%, about 10% to about 75%, about 10% to about 70%, about 10% to about 65%, about 10% to about 60%, about 10% to about 65%, about 10% to about 60%, about 10% to about 55%, about 10% to about 50%, about 10% to about 45%, about 10% to about 40%, about 10% to about 35%, about 10% to about 30%, about 10% to about 25%, about 10% to about 20%, about 15% to about 100%, about 15% to about 95%, about 15% to about 90%, about 15% to about 85%, about 15% to about 80%, about 15% to about 75%, about 15% to about 70%, about 15% to about 65%, about 15% to about 60%, about 15% to about 65%, about 15% to about 60%, about 15% to about 55%, about 15% to about 50%, about 15% to about 45%, about 15% to about 40%, about 15% to about 35%, about 15% to about 30%, about 15% to about 25%, about 20% to about 100%, about 20% to about 95%, about 20% to about 90%, about 20% to about 85%, about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 25% to about 100%, about 25% to about 95%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, or about 25% to about 35%, retention. In embodiments, other ASOs useful for this purpose are identified, using, e.g., methods described herein.

[00166] In some embodiments, the ROM1 intron numbering corresponds to the mRNA sequence at NM_00327. In embodiments, the targeted portion of the ROM1 RIC pre-mRNA is in intron 1. In embodiments, the percent retained intron can be 32. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 1 and subsequently increases ROM1 protein production. It is understood that the intron numbering may change in reference to a different ROM1 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000327. One of skill in the art also can determine the sequences of flanking exons in any ROM1 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000327.

[00167] In some embodiments, the TEAD1 intron numbering corresponds to the mRNA sequence at NM_021961. In embodiments, the targeted portion of the TEAD1 RIC pre-mRNA is

in intron 4. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of at least one of retained intron 4 and subsequently increases TEAD1 protein production. It is understood that the intron numbering may change in reference to a different TEAD1 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_021961. One of skill in the art also can determine the sequences of flanking exons in any TEAD1 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_021961.

[00168] In some embodiments, the RDH5 intron numbering corresponds to the mRNA sequence at NM_002905 or NM_001199771. In embodiments, the targeted portion of the RDH5 RIC pre-mRNA is in intron 1 and/or 2 In embodiments, the percent retained intron can be 59%. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 1 and/or 2 and subsequently increases RDH5 protein production. It is understood that the intron numbering may change in reference to a different RDH5 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_002905 or NM_001199771. One of skill in the art also can determine the sequences of flanking exons in any RDH5 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_002905 or NM_001199771.

[00169] In some embodiments, the PAX6 intron numbering corresponds to the mRNA sequence at NM_001310160, NM_001310161, NM_001258465, NM_000280, NM_001258464, NM_000280, NM_001258464, NM_001604, NM_001127612, NM_001258462, NM_001310159, NM_001310158, or NM_001258462._In embodiments, the targeted portion of the PAX6 RIC pre-mRNA is in intron 2 and/or 3 or 1 and/or 3 and/or 4 or 3 and/or 4 and/or 5 or 4 and/or 5 and/or 6 or 4 and/or 6 and/or 7 or 2 and/or 3 and/or 4. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 2 and/or 3. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 1 and/or 3 and/or 4. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 3 and/or 4 and/or 5. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 4 and/or 5 and/or 6. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 4

and/or 6 and/or 7. In some embodiments, the targeted portion of the PAX 6 RIC pre-mRNA is in intron 2 and/or 3 and/or 4. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of a retained intron and subsequently increases PAX6 protein production. It is understood that the intron numbering may change in reference to a different PAX6 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_001310160, NM_001310161, NM_001258465, NM_000280, NM_001258464, NM_000280, NM_001258464, NM_001604, NM_001127612, NM_001258462, NM_001310159, NM_001310158, or NM_001258462. One of skill in the art also can determine the sequences of flanking exons in any PAX6 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_001310160, NM_001310161, NM_001258465, NM_000280, NM_001258464, NM_000280, NM_001258464, NM_001604, NM_001127612, NM_001258462, NM_001310159, NM_001310158, or NM_001258462.

[00170] In some embodiments, the FSCN2 intron numbering corresponds to the mRNA sequence at NM_012418 or NM_001077182. In embodiments, the targeted portion of the FSCN2 RIC pre-mRNA is in intron 1 and/or 3. In embodiments, the percent retained intron can be 12 or 17. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 1 and/or 3 and subsequently increases FSCN2 protein production. It is understood that the intron numbering may change in reference to a different FSCN2 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_012418 or NM_001077182. One of skill in the art also can determine the sequences of flanking exons in any FSCN2 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_012418 or NM_001077182.

[00171] In embodiments, the TCF4 intron numbering corresponds to the mRNA sequence at NM_001243236, NM_00123235, NM_001243234, NM_001243233, NM_001243232, NM_001243231, NM_003199, NM_001306207, NM_ 001306208, NM_001243227, NM_001243228, NM_001243230, NM_001243226, NM_001083962, NM_001330605, and NM_001330604. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 9 or 11 or 12 or 14 or 15 or 16 or 17. In embodiments, the targeted portion of the TCF4 RIC pre-

mRNA is in intron 9. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 11. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 12. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 14. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 15. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 16. In embodiments, the targeted portion of the TCF4 RIC pre-mRNA is in intron 17. In embodiments, the percent retained intron can be 9. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of a retained intron and subsequently increases TCF4 protein production. It is understood that the intron numbering may change in reference to a different TCF4 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_001243236, NM_00123235, NM_001243234, NM_001243233, NM_001243232, NM_001243231, NM_003199, NM_001306207, NM_ 001306208, NM_001243227, NM_001243228, NM_001243230, NM_001243226, NM_001083962, NM_001330605, and NM_001330604. One of skill in the art also can determine the sequences of flanking exons in any TCF4 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_001243236, NM_00123235, NM_001243234, NM_001243233, NM_001243232, NM_001243231, NM_003199, NM_001306207, NM_ 001306208, NM_001243227, NM_001243228, NM_001243230, NM_001243226, NM_001083962, NM_001330605, and NM_001330604.

[00172] In embodiments, the MFSD8 intron numbering corresponds to the mRNA sequence at NM_152778. In embodiments, the targeted portion of the MFSD8 RIC pre-mRNA is in intron 11 and/or 12. In embodiments, and the percent retained intron can be 15 or 62. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 11 and/or 12 and subsequently increases MFSD8 protein production. It is understood that the intron numbering may change in reference to a different MFSD8 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_152778. One of skill in the art also can determine the sequences of flanking exons in any MFSD8 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_152778.

[00173] In embodiments, the CTNS intron numbering corresponds to the mRNA sequence at NM_004937 or NM_001031681. In embodiments, the targeted portion of the CTNS RIC pre-mRNA is in intron 9 and/or 10. In embodiments, the percent retained intron can be 10 or 18. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 9 and/or 10 and subsequently increases CTNS protein production. It is understood that the intron numbering may change in reference to a different CTNS isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_004937 or NM_001031681. One of skill in the art also can determine the sequences of flanking exons in any CTNS isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_004937 or NM_001031681.

[00174] In embodiments, the OPTN intron number corresponds to the mRNA sequence at NM_001008211, NM_001008212, NM_001008213, or NM_021980. In embodiments, the targeted portion of the OPTN RIC pre-mRNA is in intron 7 or 8 or 9. In embodiments, the targeted portion of the OPTN RIC pre-mRNA is in intron 7. In embodiments, the targeted portion of the OPTN RIC pre-mRNA is in intron 8. In embodiments, the targeted portion of the OPTN RIC pre-mRNA is in intron 9. In embodiments, the percent retained intron can be 24. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 7 or 8 or 9 and subsequently increases OPTN protein production. It is understood that the intron numbering may change in reference to a different OPTN isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_001008211, NM_001008212, NM_001008213, or NM_021980.. One of skill in the art also can determine the sequences of flanking exons in any OPTN isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_001008211, NM_001008212, NM_001008213, or NM_021980..

[00175] In embodiments, the RLBP1 intron numbering corresponds to the mRNA sequence at NM_000326. In embodiments, the targeted portion of the RLBP1 RIC pre-mRNA is in intron 5 and/or 2. In embodiments, the percent retained intron can be 49. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced

splicing at the splice site (5' splice site or 3' splice site) of retained intron 5 and/or 2 and subsequently increases RLBP1 protein production. It is understood that the intron numbering may change in reference to a different RLBP1 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000326. One of skill in the art also can determine the sequences of flanking exons in any RLBP1 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000326.

[00176] In embodiments, the RPE65 intron numbering corresponds to the mRNA sequence at NM_000329. In embodiments, the targeted portion of the RPE65 RIC pre-mRNA is in intron 10 and/or 9. In embodiments, the percent retained intron can be 11 or 10. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 10 and/or 9 and subsequently increases RPE65 protein production. It is understood that the intron numbering may change in reference to a different RPE65 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000329. One of skill in the art also can determine the sequences of flanking exons in any RPE65 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000329.

[00177] In embodiments, the LRAT intron numbering corresponds to the mRNA sequence at NM_001301645 or NM_004744. In embodiments, the targeted portion of the LRAT RIC pre-mRNA is in intron 2. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 2 and subsequently increases LRAT protein production. It is understood that the intron numbering may change in reference to a different LRAT isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_001301645 or NM_004744. One of skill in the art also can determine the sequences of flanking exons in any LRAT isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_001301645 or NM_004744.

[00178] In embodiments, the RDH8 intron numbering corresponds to the mRNA sequence at NM_015725. In embodiments, the targeted portion of the RDH8 RIC pre-mRNA is in intron 4.

In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 4 and subsequently increases RDH8 protein production. It is understood that the intron numbering may change in reference to a different RDH8 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_015725. One of skill in the art also can determine the sequences of flanking exons in any RDH8 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_015725.

[00179] In embodiments, the RDH12 intron numbering corresponds to the mRNA sequence at NM_152443. In embodiments, the targeted portion of the RDH12 RIC pre-mRNA is in intron 7. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 7 and subsequently increases RDH12 protein production. It is understood that the intron numbering may change in reference to a different RDH12 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_152443. One of skill in the art also can determine the sequences of flanking exons in any RDH12 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_152443.

[00180] In embodiments, the RGR intron numbering corresponds to the mRNA sequence at NM_002921, NM_001012722, or NM_001012720. In embodiments, the targeted portion of the RGR RIC pre-mRNA is in intron 1 and/or 2. . In embodiments, the percent retained intron can be 46 or 61. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 1 and/or 2 and subsequently increases RGR protein production. It is understood that the intron numbering may change in reference to a different RGR isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_002921, NM_001012722, or NM_001012720. One of skill in the art also can determine the sequences of flanking exons in any RGR isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_002921, NM_001012722, or NM_001012720.

[00181] In embodiments, the CNGA3 intron numbering corresponds to the mRNA sequence at NM_001298 or NM_001079878. In embodiments, the targeted portion of the CNGA3 RIC pre-mRNA is in intron 6 or 5. In embodiments, the targeted portion of the CNGA3 RIC pre-mRNA is in intron 6. In embodiment, the targeted portion of the CNGA3 RIC pre-mRNA is in intron 5. In embodiments, the percent retained intron can be 27. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 6 or 5 and subsequently increases CNGA3 protein production. It is understood that the intron numbering may change in reference to a different CNGA3 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_001298 or NM_001079878. One of skill in the art also can determine the sequences of flanking exons in any CNGA3 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_001298 or NM_001079878.

[00182] In embodiments, the PER1 intron numbering corresponds to the mRNA sequence at NM_002616. In embodiments, the targeted portion of the PER1 RIC pre-mRNA is in intron 1 and/or 14. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 1 and/or 14 and subsequently increases PER1 protein production. It is understood that the intron numbering may change in reference to a different PER1 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_002616. One of skill in the art also can determine the sequences of flanking exons in any PER1 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_002616.

[00183] In embodiments, the IDUA intron numbering corresponds to the mRNA sequence at NM_000203 or NR_110313. In embodiments, the targeted portion of the IDUA RIC pre-mRNA is in intron 3 and/or 4 and/or 5 and/or 6 and/or 7.. In embodiments, the percent retained intron can be 28, 29, 18, 20, or 12. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 3 and/or 4 and/or 5 and/or 6 and/or 7and subsequently increases IDUA protein production. It is understood that the intron numbering may change in reference to a

different IDUA isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000203 or NR_110313. One of skill in the art also can determine the sequences of flanking exons in any IDUA isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000203 or NR_110313.

[00184] In embodiments, the ABCA4 intron number corresponds to the mRNA sequence at NM_000350. In embodiments, the targeted portion of the ABCA4 RIC pre-mRNA is in intron 40 and/or 38 and/or 36 and/or 44 and/or 39. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained intron 40 and/or 38 and/or 36 and/or 44 and/or 39 and subsequently increases ABCA4 protein production. It is understood that the intron numbering may change in reference to a different ABCA4 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000350. One of skill in the art also can determine the sequences of flanking exons in any ABCA4 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000350.

[00185] In embodiments, the MYOC intron number corresponds to the mRNA sequence at NM_000261. In embodiments, the targeted portion of the MYOC RIC pre-mRNA is in intron 1 and/or 2. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained 1 and/or 2 and subsequently increases MYOC protein production. It is understood that the intron numbering may change in reference to a different MYOC isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000261. One of skill in the art also can determine the sequences of flanking exons in any MYOC isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000261.

[00186] In embodiments, the NR2E3 intron number corresponds to the mRNA sequence at NM_014249 or NM_016346. In embodiments, the targeted portion of the NR2E3 RIC pre-mRNA is in intron 1 and/or 2 and/or 3 and/or 4 and/or 5 and/or 6 and/or 7. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained 1 and/or 2 and/or 3 and/or 4

and/or 5 and/or 6 and/or 7 and subsequently increases NR2E3 protein production. It is understood that the intron numbering may change in reference to a different NR2E3 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_014249 or NM_016346. One of skill in the art also can determine the sequences of flanking exons in any NR2E3 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_014249 or NM_016346.

[00187] In embodiments, the NXNL1 intron number corresponds to the mRNA sequence at NM_138454. In embodiments, the targeted portion of the NXNL1 RIC pre-mRNA is in intron 1. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained 1 and subsequently increases NXNL1 protein production. It is understood that the intron numbering may change in reference to a different NXNL1 isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_138454. One of skill in the art also can determine the sequences of flanking exons in any NXNL1 isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_138454.

[00188] In embodiments, the CRX intron number corresponds to the mRNA sequence at NM_000554. In embodiments, the targeted portion of the CRX RIC pre-mRNA is in intron 1 and/or 2 and/or 3. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of retained 1 and/or 2 and/or 3 and subsequently increases CRX protein production. It is understood that the intron numbering may change in reference to a different CRX isoform sequence. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_000554. One of skill in the art also can determine the sequences of flanking exons in any CRX isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_000554.

ABCA4

[00189] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from an ABCA4 genomic sequence (an ABCA4 RIC pre-mRNA). In some

embodiments, the ABCA4 genomic sequence is SEQ ID NO: 1. In some embodiments, the ABCA4 RIC pre-mRNA is SEQ ID NO: 24. In some embodiments, the ABCA4 RIC pre-mRNA transcript comprises retained intron 40 and/or 38 and/or 36 and/or 44 and/or 39. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 40, the ASOs disclosed herein target SEQ ID NO: 26674. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 38, the ASOs disclosed herein target SEQ ID NO: 26706. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 36, the ASOs disclosed herein target SEQ ID NO: 26656. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 44, the ASOs disclosed herein target SEQ ID NO: 26681. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 39, the ASOs disclosed herein target SEQ ID NO: 26664. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 40, the ASO has a sequence according to any one of SEQ ID NOs: 84-315. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 38, the ASO has a sequence according to any one of SEQ ID NOs: 316-543. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 36, the ASO has a sequence according to any one of SEQ ID NOs: 544-774. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 44, the ASO has a sequence according to any one of SEQ ID NOs: 775-1016. In some embodiments, when the ABCA4 RIC pre-mRNA transcript comprises retained intron 39, the ASO has a sequence according to any one of SEQ ID NOs: 1017-1126. In some embodiments, the ASOs target an ABCA4 RIC pre-mRNA sequence.

RPE65

[00190] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RPE65 genomic sequence (an RPE65 RIC pre-mRNA). In some embodiments, the RPE65 genomic sequence is SEQ ID NO: 2. In some embodiments, the RPE65 RIC pre-mRNA is SEQ ID NO: 25. In some embodiments, the RPE65 RIC pre-mRNA transcript comprises retained intron 9 and/or 10. In some embodiments, when the RPE65 RIC pre-mRNA transcript comprises retained intron 9, the ASOs disclosed herein target SEQ ID NO: 26691. In some embodiments, when the RPE65 RIC pre-mRNA transcript comprises retained intron 10, the ASOs disclosed herein target SEQ ID NO: 26671. In some embodiments, when the RPE65 RIC pre-mRNA transcript comprises retained intron 9, the ASO has a sequence according to any one of SEQ ID NOs: 1127-1293. In some embodiments, when the RPE65 RIC pre-mRNA transcript comprises retained intron 10, the ASO has a sequence according to any one of SEQ ID NOs: 1294-1528. In some embodiments, the ASOs target an RPE65 RIC pre-mRNA sequence.

MYOC

[00191] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a MYOC genomic sequence (a MYOC RIC pre-mRNA). In some embodiments, the MYOC genomic sequence is SEQ ID NO: 3. In some embodiments, the MYOC RIC pre-mRNA is SEQ ID NO: 26. In some embodiments, the MYOC RIC pre-mRNA transcript comprises retained intron 1 and/or 2. In some embodiments, when the MYOC RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26669. In some embodiments, when the MYOC RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26696. In some embodiments, when the MYOC RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 1529-1855. In some embodiments, when the MYOC RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 1856-2318. In some embodiments, the ASOs target a MYOC RIC pre-mRNA sequence.

CNGA3

[00192] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a CNGA3 genomic sequence (a CNGA3 RIC pre-mRNA). In some embodiments, the CNGA3 genomic sequence is SEQ ID NO: 4. In some embodiments, the CNGA3 RIC pre-mRNA is SEQ ID NO: 27 or 28. In some embodiments, the CNGA3 RIC pre-mRNA transcript comprises retained intron 6 and/or 5. In some embodiments, when the CNGA3 RIC pre-mRNA transcript comprises retained intron 6, the ASOs disclosed herein target SEQ ID NO: 26711. In some embodiments, when the CNGA3 RIC pre-mRNA transcript comprises retained intron 5, the ASOs disclosed herein target SEQ ID NO: 26711. In some embodiments, when the CNGA3 RIC pre-mRNA transcript comprises retained intron 6, the ASO has a sequence according to any one of SEQ ID NOs: 2319-2544. In some embodiments, when the CNGA3 RIC pre-mRNA transcript comprises retained intron 5, the ASO has a sequence according to any one of SEQ ID NOs: 2545-2770. In some embodiments, the ASOs target a CNGA3 RIC pre-mRNA sequence.

MFSD8

[00193] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a MFSD8 genomic sequence (an MFSD8 RIC pre-mRNA). In some embodiments, the MFSD8 genomic sequence is SEQ ID NO: 5. In some embodiments, the MFSD8 RIC pre-mRNA is SEQ ID NO: 29. In some embodiments, the MFSD8 RIC pre-mRNA transcript comprises retained intron 11 and/or 12. In some embodiments, when the MFSD8 RIC pre-mRNA transcript comprises retained intron 11, the ASOs disclosed herein target SEQ ID

NO: 26703. In some embodiments, when the MFSD8 RIC pre-mRNA transcript comprises retained intron 12, the ASOs disclosed herein target SEQ ID NO: 26708. In some embodiments, when the MFSD8 RIC pre-mRNA transcript comprises retained intron 11, the ASO has a sequence according to any one of SEQ ID NOs: 2771-2852. In some embodiments, when the MFSD8 RIC pre-mRNA transcript comprises retained intron 12, the ASO has a sequence according to any one of SEQ ID NOs: 2853-3631. In some embodiments, the ASOs target an MFSD8 RIC pre-mRNA sequence.

IDUA

[00194] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a IDUA genomic sequence (an IDUA RIC pre-mRNA). In some embodiments, the IDUA genomic sequence is SEQ ID NO: 6. In some embodiments, the IDUA RIC pre-mRNA is SEQ ID NO: 30 or 31. In some embodiments, the IDUA RIC pre-mRNA transcript comprises retained intron 3 and/or 4 and/or 5 and/or 6 and/or 7. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 3, the ASOs disclosed herein target SEQ ID NO: 26668. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 4, the ASOs disclosed herein target SEQ ID NO: 26679. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 5, the ASOs disclosed herein target SEQ ID NO: 26700. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 6, the ASOs disclosed herein target SEQ ID NO: 26655. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 7, the ASOs disclosed herein target SEQ ID NO: 26663. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 3, the ASO has a sequence according to any one of SEQ ID NOs: 3632-3697 or 4038-4103. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 4, the ASO has a sequence according to any one of SEQ ID NOs: 3698-3813 or 4104-4219. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 5, the ASO has a sequence according to any one of SEQ ID NOs: 3814-3879 or 4220-4285. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 6, the ASO has a sequence according to any one of SEQ ID NOs: 3880-3952 or 4286-4358. In some embodiments, when the IDUA RIC pre-mRNA transcript comprises retained intron 7, the ASO has a sequence according to any one of SEQ ID NOs: 3953-4037 or 4359-4443. In some embodiments, the ASOs target an IDUA RIC pre-mRNA sequence.

LRAT

[00195] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a LRAT genomic sequence (an LRAT RIC pre-mRNA). In some embodiments, the LRAT genomic sequence is SEQ ID NO: 7. In some embodiments, the LRAT RIC pre-mRNA is SEQ ID NO: 32 or 33. In some embodiments, the LRAT RIC pre-mRNA transcript comprises retained intron 2. In some embodiments, when the LRAT RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26685. In some embodiments, when the LRAT RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 4444-6647. In some embodiments, the ASOs target an LRAT RIC pre-mRNA sequence.

OPTN

[00196] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a OPTN genomic sequence (an OPTN RIC pre-mRNA). In some embodiments, the OPTN genomic sequence is SEQ ID NO: 8. In some embodiments, the OPTN RIC pre-mRNA is SEQ ID NO: 34, 35, 36, or 37. In some embodiments, the OPTN RIC pre-mRNA transcript comprises retained intron 9 or 8 or 7. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 9, the ASOs disclosed herein target SEQ ID NO: 26714. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 8, the ASOs disclosed herein target SEQ ID NO: 26714. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 7, the ASOs disclosed herein target SEQ ID NO: 26714. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 9, the ASO has a sequence according to any one of SEQ ID NOs: 6648-6880 or 7114-7346. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 8, the ASO has a sequence according to any one of SEQ ID NOs: 6881-7113. In some embodiments, when the OPTN RIC pre-mRNA transcript comprises retained intron 7, the ASO has a sequence according to any one of SEQ ID NOs: 7347-7579. In some embodiments, the ASOs target an OPTN RIC pre-mRNA sequence.

RGR

[00197] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RGR genomic sequence (an RGR RIC pre-mRNA). In some embodiments, the RGR genomic sequence is SEQ ID NO: 9. In some embodiments, the RGR RIC pre-mRNA is SEQ ID NO: 38, 39, or 40. In some embodiments, the RGR RIC pre-mRNA transcript comprises retained intron 1 and/or 2. In some embodiments, when the RGR RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26657. In some embodiments, when the RGR RIC pre-mRNA transcript comprises retained intron 2, the

ASOs disclosed herein target SEQ ID NO: 26687 or 26683. In some embodiments, when the RGR RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 7580-7806, 8041-8267, or 8500-8726. In some embodiments, when the RGR RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 7807-8040, 8268-8499, or 8727-8958. In some embodiments, the ASOs target an RGR RIC pre-mRNA sequence.

TEAD1

[00198] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a TEAD1 genomic sequence (a TEAD1 RIC pre-mRNA). In some embodiments, the TEAD1 genomic sequence is SEQ ID NO: 10. In some embodiments, the TEAD1 RIC pre-mRNA is SEQ ID NO: 41. In some embodiments, the TEAD1 RIC pre-mRNA transcript comprises retained intron 4. In some embodiments, when the TEAD1 RIC pre-mRNA transcript comprises retained intron 4, the ASOs disclosed herein target SEQ ID NO: 26672. In some embodiments, when the TEAD1 RIC pre-mRNA transcript comprises retained intron 4, the ASO has a sequence according to any one of SEQ ID NOs: 8959-9163. In some embodiments, the ASOs target a TEAD1 RIC pre-mRNA sequence.

[00199]

PAX6

[00200] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a PAX6 genomic sequence (a PAX6 RIC pre-mRNA). In some embodiments, the PAX6 genomic sequence is SEQ ID NO: 11. In some embodiments, the PAX6 RIC pre-mRNA is SEQ ID NO: 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52. In some embodiments, the PAX6 RIC pre-mRNA transcript comprises retained intron 2 and/or 3 or 1 and/or 3 and/or 4 or 3 and/or 4 and/or 5 or 4 and/or 5 and/or 6 or 4 and/or 6 and/or 7 or 2 and/or 3 and/or 4. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26707. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26697 or 26694. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 3, the ASOs disclosed herein target SEQ ID NO: 26677, 26678, 26694, or 26659. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 4, the ASOs disclosed herein target SEQ ID NO: 26713, 26659, or 26694. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 5, the ASOs disclosed herein target SEQ ID NO: 26713 or 26659. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 6, the ASOs disclosed herein target SEQ ID NO:

26713 or 26678. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 7, the ASOs disclosed herein target SEQ ID NO: 26713. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 9508-9774. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 9164-9296 or 13581-13780. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 3, the ASO has a sequence according to any one of SEQ ID NOs: 9297-9507, 9775-9841, 10053-10252, or 13781-14012. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 4, the ASO has a sequence according to any one of SEQ ID NOs: 9842-10052, 10253-10484, 10696-10895, 11339-11538, 11982-12181, 12460-12659, 13103-13302, 14013-14423, or 14702-14901. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 5, the ASO has a sequence according to any one of SEQ ID NOs: 10485-10695, 10896-11127, 11539-11770, or 12660-12891. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 6, the ASO has a sequence according to any one of SEQ ID NOs: 11128-11338, 11771-11981, 12182-12248, 12892-13102, 13303-13369, 14424-14490, or 14902-14968. In some embodiments, when the PAX6 RIC pre-mRNA transcript comprises retained intron 7, the ASO has a sequence according to any one of SEQ ID NOs: 12249-12459, 13370-13580, 14491-14701, or 14969-15179. In some embodiments, the ASOs target a PAX6 RIC pre-mRNA sequence.

ROM1

[00201] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a ROM1 genomic sequence (a ROM1 RIC pre-mRNA). In some embodiments, the ROM1 genomic sequence is SEQ ID NO: 12. In some embodiments, the ROM1 RIC pre-mRNA is SEQ ID NO: 53. In some embodiments, the ROM1 RIC pre-mRNA transcript comprises retained intron 1. In some embodiments, when the ROM1 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26665. In some embodiments, when the ROM1 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 15180-15486. In some embodiments, the ASOs target a ROM1 RIC pre-mRNA sequence.

RDH5

[00202] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RDH5 genomic sequence (an RDH5 RIC pre-mRNA). In some embodiments, the RDH5 genomic sequence is SEQ ID NO: 13. In some embodiments, the RDH5 RIC pre-

mRNA is SEQ ID NO: 54 or 55. In some embodiments, the RDH5 RIC pre-mRNA transcript comprises retained intron 1 and/or 2. In some embodiments, when the RDH5 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26704 or 26709. In some embodiments, when the RDH5 RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26666 or 26684. In some embodiments, when the RDH5 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 15487-15700 or 15845-16057. In some embodiments, when the RDH5 RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 15701-15844 or 16058-16202. In some embodiments, the ASOs target an RDH5 RIC pre-mRNA sequence.

RDH12

[00203] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RDH12 genomic sequence (an RDH12 RIC pre-mRNA). In some embodiments, the RDH12 genomic sequence is SEQ ID NO: 14. In some embodiments, the RDH12 RIC pre-mRNA is SEQ ID NO: 56. In some embodiments, the RDH12 RIC pre-mRNA transcript comprises retained intron 7. In some embodiments, when the RDH12 RIC pre-mRNA transcript comprises retained intron 7, the ASOs disclosed herein target SEQ ID NO: 26693. In some embodiments, when the RDH12 RIC pre-mRNA transcript comprises retained intron 7, the ASO has a sequence according to any one of SEQ ID NOs: 16203-16458. In some embodiments, the ASOs target an RDH12 RIC pre-mRNA sequence.

NR2E3

[00204] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a NR2E3 genomic sequence (an NR2E3 RIC pre-mRNA). In some embodiments, the NR2E3 genomic sequence is SEQ ID NO: 15. In some embodiments, the NR2E3 RIC pre-mRNA is SEQ ID NO: 57 or 58. In some embodiments, the NR2E3 RIC pre-mRNA transcript comprises retained intron 1 and/or 2 and/or 3 and/or 4 and/or 5 and/or 6 and/or 7. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26702. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26660. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 3, the ASOs disclosed herein target SEQ ID NO: 26705. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 4, the ASOs disclosed herein target SEQ ID NO: 26698. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 5, the ASOs disclosed herein target SEQ ID NO: 26658. In

some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 6, the ASOs disclosed herein target SEQ ID NO: 26676. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 7, the ASOs disclosed herein target SEQ ID NO: 26712 or 26701. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 16459-1661 or 17255-17457. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 16662-16272 or 17458-17523. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 3, the ASO has a sequence according to any one of SEQ ID NOs: 16728-16798 or 17524-17594. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 4, the ASO has a sequence according to any one of SEQ ID NOs: 16799-16890 or 17595-17686. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 5, the ASO has a sequence according to any one of SEQ ID NOs: 16891-17127 or 17687-17923. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 6, the ASO has a sequence according to any one of SEQ ID NOs: 17128-17169 or 17924-17965. In some embodiments, when the NR2E3 RIC pre-mRNA transcript comprises retained intron 7, the ASO has a sequence according to any one of SEQ ID NOs: 17170-17254 or 17966-18209. In some embodiments, the ASOs target an NR2E3 RIC pre-mRNA sequence.

RLBP1

[00205] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RLBP1 genomic sequence (an RLBP1 RIC pre-mRNA). In some embodiments, the RLBP1 genomic sequence is SEQ ID NO: 16. In some embodiments, the RLBP1 RIC pre-mRNA is SEQ ID NO: 59. In some embodiments, the RLBP1 RIC pre-mRNA transcript comprises retained intron 2 and/or 5 In some embodiments, when the RLBP1 RIC pre-mRNA transcript comprises retained intron 2, the ASOs disclosed herein target SEQ ID NO: 26673. In some embodiments, when the RLBP1 RIC pre-mRNA transcript comprises retained intron 5, the ASOs disclosed herein target SEQ ID NO: 26667. In some embodiments, when the RLBP1 RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 18210-18383. In some embodiments, when the RLBP1 RIC pre-mRNA transcript comprises retained intron 5, the ASO has a sequence according to any one of SEQ ID NOs: 18384-18638. In some embodiments, the ASOs target an RLBP1 RIC pre-mRNA sequence.

CTNS

[00206] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a CTNS genomic sequence (a CTNS RIC pre-mRNA). In some embodiments, the CTNS genomic sequence is SEQ ID NO: 17. In some embodiments, the CTNS RIC pre-mRNA is SEQ ID NO: 60 or 61. In some embodiments, the CTNS RIC pre-mRNA transcript comprises retained intron 9 and/or 10. In some embodiments, when the CTNS RIC pre-mRNA transcript comprises retained intron 9, the ASOs disclosed herein target SEQ ID NO: 26690. In some embodiments, when the CTNS RIC pre-mRNA transcript comprises retained intron 10, the ASOs disclosed herein target SEQ ID NO: 26692. In some embodiments, when the CTNS RIC pre-mRNA transcript comprises retained intron 9, the ASO has a sequence according to any one of SEQ ID NOs: 18639-18861 or 19087-19309. In some embodiments, when the CTNS RIC pre-mRNA transcript comprises retained intron 10, the ASO has a sequence according to any one of SEQ ID NOs: 18862-19086 or 19310-19534. In some embodiments, the ASOs target a CTNS RIC pre-mRNA sequence.

PER1

[00207] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a PER1 genomic sequence (a PER1 RIC pre-mRNA). In some embodiments, the PER1 genomic sequence is SEQ ID NO: 18. In some embodiments, the PER1 RIC pre-mRNA is SEQ ID NO: 62. In some embodiments, the PER1 RIC pre-mRNA transcript comprises retained intron 1 and/or 14. In some embodiments, when the PER1 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26682. In some embodiments, when the PER1 RIC pre-mRNA transcript comprises retained intron 14, the ASOs disclosed herein target SEQ ID NO: 26710. In some embodiments, when the PER1 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 19535-19782. In some embodiments, when the PER1 RIC pre-mRNA transcript comprises retained intron 14, the ASO has a sequence according to any one of SEQ ID NOs: 19783-19845. In some embodiments, the ASOs target a PER1 RIC pre-mRNA sequence.

FSCN2

[00208] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a FSCN2 genomic sequence (an FSCN2 RIC pre-mRNA). In some embodiments, the FSCN2 genomic sequence is SEQ ID NO: 19. In some embodiments, the FSCN2 RIC pre-mRNA is SEQ ID NO: 63 or 64. In some embodiments, the FSCN2 RIC pre-mRNA transcript comprises retained intron 1 and/or 3. In some embodiments, when the FSCN2 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26670. In some embodiments, when the FSCN2 RIC pre-mRNA transcript comprises

retained intron 3, the ASOs disclosed herein target SEQ ID NO: 26662 or 26661. In some embodiments, when the FSCN2 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 19846-20232 or 20348-20734. In some embodiments, when the FSCN2 RIC pre-mRNA transcript comprises retained intron 3, the ASO has a sequence according to any one of SEQ ID NOs: 20233-20347 or 20735-20849. In some embodiments, the ASOs target an FSCN2 RIC pre-mRNA sequence.

TCF4

[00209] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a TCF4 genomic sequence (a TCF4 RIC pre-mRNA). In some embodiments, the TCF4 genomic sequence is SEQ ID NO: 20. In some embodiments, the TCF4 RIC pre-mRNA is SEQ ID NO: 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80. In some embodiments, the TCF4 RIC pre-mRNA transcript comprises retained intron 9 or 12 or 14 or 16 or 15 or 17 or 11.

In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 9, the ASOs disclosed herein target SEQ ID NO: 26688. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 12, the ASOs disclosed herein target SEQ ID NO: 26688 or 26689. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 14, the ASOs disclosed herein target SEQ ID NO: 26688. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 16, the ASOs disclosed herein target SEQ ID NO: 26688 or 26689. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 15, the ASOs disclosed herein target SEQ ID NO: 26688 or 26689. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 17, the ASOs disclosed herein target SEQ ID NO: 26689. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 11, the ASOs disclosed herein target SEQ ID NO: 26689. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 9, the ASO has a sequence according to any one of SEQ ID NOs: 20860-21577. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 12, the ASO has a sequence according to any one of SEQ ID NOs: 21578-22063 or 22790-23031. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 14, the ASO has a sequence according to any one of SEQ ID NOs: 22064-22305. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 16, the ASO has a sequence according to any one of SEQ ID NOs: 22306-22547, 23276-23519, 24006-24249, or 24494-24737. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 15, the ASO has a sequence according to any one of

SEQ ID NOs: 22548-22789, 23032-23275, or 23510-23761. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 17, the ASO has a sequence according to any one of SEQ ID NOs: 23762-24005. In some embodiments, when the TCF4 RIC pre-mRNA transcript comprises retained intron 11, the ASO has a sequence according to any one of SEQ ID NOs: 24250-24493. In some embodiments, the ASOs target a TCF4 RIC pre-mRNA sequence.

RDH8

[00210] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a RDH8 genomic sequence (an RDH8 RIC pre-mRNA). In some embodiments, the RDH8 genomic sequence is SEQ ID NO: 21. In some embodiments, the RDH8 RIC pre-mRNA is SEQ ID NO: 81. In some embodiments, the RDH8 RIC pre-mRNA transcript comprises retained intron 4. In some embodiments, when the RDH8 RIC pre-mRNA transcript comprises retained intron 4, the ASOs disclosed herein target SEQ ID NO: 26680. In some embodiments, when the RDH8 RIC pre-mRNA transcript comprises retained intron 4, the ASO has a sequence according to any one of SEQ ID NOs: 24738-24873. In some embodiments, the ASOs target an RDH8 RIC pre-mRNA sequence.

NXNL1

[00211] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a NXNL1 genomic sequence (an NXNL1 RIC pre-mRNA). In some embodiments, the NXNL1 genomic sequence is SEQ ID NO: 22. In some embodiments, the NXNL1 RIC pre-mRNA is SEQ ID NO: 82. In some embodiments, the NXNL1 RIC pre-mRNA transcript comprises retained intron 1. In some embodiments, when the NXNL1 RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26699. In some embodiments, when the NXNL1 RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 24874-25231. In some embodiments, the ASOs target an NXNL1 RIC pre-mRNA sequence.

CRX

[00212] In some embodiments, the ASOs disclosed herein target a RIC pre-mRNA transcribed from a CRX genomic sequence (a CRX RIC pre-mRNA). In some embodiments, the CRX genomic sequence is SEQ ID NO: 23. In some embodiments, the CRX RIC pre-mRNA is SEQ ID NO: 83. In some embodiments, the CRX RIC pre-mRNA transcript comprises retained intron 1 and/or 2 and/or or 3. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 1, the ASOs disclosed herein target SEQ ID NO: 26675. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 2, the ASOs

disclosed herein target SEQ ID NO: 26695. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 3, the ASOs disclosed herein target SEQ ID NO: 26686. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 1, the ASO has a sequence according to any one of SEQ ID NOs: 25232-25465. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 2, the ASO has a sequence according to any one of SEQ ID NOs: 25466-25695. In some embodiments, when the CRX RIC pre-mRNA transcript comprises retained intron 3, the ASO has a sequence according to any one of SEQ ID NOs: 25696-26654. In some embodiments, the ASOs target a CRX RIC pre-mRNA sequence.

[00213] In some embodiments the RIC pre-mRNA transcript comprises a retained intron. In some embodiments, the ASO targets an exon flanking the 5' splice site. In some embodiments, the ASO targets the retained intron. In some embodiments, the ASO targets an exon flanking the 3' splice site. A subsequent example of ASO targeting is provided below using TEAD1.

[00214] In some embodiments, the ASO targets exon 4 of TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an exon 4 sequence upstream (or 5') from the 5' splice site of a TEAD RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an exon sequence about 4 to about 44 nucleotides upstream (or 5') from the 5' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 8959-8967.

[00215] In some embodiments, the ASO targets intron 4 in a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an intron 4 sequence downstream (or 3') from the 5' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an intron 4 sequence about 6 to about 496 nucleotides downstream (or 3') from the 5' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 8968-9064.

[00216] In some embodiments, the ASO targets an intron 4 sequence upstream (or 5') from the 3' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an intron 4 sequence about 16 to about 499 nucleotides upstream (or 5') from the 3' splice site of a TEAD1 RIC pre-mRNA a comprising retained intron 4. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 9065-9154.

[00217] In some embodiments, the ASO targets exon 5 in a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an exon 5 sequence

downstream (or 3') from the 3' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO targets an exon 5 sequence about 2 to about 42 nucleotides downstream (or 3') from the 3' splice site of a TEAD1 RIC pre-mRNA comprising a retained intron 4. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 9255-9163.

[00218] In embodiments, the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA is in intron 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In embodiments, hybridization of an ASO to the targeted portion of the RIC pre-mRNA results in enhanced splicing at the splice site (5' splice site or 3' splice site) of at least one of retained introns 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, and subsequently increases ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein production.

[00219] The degree of intron retention can be expressed as percent intron retention (PIR), the percentage of transcripts in which a given intron is retained. In brief, PIR can be calculated as the percentage of the average number of reads mapping to the exon–intron junctions, over the sum of the average of the exon–intron junction reads plus the exon–exon junction reads.

[00220] PIR values for SCN1A have been reported, e.g., by Braunschweig, et al., 2014, (see, *e.g.*, Supplemental Table S9), incorporated by reference herein in its entirety.

[00221] In embodiments, the methods described herein are used to increase the production of a functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. As used herein, the term "functional" refers to the amount of activity or function of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein that is necessary to eliminate any one or more symptoms of a treated condition. In embodiments, the methods are used to increase the production of a partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. As used herein, the term "partially functional" refers to any amount of activity or function of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1,

RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein that is less than the amount of activity or function that is necessary to eliminate or prevent any one or more symptoms of a disease or condition. In some embodiments, a partially functional protein or RNA will have at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, 85%, at least 90%, or at least 95% less activity relative to the fully functional protein or RNA.

[00222] In embodiments, the method is a method of increasing the expression of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein by cells of a subject having a RIC pre-mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, wherein the subject has a deficient amount of activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and wherein the deficient amount of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is caused by haploinsufficiency of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In such an embodiment, the subject has a first allele encoding a functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and a second allele from which the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is not produced. In another such embodiment, the subject has a first allele encoding a functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and a second allele encoding a nonfunctional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In another such embodiment, the subject has a first allele encoding a functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1,

OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and a second allele encoding a partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In any of these embodiments, the antisense oligomer binds to a targeted portion of the RIC pre-mRNA transcribed from the first allele (encoding functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein), thereby inducing constitutive splicing of the retained intron from the RIC pre-mRNA, and causing an increase in the level of mature mRNA encoding functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and an increase in the expression of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the cells of the subject

[00223] In embodiments, the subject has a first allele encoding a functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and a second allele encoding a partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and the antisense oligomer binds to a targeted portion of the RIC pre-mRNA transcribed from the first allele (encoding functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein) or a targeted portion of the RIC pre-mRNA transcribed from the second allele (encoding partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein), thereby inducing constitutive splicing of the retained intron from the RIC pre-mRNA, and causing an increase in the level of mature mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and an increase in the expression of functional or partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1,

RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the cells of the subject.

[00224] In related embodiments, the method is a method of using an ASO to increase the expression of a protein or functional RNA. In embodiments, an ASO is used to increase the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in cells of a subject having a RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, wherein the subject has a deficiency in the amount or function of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein.

[00225] In embodiments, the RIC pre-mRNA transcript that encodes the protein that is causative of the disease or condition is targeted by the ASOs described herein. In some embodiments, a RIC pre-mRNA transcript that encodes a protein that is not causative of the disease is targeted by the ASOs. For example, a disease that is the result of a mutation or deficiency of a first protein in a particular pathway may be ameliorated by targeting a RIC pre-mRNA that encodes a second protein, thereby increasing production of the second protein. In some embodiments, the function of the second protein is able to compensate for the mutation or deficiency of the first protein (which is causative of the disease or condition).

[00226] In embodiments, the subject has:

[00227] a. a first mutant allele from which

i) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is produced at a reduced level compared to production from a wild-type allele,

ii) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is produced in a form having reduced function compared to an equivalent wild-type protein, or

iii) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4,

MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein or functional RNA is not produced; and

b.a second mutant allele from which

i) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is produced at a reduced level compared to production from a wild-type allele,

ii) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is produced in a form having reduced function compared to an equivalent wild-type protein, or

iii) the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is not produced, and

[00228] wherein the RIC pre-mRNA is transcribed from the first allele and/or the second allele. In these embodiments, the ASO binds to a targeted portion of the RIC pre-mRNA transcribed from the first allele or the second allele, thereby inducing constitutive splicing of the retained intron from the RIC pre-mRNA, and causing an increase in the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein and an increase in the expression of the target protein or functional RNA in the cells of the subject. In these embodiments, the target protein or functional RNA having an increase in expression level resulting from the constitutive splicing of the retained intron from the RIC pre-mRNA is either in a form having reduced function compared to the equivalent wild-type protein (partially-functional), or having full function compared to the equivalent wild-type protein (fully-functional).

[00229] In embodiments, the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is increased 1.1

to 10-fold, when compared to the amount of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA that is produced in a control cell, *e.g.*, one that is not treated with the antisense oligomer or one that is treated with an antisense oligomer that does not bind to the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA.

[00230] In embodiments, the condition caused by a deficient amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is not a condition caused by alternative or aberrant splicing of the retained intron to which the ASO is targeted. In embodiments, the condition caused by a deficient amount or activity of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is not a condition caused by alternative or aberrant splicing of any retained intron in a RIC pre-mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In embodiments, alternative or aberrant splicing may occur in a pre-mRNA transcribed from the gene, however the compositions and methods of the invention do not prevent or correct this alternative or aberrant splicing.

[00231] In embodiments, a subject treated using the methods of the invention expresses a partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein from one allele, wherein the partially functional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, or a partial gene deletion. In embodiments, a subject treated using the methods of the invention expresses a nonfunctional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein from one allele, wherein the nonfunctional ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4,

MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, a partial gene deletion, in one allele. In embodiments, a subject treated using the methods of the invention has a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA whole gene deletion, in one allele.

Use of TANGO for Increasing Protein Expression

[00232] As described above, in embodiments, Targeted Augmentation of Nuclear Gene Output (TANGO) can be used in the methods of the invention to increase expression of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In these embodiments, a retained-intron-containing pre-mRNA (RIC pre-mRNA) encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is present in the nucleus of a cell. Cells having a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that comprises a retained intron, an exon flanking the 5' splice site, and an exon flanking the 3' splice site, encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, can be contacted with antisense oligomers (ASOs) that are complementary to a targeted portion of the RIC pre-mRNA. Hybridization of the ASOs to the targeted portion of the RIC pre-mRNA can result in enhanced splicing at the splice site (5' splice site or 3' splice site) of the retained intron and subsequently increases target protein production.

[00233] The terms "pre-mRNA," and "pre-mRNA transcript" may be used interchangeably and refer to any pre-mRNA species that contains at least one intron. In embodiments, pre-mRNA or pre-mRNA transcripts comprise a 5'-7-methylguanosine cap and/or a poly-A tail. In embodiments, pre-mRNA or pre-mRNA transcripts comprise both a 5'-7-methylguanosine cap and a poly-A tail. In some embodiments, the pre-mRNA transcript does not comprise a 5'-7-methylguanosine cap and/or a poly-A tail. A pre-mRNA transcript is a non-productive messenger RNA (mRNA) molecule if it is not translated into a protein (or transported into the cytoplasm from the nucleus).

[00234] As used herein, a "retained-intron-containing pre-mRNA" ("RIC pre-mRNA") is a pre-mRNA transcript that contains at least one retained intron. The RIC pre-mRNA contains a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and encodes the target protein. An "RIC pre-mRNA encoding a target protein" is understood to encode the target protein when fully spliced. A "retained intron" is any intron that is present in a pre-mRNA transcript when one or more other introns, such as an adjacent intron, encoded by the same gene have been spliced out of the same pre-mRNA transcript. In some embodiments, the retained intron is the most abundant intron in RIC pre-mRNA encoding the target protein. In embodiments, the retained intron is the most abundant intron in a population of RIC pre-mRNAs transcribed from the gene encoding the target protein in a cell, wherein the population of RIC pre-mRNAs comprises two or more retained introns. In embodiments, an antisense oligomer targeted to the most abundant intron in the population of RIC pre-mRNAs encoding the target protein induces splicing out of two or more retained introns in the population, including the retained intron to which the antisense oligomer is targeted or binds. In embodiments, a mature mRNA encoding the target protein is thereby produced. The terms "mature mRNA," and "fully-spliced mRNA," are used interchangeably herein to describe a fully processed mRNA encoding a target protein (*e.g.*, mRNA that is exported from the nucleus into the cytoplasm and translated into target protein) or a fully processed functional RNA. The term "productive mRNA," also can be used to describe a fully processed mRNA encoding a target protein. In embodiments, the targeted region is in a retained intron that is the most abundant intron in a RIC pre-mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein.

[00235] As used herein, the term "comprise" or variations thereof such as "comprises" or "comprising" are to be read to indicate the inclusion of any recited feature (*e.g.* in the case of an antisense oligomer, a defined nucleobase sequence) but not the exclusion of any other features. Thus, as used herein, the term "comprising" is inclusive and does not exclude additional, unrecited features (*e.g.* in the case of an antisense oligomer, the presence of additional, unrecited nucleobases).

[00236] In embodiments of any of the compositions and methods provided herein, "comprising" may be replaced with "consisting essentially of " or "consisting of." The phrase "consisting essentially of" is used herein to require the specified feature(s) (*e.g.* nucleobase sequence) as well as those which do not materially affect the character or function of the claimed invention. As used herein, the term "consisting" is used to indicate the presence of the recited

feature (*e.g.* nucleobase sequence) alone (so that in the case of an antisense oligomer consisting of a specified nucleobase sequence, the presence of additional, unrecited nucleobases is excluded).

[00237] In embodiments, the targeted region is in a retained intron that is the second most abundant intron in a RIC pre-mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. For example, the second most abundant retained intron may be targeted rather than the most abundant retained intron due to the uniqueness of the nucleotide sequence of the second most abundant retained intron, ease of ASO design to target a particular nucleotide sequence, and/or amount of increase in protein production resulting from targeting the intron with an ASO. In embodiments, the retained intron is the second most abundant intron in a population of RIC pre-mRNAs transcribed from the gene encoding the target protein in a cell, wherein the population of RIC pre-mRNAs comprises two or more retained introns. In embodiments, an antisense oligomer targeted to the second most abundant intron in the population of RIC pre-mRNAs encoding the target protein induces splicing out of two or more retained introns in the population, including the retained intron to which the antisense oligomer is targeted or binds. In embodiments, fully-spliced (mature) RNA encoding the target protein is thereby produced.

[00238] In embodiments, an ASO is complementary to a targeted region that is within a non-retained intron in a RIC pre-mRNA. In embodiments, the targeted portion of the RIC pre-mRNA is within: the region +6 to +100 relative to the 5' splice site of the non-retained intron; or the region -16 to -100 relative to the 3' splice site of the non-retained intron. In embodiments, the targeted portion of the RIC pre-mRNA is within the region +100 relative to the 5' splice site of the non-retained intron to -100 relative to the 3' splice site of the non-retained intron. As used to identify the location of a region or sequence, "within" is understood to include the residues at the positions recited. For example, a region +6 to +100 includes the residues at positions +6 and +100. In embodiments, fully-spliced (mature) RNA encoding the target protein is thereby produced.

[00239] In embodiments, the retained intron of the RIC pre-mRNA is an inefficiently spliced intron. As used herein, "inefficiently spliced" may refer to a relatively low frequency of splicing at a splice site adjacent to the retained intron (5' splice site or 3' splice site) as compared to the frequency of splicing at another splice site in the RIC pre-mRNA. The term "inefficiently spliced" may also refer to the relative rate or kinetics of splicing at a splice site, in which an

"inefficiently spliced" intron may be spliced or removed at a slower rate as compared to another intron in a RIC pre-mRNA.

[00240] In embodiments, the 9-nucleotide sequence at -3e to -1e of the exon flanking the 5' splice site and +1 to +6 of the retained intron is identical to the corresponding wild-type sequence. In embodiments, the 16 nucleotide sequence at -15 to -1 of the retained intron and +1e of the exon flanking the 3' splice site is identical to the corresponding wild-type sequence. As used herein, the "wild-type sequence" refers to the nucleotide sequence for the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene in the published reference genome deposited in the NCBI repository of biological and scientific information (operated by National Center for Biotechnology Information, National Library of Medicine, 8600 Rockville Pike, Bethesda, MD USA 20894). As used herein, the "wild-type sequence" refers to NCBI Gene ID: (ROM1:6094; TEAD1:7003; RDH5:5959; NR2E3:10002; PAX6:5080; CRX: 1406; FSCN2: 25794; ABCA4:24; MYOC:4653; TCF4:6925; MFSD8:256471; CTNS:1497; NXNL1:115861). Also used herein, a nucleotide position denoted with an "e" indicates the nucleotide is present in the sequence of an exon (*e.g.*, the exon flanking the 5' splice site or the exon flanking the 3' splice site).

[00241] The methods involve contacting cells with an ASO that is complementary to a portion of a pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, resulting in increased expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA. As used herein, "contacting" or administering to cells refers to any method of providing an ASO in immediate proximity with the cells such that the ASO and the cells interact. A cell that is contacted with an ASO will take up or transport the ASO into the cell. The method involves contacting a condition or disease-associated or condition or disease-relevant cell with any of the ASOs described herein. In some embodiments, the ASO may be further modified or attached (*e.g.*, covalently attached) to another molecule to target the ASO to a cell type, enhance contact between the ASO and the condition or disease-associated or condition or disease-relevant cell, or enhance uptake of the ASO.

[00242] As used herein, the term "increasing protein production" or "increasing expression of a target protein" means enhancing the amount of protein that is translated from an mRNA in a cell. A "target protein" may be any protein for which increased expression/production is desired.

[00243] In embodiments, contacting a cell that expresses a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA with an ASO that is complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript results in a measurable increase in the amount of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein (*e.g.*, a target protein) encoded by the pre-mRNA. Methods of measuring or detecting production of a protein will be evident to one of skill in the art and include any known method, for example, Western blotting, flow cytometry, immunofluorescence microscopy, and ELISA.

[00244] In embodiments, contacting cells with an ASO that is complementary to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript results in an increase in the amount of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein produced by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In embodiments, the total amount of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein produced by the cell to which the antisense oligomer was contacted is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the amount of target protein produced by an control compound. A control compound can be, for

example, an oligonucleotide that is not complementary to the targeted portion of the RIC pre-mRNA.

[00245] In some embodiments, contacting cells with an ASO that is complementary to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript results in an increase in the amount of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA respectively, including the mature mRNA encoding the target protein. In some embodiments, the amount of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, or the mature mRNA encoding the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, is increased by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In embodiments, the total amount of the mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, or the mature mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein produced in the cell to which the antisense oligomer was contacted is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold compared to the amount of mature RNA produced in an untreated cell, *e.g.*, an untreated cell or a cell treated with a control compound. A control compound can be, for example, an oligonucleotide that is not complementary to the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX,

FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA.

Constitutive Splicing of a Retained Intron from a RIC pre-mRNA

[00246] The methods and antisense oligonucleotide compositions provided herein are useful for increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in cells, for example, in a subject having a deficiency in the amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, by increasing the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, or the mature mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein. In particular, the methods and compositions as described herein can induce the constitutive splicing of a retained intron from a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, thereby increasing the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, or the mature mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein and increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein.

[00247] Constitutive splicing of a retained intron from a RIC pre-mRNA correctly removes the retained intron from the RIC pre-mRNA, wherein the retained intron has wild-type splice sequences. Constitutive splicing, as used herein, does not encompass splicing of a retained intron from a RIC pre-mRNA transcribed from a gene or allele having a mutation that causes

alternative splicing or aberrant splicing of a pre-mRNA transcribed from the gene or allele. For example, constitutive splicing of a retained intron, as induced using the methods and antisense oligonucleotides provided herein, does not correct aberrant splicing in or influence alternative splicing of a pre-mRNA to result in an increased expression of a target protein or functional RNA.

[00248] In embodiments, constitutive splicing can correctly remove a retained intron from a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA, wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA is transcribed from a wild-type gene or allele, or a polymorphic gene or allele, that encodes a fully-functional target protein or functional RNA, and wherein the gene or allele does not have a mutation that causes alternative splicing or aberrant splicing of the retained intron.

[00249] In some embodiments, constitutive splicing of a retained intron from a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein correctly removes a retained intron from a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA is transcribed from a gene or allele from which the target gene or functional RNA is produced at a reduced level compared to production from a wild-type allele, and wherein the gene or allele does not have a mutation that causes alternative splicing or aberrant splicing of the retained intron. In these embodiments, the correct removal of the constitutively spliced retained intron results in production of target protein or functional RNA that is functional when compared to an equivalent wild-type protein or functional RNA.

[00250] In other embodiments, constitutive splicing can correctly remove a retained intron from a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA, wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA is transcribed from a gene or allele that encodes a target protein or functional RNA produced in a form having reduced function compared to an equivalent wild-type protein or functional RNA, and wherein the gene or allele does not have a mutation that causes alternative splicing or aberrant splicing of the retained intron. In these embodiments, the correct removal of the constitutively spliced retained intron results in production of partially functional target protein, or functional RNA that is partially functional when compared to an equivalent wild-type protein or functional RNA.

[00251] "Correct removal" of the retained intron by constitutive splicing refers to removal of the entire intron, without removal of any part of an exon.

[00252] In embodiments, an antisense oligomer as described herein or used in any method described herein does not increase the amount of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein or the amount of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein by modulating alternative splicing or aberrant splicing of a pre-mRNA transcribed from the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene. Modulation of alternative splicing or aberrant splicing can be measured using any known method for analyzing the sequence and length of RNA species, *e.g.*, by RT-PCR and using methods described elsewhere herein and in the literature. In embodiments, modulation of alternative or aberrant splicing is determined based on an increase or decrease in the amount of the spliced species of interest of at least 10% or 1.1-fold. In embodiments, modulation is determined based on an increase or decrease at a level that is at least 10% to 100% or 1.1 to 10-fold, as described herein regarding determining an increase in mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the methods of the invention.

[00253] In embodiments, the method is a method wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA can be produce by partial splicing of a wild-type ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA. In embodiments, the method is a method wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA can be produce by partial splicing of a full-length wild-type ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA. In embodiments, the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA can be produce by partial splicing of a full-length ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA. In these embodiments, a full-length ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA pre-mRNA may have a polymorphism in a splice site of the retained intron that does not impair correct splicing of the retained intron as compared to splicing of the retained intron having the wild-type splice site sequence.

[00254] In embodiments, the mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein is a full-length mature mRNA, or a wild-type mature mRNA. In these embodiments, a full-length mature mRNA may have a polymorphism that does not affect the activity of the target protein or the functional RNA encoded by the mature mRNA, as compared to the activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein encoded by the wild-type mature mRNA.

Antisense Oligomers

[00255] One aspect of the present disclosure is a composition comprising antisense oligomers that enhances splicing by binding to a targeted portion of a ROM1, TEAD1, RDH5,

NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA. As used herein, the terms "ASO" and "antisense oligomer" are used interchangeably and refer to an oligomer such as a polynucleotide, comprising nucleobases, that hybridizes to a target nucleic acid (*e.g.*, a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA) sequence by Watson-Crick base pairing or wobble base pairing (G-U). The ASO may have exact sequence complementary to the target sequence or near complementarity (*e.g.*, sufficient complementarity to bind the target sequence and enhancing splicing at a splice site). ASOs are designed so that they bind (hybridize) to a target nucleic acid (*e.g.*, a targeted portion of a pre-mRNA transcript) and remain hybridized under physiological conditions. Typically, if they hybridize to a site other than the intended (targeted) nucleic acid sequence, they hybridize to a limited number of sequences that are not a target nucleic acid (to a few sites other than a target nucleic acid). Design of an ASO can take into consideration the occurrence of the nucleic acid sequence of the targeted portion of the pre-mRNA transcript or a sufficiently similar nucleic acid sequence in other locations in the genome or cellular pre-mRNA or transcriptome, such that the likelihood the ASO will bind other sites and cause "off-target" effects is limited. Any antisense oligomers known in the art, for example in PCT Application No. PCT/US2014/054151, published as WO 2015/035091, titled "Reducing Nonsense-Mediated mRNA Decay," can be used to practice the methods described herein.

[00256] In some embodiments, ASOs "specifically hybridize" to or are "specific" to a target nucleic acid or a targeted portion of a RIC pre-mRNA. Typically such hybridization occurs with a Tm substantially greater than 37°C, preferably at least 50°C, and typically between 60°C to approximately 90°C. Such hybridization preferably corresponds to stringent hybridization conditions. At a given ionic strength and pH, the Tm is the temperature at which 50% of a target sequence hybridizes to a complementary oligonucleotide.

[00257] Oligomers, such as oligonucleotides, are "complementary" to one another when hybridization occurs in an antiparallel configuration between two single-stranded polynucleotides. A double-stranded polynucleotide can be "complementary" to another polynucleotide, if hybridization can occur between one of the strands of the first polynucleotide and the second. Complementarity (the degree to which one polynucleotide is complementary with another) is quantifiable in terms of the proportion (*e.g.*, the percentage) of bases in opposing strands that are expected to form hydrogen bonds with each other, according to generally accepted base-pairing rules. The sequence of an antisense oligomer (ASO) need not be 100%

complementary to that of its target nucleic acid to hybridize. In certain embodiments, ASOs can comprise at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence complementarity to a target region within the target nucleic acid sequence to which they are targeted. For example, an ASO in which 18 of 20 nucleobases of the oligomeric compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered together or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. Percent complementarity of an ASO with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 7, 649-656).

[00258] An ASO need not hybridize to all nucleobases in a target sequence and the nucleobases to which it does hybridize may be contiguous or noncontiguous. ASOs may hybridize over one or more segments of a pre-mRNA transcript, such that intervening or adjacent segments are not involved in the hybridization event (*e.g.*, a loop structure or hairpin structure may be formed). In certain embodiments, an ASO hybridizes to noncontiguous nucleobases in a target pre-mRNA transcript. For example, an ASO can hybridize to nucleobases in a pre-mRNA transcript that are separated by one or more nucleobase(s) to which the ASO does not hybridize.

[00259] The ASOs described herein comprise nucleobases that are complementary to nucleobases present in a target portion of a RIC pre-mRNA. The term ASO embodies oligonucleotides and any other oligomeric molecule that comprises nucleobases capable of hybridizing to a complementary nucleobase on a target mRNA but does not comprise a sugar moiety, such as a peptide nucleic acid (PNA). The ASOs may comprise naturally-occurring nucleotides, nucleotide analogs, modified nucleotides, or any combination of two or three of the preceding. The term “naturally occurring nucleotides” includes deoxyribonucleotides and ribonucleotides. The term “modified nucleotides” includes nucleotides with modified or substituted sugar groups and/or having a modified backbone. In some embodiments, all of the nucleotides of the ASO are modified nucleotides. Chemical modifications of ASOs or components of ASOs that are compatible with the methods and compositions described herein will be evident to one of skill in the art and can be found, for example, in U.S. Patent No. 8,258,109 B2, U.S. Patent No. 5,656,612, U.S. Patent Publication No. 2012/0190728, and Dias and Stein, Mol. Cancer Ther. 2002, 1 , 347-355, herein incorporated by reference in their entirety.

[00260] The nucleobase of an ASO may be any naturally occurring, unmodified nucleobase such as adenine, guanine, cytosine, thymine and uracil, or any synthetic or modified nucleobase that is sufficiently similar to an unmodified nucleobase such that it is capable of hydrogen bonding with a nucleobase present on a target pre-mRNA. Examples of modified nucleobases include, without limitation, hypoxanthine, xanthine, 7-methylguanine, 5,6-dihydrouracil, 5-methylcytosine, and 5-hydroxymethoylcytosine.

[00261] The ASOs described herein also comprise a backbone structure that connects the components of an oligomer. The term "backbone structure" and "oligomer linkages" may be used interchangeably and refer to the connection between monomers of the ASO. In naturally occurring oligonucleotides, the backbone comprises a 3'-5' phosphodiester linkage connecting sugar moieties of the oligomer. The backbone structure or oligomer linkages of the ASOs described herein may include (but are not limited to) phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoramidate, and the like. See *e.g.*, LaPlanche et al., Nucleic Acids Res. 14:9081 (1986); Stec et al., J. Am. Chem. Soc. 106:6077 (1984), Stein et al., Nucleic Acids Res. 16:3209 (1988), Zon et al., Anti Cancer Drug Design 6:539 (1991); Zon et al., Oligonucleotides and Analogues: A Practical Approach, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al., U.S. Pat. No. 5,151,510; Uhlmann and Peyman, Chemical Reviews 90:543 (1990). In some embodiments, the backbone structure of the ASO does not contain phosphorous but rather contains peptide bonds, for example in a peptide nucleic acid (PNA), or linking groups including carbamate, amides, and linear and cyclic hydrocarbon groups. In some embodiments, the backbone modification is a phosphorothioate linkage. In some embodiments, the backbone modification is a phosphoramidate linkage.

[00262] In embodiments, the stereochemistry at each of the phosphorus internucleotide linkages of the ASO backbone is random. In embodiments, the stereochemistry at each of the phosphorus internucleotide linkages of the ASO backbone is controlled and is not random. For example, U.S. Pat. App. Pub. No. 2014/0194610, "Methods for the Synthesis of Functionalized Nucleic Acids," incorporated herein by reference, describes methods for independently selecting the handedness of chirality at each phosphorous atom in a nucleic acid oligomer. In embodiments, an ASO used in the methods of the inventioncomprises an ASO having phosphorus internucleotide linkages that are not random. In embodiments, a composition used in the methods of the invention comprises a pure diastereomeric ASO. In embodiments, a composition used in the methods of the invention comprises an ASO that has diastereomeric purity of 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%, about 100%, about 90% to about 100%, about 91% to about 100%, about 92% to about 100%, about 93% to about 100%, about 94% to about 100%, about 95% to about 100%, about 96% to about 100%, about 97% to about 100%, about 98% to about 100% , or about 99% to about 100%.

[00263] In embodiments, the ASO has a nonrandom mixture of Rp and Sp configurations at its phosphorus internucleotide linkages. For example, it has been suggested that a mix of Rp and Sp is required in antisense oligonucleotides to achieve a balance between good activity and nuclease stability (Wan, et al., 2014, "Synthesis, biophysical properties and biological activity of second generation antisense oligonucleotides containing chiral phosphorothioate linkages," Nucleic Acids Research 42(22): 13456-13468, incorporated herein by reference). In embodiments, an ASO used in the methods of the inventioncomprises about 5-100% Rp, at least about 5% Rp, at least about 10% Rp, at least about 15% Rp, at least about 20% Rp, at least about 25% Rp, at least about 30% Rp, at least about 35% Rp, at least about 40% Rp, at least about 45% Rp, at least about 50% Rp, at least about 55% Rp, at least about 60% Rp, at least about 65% Rp, at least about 70% Rp, at least about 75% Rp, at least about 80% Rp, at least about 85% Rp, at least about 90% Rp, or at least about 95% Rp, with the remainder Sp, or about 100% Rp. In embodiments, an ASO used in the methods of the inventioncomprises about 10% to about 100% Rp, about 15% to about 100% Rp, about 20% to about 100% Rp, about 25% to about 100% Rp, about 30% to about 100% Rp, about 35% to about 100% Rp, about 40% to about 100% Rp, about 45% to about 100% Rp, about 50% to about 100% Rp, about 55% to about 100% Rp, about 60% to about 100% Rp, about 65% to about 100% Rp, about 70% to about 100% Rp, about 75% to about 100% Rp, about 80% to about 100% Rp, about 85% to about 100% Rp, about 90% to about 100% Rp, or about 95% to about 100% Rp, about 20% to about 80% Rp, about 25% to about 75% Rp, about 30% to about 70% Rp, about 40% to about 60% Rp, or about 45% to about 55% Rp, with the remainder Sp.

[00264] In embodiments, an ASO used in the methods of the inventioncomprises about 5-100% Sp, at least about 5% Sp, at least about 10% Sp, at least about 15% Sp, at least about 20% Sp, at least about 25% Sp, at least about 30% Sp, at least about 35% Sp, at least about 40% Sp, at least about 45% Sp, at least about 50% Sp, at least about 55% Sp, at least about 60% Sp, at least about 65% Sp, at least about 70% Sp, at least about 75% Sp, at least about 80% Sp, at least about 85% Sp, at least about 90% Sp, or at least about 95% Sp, with the remainder Rp, or about 100% Sp. In embodiments, an ASO used in the methods of the invention, comprises about 10% to about 100% Sp, about 15% to about 100% Sp, about 20% to about 100% Sp, about 25% to about

100% Sp, about 30% to about 100% Sp, about 35% to about 100% Sp, about 40% to about 100% Sp, about 45% to about 100% Sp, about 50% to about 100% Sp, about 55% to about 100% Sp, about 60% to about 100% Sp, about 65% to about 100% Sp, about 70% to about 100% Sp, about 75% to about 100% Sp, about 80% to about 100% Sp, about 85% to about 100% Sp, about 90% to about 100% Sp, or about 95% to about 100% Sp, about 20% to about 80% Sp, about 25% to about 75% Sp, about 30% to about 70% Sp, about 40% to about 60% Sp, or about 45% to about 55% Sp, with the remainder Rp.

[00265] Any of the ASOs described herein may contain a sugar moiety that comprises ribose or deoxyribose, as present in naturally occurring nucleotides, or a modified sugar moiety or sugar analog, including a morpholine ring. Non-limiting examples of modified sugar moieties include 2' substitutions such as 2'-O-methyl (2′-O-Me), 2'-O-methoxyethyl (2'MOE), 2'-O-aminoethyl, 2'F; N3'->P5' phosphoramidate, 2'dimethylaminooxyethoxy, 2'dimethylaminoethoxyethoxy, 2'-guanidinidium, 2'-O-guanidinium ethyl, carbamate modified sugars, and bicyclic modified sugars. In some embodiments, the sugar moiety modification is selected from 2′-O-Me, 2'F, and 2'MOE. In some embodiments, the sugar moiety modification is an extra bridge bond, such as in a locked nucleic acid (LNA). In some embodiments the sugar analog contains a morpholine ring, such as phosphorodiamidate morpholino (PMO). In some embodiments, the sugar moiety comprises a ribofuransyl or 2'deoxyribofuransyl modification. In some embodiments, the sugar moiety comprises 2'4'-constrained 2'O-methyloxyethyl (cMOE) modifications. In some embodiments, the sugar moiety comprises cEt 2', 4' constrained 2'-O ethyl BNA modifications. In some embodiments, the sugar moiety comprises tricycloDNA (tcDNA) modifications. In some embodiments, the sugar moiety comprises ethylene nucleic acid (ENA) modifications. In some embodiments, the sugar moiety comprises MCE modifications. Modifications are known in the art and described in the literature, *e.g.*, by Jarver, et al., 2014, "A Chemical View of Oligonucleotides for Exon Skipping and Related Drug Applications," Nucleic Acid Therapeutics 24(1): 37-47, incorporated by reference for this purpose herein.

[00266] In some examples, each monomer of the ASO is modified in the same way, for example each linkage of the backbone of the ASO comprises a phosphorothioate linkage or each ribose sugar moiety comprises a 2'O-methyl modification. Such modifications that are present on each of the monomer components of an ASO are referred to as "uniform modifications." In some examples, a combination of different modifications may be desired, for example, an ASO may comprise a combination of phosphorodiamidate linkages and sugar moieties comprising morpholine rings (morpholinos). Combinations of different modifications to an ASO are referred to as "mixed modifications" or "mixed chemistries."

[00267] In some embodiments, the ASO comprises one or more backbone modification. In some embodiments, the ASO comprises one or more sugar moiety modification. In some embodiments, the ASO comprises one or more backbone modification and one or more sugar moiety modification. In some embodiments, the ASO comprises 2'MOE modifications and a phosphorothioate backbone. In some embodiments, the ASO comprises a phosphorodiamidate morpholino (PMO). In some embodiments, the ASO comprises a peptide nucleic acid (PNA). Any of the ASOs or any component of an ASO (*e.g.*, a nucleobase, sugar moiety, backbone) described herein may be modified in order to achieve desired properties or activities of the ASO or reduce undesired properties or activities of the ASO. For example, an ASO or one or more component of any ASO may be modified to enhance binding affinity to a target sequence on a pre-mRNA transcript; reduce binding to any non-target sequence; reduce degradation by cellular nucleases (i.e., RNase H); improve uptake of the ASO into a cell and/or into the nucleus of a cell; alter the pharmacokinetics or pharmacodynamics of the ASO; and modulate the half-life of the ASO.

[00268] In some embodiments, the ASOs are comprised of 2'-O-(2-methoxyethyl) (MOE) phosphorothioate-modified nucleotides. ASOs comprised of such nucleotides are especially well-suited to the methods disclosed herein; oligomers having such modifications have been shown to have significantly enhanced resistance to nuclease degradation and increased bioavailability, making them suitable, for example, for oral delivery in some embodiments described herein. See *e.g.*, Geary et al., J Pharmacol Exp Ther. 2001; 296(3):890-7; Geary et al., J Pharmacol Exp Ther. 2001; 296(3):898-904.

[00269] Methods of synthesizing ASOs will be known to one of skill in the art. Alternatively or in addition, ASOs may be obtained from a commercial source.

[00270] Unless specified otherwise, the left-hand end of single-stranded nucleic acid (*e.g.*, pre-mRNA transcript, oligonucleotide, ASO, etc.) sequences is the 5′ end and the left-hand direction of single or double-stranded nucleic acid sequences is referred to as the 5′ direction. Similarly, the right-hand end or direction of a nucleic acid sequence (single or double stranded) is the 3′ end or direction. Generally, a region or sequence that is 5′ to a reference point in a nucleic acid is referred to as "upstream," and a region or sequence that is 3′ to a reference point in a nucleic acid is referred to as "downstream." Generally, the 5′ direction or end of an mRNA is where the initiation or start codon is located, while the 3′ end or direction is where the termination codon is located. In some aspects, nucleotides that are upstream of a reference point in a nucleic acid may be designated by a negative number, while nucleotides that are downstream of a reference point may be designated by a positive number. For example, a reference point

(*e.g.*, an exon-exon junction in mRNA) may be designated as the "zero" site, and a nucleotide that is directly adjacent and upstream of the reference point is designated "minus one," *e.g.*, "-1," while a nucleotide that is directly adjacent and downstream of the reference point is designated "plus one," *e.g.*, "+1."

[00271] In other embodiments, the ASOs are complementary to (and bind to) a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is downstream (in the 3' direction) of the 5' splice site of the retained intron in a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA (*e.g.*, the direction designated by positive numbers relative to the 5' splice site) (Figure 1). In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region +6 to +100 relative to the 5' splice site of the retained intron. In some embodiments, the ASO is not complementary to nucleotides +1 to +5 relative to the 5' splice site (the first five nucleotides located downstream of the 5' splice site). In some embodiments, the ASOs may be complementary to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region between nucleotides +6 and +50 relative to the 5' splice site of the retained intron. In some aspects, the ASOs are complementary to a targeted portion that is within the region +6 to +90, +6 to +80, +6 to +70, +6 to +60, +6 to +50, +6 to +40, +6 to +30, or +6 to +20 relative to 5' splice site of the retained intron.

[00272] In some embodiments, the ASOs are complementary to a targeted region of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is upstream (5' relative) of the 3' splice site of the retained intron in a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA (*e.g.*, in the direction designated by negative numbers) (Figure 1). In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8,

CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region -16 to -100 relative to the 3' splice site of the retained intron. In some embodiments, the ASO is not complementary to nucleotides -1 to -15 relative to the 3' splice site (the first 15 nucleotides located upstream of the 3' splice site). In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region -16 to -50 relative to the 3' splice site of the retained intron. In some aspects, the ASOs are complementary to a targeted portion that is within the region -16 to -90, -16 to -80, -16 to -70, -16 to -60, -16 to -50, -16 to -40, or -16 to -30 relative to 3' splice site of the retained intron.

[00273] In embodiments, the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA is within the region +100 relative to the 5' splice site of the retained intron to -100 relative to the 3' splice site of the retained intron.

[00274] In some embodiments, the ASOs are complementary to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the exon flanking the 5' splice site (upstream) of the retained intron (Figure 1). In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region +2e to -4e in the exon flanking the 5' splice site of the retained intron. In some embodiments, the ASOs are not complementary to nucleotides -1e to -3e relative to the 5' splice site of the retained intron. In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region -4e to-100e, -4e to -90e, -4e to -80e, -4e to -70e, -4e to -60e, -4e to -50e, -4 to -40e, -4e to -30e, or -4e to -20e relative to the 5' splice site of the retained intron.

[00275] In some embodiments, the ASOs are complementary to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1,

PER1 or IDUA RIC pre-mRNA that is within the exon flanking the 3' splice site (downstream) of the retained intron (Figure 1). In some embodiments, the ASOs are complementary to a targeted portion to the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region +2e to -4e in the exon flanking the 3' splice site of the retained intron. In some embodiments, the ASOs are not complementary to nucleotide +1e relative to the 3' splice site of the retained intron. In some embodiments, the ASOs are complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA that is within the region+2e to +100e, +2e to +90e, +2e to +80e, +2e to +70e, +2e to +60e, +2e to +50e, +2e to +40e, +2e to +30e, or +2 to +20e relative to the 3' splice site of the retained intron. The ASOs may be of any length suitable for specific binding and effective enhancement of splicing. In some embodiments, the ASOs consist of 8 to 50 nucleobases. For example, the ASO may be 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 40, 45, or 50 nucleobases in length. In some embodiments, the ASOs consist of more than 50 nucleobases. In some embodiments, the ASO is from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, 12 to 15 nucleobases, 13 to 50 nucleobases, 13 to 40 nucleobases, 13 to 35 nucleobases, 13 to 30 nucleobases, 13 to 25 nucleobases, 13 to 20 nucleobases, 14 to 50 nucleobases, 14 to 40 nucleobases, 14 to 35 nucleobases, 14 to 30 nucleobases, 14 to 25 nucleobases, 14 to 20 nucleobases, 15 to 50 nucleobases, 15 to 40 nucleobases, 15 to 35 nucleobases, 15 to 30 nucleobases, 15 to 25 nucleobases, 15 to 20 nucleobases, 20 to 50 nucleobases, 20 to 40 nucleobases, 20 to 35 nucleobases, 20 to 30 nucleobases, 20 to 25 nucleobases, 25 to 50 nucleobases, 25 to 40 nucleobases, 25 to 35 nucleobases, or 25 to 30 nucleobases in length. In some embodiments, the ASOs are 18 nucleotides in length. In some embodiments, the ASOs are 15 nucleotides in length. In some embodiments, the ASOs are 25 nucleotides in length.

[00276] In some embodiments, two or more ASOs with different chemistries but complementary to the same targeted portion of the RIC pre-mRNA are used. In some embodiments, two or more ASOs that are complementary to different targeted portions of the RIC pre-mRNA are used.

[00277] In embodiments, the antisense oligonucleotides of the invention are chemically linked to one or more moieties or conjugates, *e.g.*, a targeting moiety or other conjugate that enhances the activity or cellular uptake of the oligonucleotide. Such moieties include, but are not limited to, a lipid moiety, *e.g.*, as a cholesterol moiety, a cholesteryl moiety, an aliphatic chain, *e.g.*, dodecandiol or undecyl residues, a polyamine or a polyethylene glycol chain, or adamantane acetic acid. Oligonucleotides comprising lipophilic moieties, and preparation methods have been described in the published literature. In embodiments, the antisense oligonucleotide is conjugated with a moiety including, but not limited to, an abasic nucleotide, a polyether, a polyamine, a polyamide, a peptides, a carbohydrate, *e.g.*, N-acetylgalactosamine (GalNAc), N-Ac-Glucosamine (GluNAc), or mannose (*e.g.*, mannose-6-phosphate), a lipid, or a polyhydrocarbon compound. Conjugates can be linked to one or more of any nucleotides comprising the antisense oligonucleotide at any of several positions on the sugar, base or phosphate group, as understood in the art and described in the literature, *e.g.*, using a linker. Linkers can include a bivalent or trivalent branched linker. In embodiments, the conjugate is attached to the 3' end of the antisense oligonucleotide. Methods of preparing oligonucleotide conjugates are described, *e.g.*, in U.S. Pat. No. 8,450,467, "Carbohydrate conjugates as delivery agents for oligonucleotides," incorporated by reference herein.

[00278] In some embodiments, the nucleic acid to be targeted by an ASO is a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA expressed in a cell, such as a eukaryotic cell. In some embodiments, the term "cell" may refer to a population of cells. In some embodiments, the cell is in a subject. In some embodiments, the cell is isolated from a subject. In some embodiments, the cell is *ex vivo*. In some embodiments, the cell is a condition or disease-relevant cell or a cell line. In some embodiments, the cell is *in vitro* (*e.g.*, in cell culture).

Pharmaceutical Compositions

[00279] Pharmaceutical compositions or formulations comprising the antisense oligonucleotide of the described compositions and for use in any of the described methods can be prepared according to conventional techniques well known in the pharmaceutical industry and described in the published literature. In embodiments, a pharmaceutical composition or

formulation for treating a subject comprises an effective amount of any antisense oligomer as described above, or a pharmaceutically acceptable salt, solvate, hydrate or ester thereof, and a pharmaceutically acceptable diluent. The antisense oligomer of a pharmaceutical formulation may further comprise a pharmaceutically acceptable excipient, diluent or carrier.

[00280] Pharmaceutically acceptable salts are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, etc., and are commensurate with a reasonable benefit/risk ratio. (See, e.g., S. M. Berge, et al., J. Pharmaceutical Sciences, 66: 1-19 (1977), incorporated herein by reference for this purpose. The salts can be prepared in situ during the final isolation and purification of the compounds, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other documented methodologies such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00281] In embodiments, the compositions are formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. In embodiments, the compositions are formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers. In embodiments, a pharmaceutical formulation or composition of the present invention includes, but is not limited

to, a solution, emulsion, microemulsion, foam or liposome-containing formulation (e.g., cationic or noncationic liposomes).

[00282] The pharmaceutical composition or formulation of the present invention may comprise one or more penetration enhancer, carrier, excipients or other active or inactive ingredients as appropriate and well known to those of skill in the art or described in the published literature. In embodiments, liposomes also include sterically stabilized liposomes, e.g., liposomes comprising one or more specialized lipids. These specialized lipids result in liposomes with enhanced circulation lifetimes. In embodiments, a sterically stabilized liposome comprises one or more glycolipids or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. In embodiments, a surfactant is included in the pharmaceutical formulation or compositions. The use of surfactants in drug products, formulations and emulsions is well known in the art. In embodiments, the present invention employs a penetration enhancer to effect the efficient delivery of the antisense oligonucleotide, e.g., to aid diffusion across cell membranes and /or enhance the permeability of a lipophilic drug. In embodiments, the penetration enhancers is a surfactant, fatty acid, bile salt, chelating agent, or non-chelating nonsurfactant.

[00283] In embodiments, the pharmaceutical formulation comprises multiple antisense oligonucleotides. In embodiments, the antisense oligonucleotide is administered in combination with another drug or therapeutic agent. In embodiments, the antisense oligonucleotide is administered with one or more agents capable of promoting penetration of the subject antisense oligonucleotide across the blood-brain barrier by any method known in the art. For example, delivery of agents by administration of an adenovirus vector to motor neurons in muscle tissue is described in U.S. Pat. No. 6,632,427, "Adenoviral-vector-mediated gene transfer into medullary motor neurons," incorporated herein by reference. Delivery of vectors directly to the brain, e.g., the striatum, the thalamus, the hippocampus, or the substantia nigra, is described, e.g., in U.S. Pat. No. 6,756,523, "Adenovirus vectors for the transfer of foreign genes into cells of the central nervous system particularly in brain," incorporated herein by reference.

[00284] In embodiments, the antisense oligonucleotides are linked or conjugated with agents that provide desirable pharmaceutical or pharmacodynamic properties. In embodiments, the antisense oligonucleotide is coupled to a substance, known in the art to promote penetration or transport across the blood-brain barrier, e.g., an antibody to the transferrin receptor. In embodiments, the antisense oligonucleotide is linked with a viral vector, e.g., to render the antisense compound more effective or increase transport across the blood-brain barrier. In embodiments, osmotic blood brain barrier disruption is assisted by infusion of sugars, e.g., meso

erythritol, xylitol, D(+) galactose, D(+) lactose, D(+) xylose, dulcitol, myo-inositol, L(-) fructose, D(-) mannitol, D(+) glucose, D(+) arabinose, D(-) arabinose, cellobiose, D(+) maltose, D(+) raffinose, L(+) rhamnose, D(+) melibiose, D(-) ribose, adonitol, D(+) arabitol, L(-) arabitol, D(+) fucose, L(-) fucose, D(-) lyxose, L(+) lyxose, and L(-) lyxose, or amino acids, e.g., glutamine, lysine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine, and taurine. Methods and materials for enhancing blood brain barrier penetration are described, e.g., in U.S. Pat. No. 4,866,042, "Method for the delivery of genetic material across the blood brain barrier," U.S. Pat. No. 6,294,520, "Material for passage through the blood-brain barrier," and U.S. Pat. No. 6,936,589, "Parenteral delivery systems," each incorporated herein by reference.

[00285] In embodiments, the antisense oligonucleotides of the invention are chemically linked to one or more moieties or conjugates, e.g., a targeting moiety or other conjugate that enhances the activity or cellular uptake of the oligonucleotide. Such moieties include, but are not limited to, a lipid moiety, e.g., as a cholesterol moiety, a cholesteryl moiety, an aliphatic chain, e.g., dodecandiol or undecyl residues, a polyamine or a polyethylene glycol chain, or adamantane acetic acid. Oligonucleotides comprising lipophilic moieties, and preparation methods have been described in the published literature. In embodiments, the antisense oligonucleotide is conjugated with a moiety including, but not limited to, an abasic nucleotide, a polyether, a polyamine, a polyamide, a peptides, a carbohydrate, e.g., N-acetylgalactosamine (GalNAc), N-Ac-Glucosamine (GluNAc), or mannose (e.g., mannose-6-phosphate), a lipid, or a polyhydrocarbon compound. Conjugates can be linked to one or more of any nucleotides comprising the antisense oligonucleotide at any of several positions on the sugar, base or phosphate group, as understood in the art and described in the literature, e.g., using a linker. Linkers can include a bivalent or trivalent branched linker. In embodiments, the conjugate is attached to the 3' end of the antisense oligonucleotide. Methods of preparing oligonucleotide conjugates are described, *e.g.*, in U.S. Pat. No. 8,450,467, “Carbohydrate conjugates as delivery agents for oligonucleotides,” incorporated by reference herein.

Treatment of Subjects

[00286] Any of the compositions provided herein may be administered to an individual. “Individual” may be used interchangeably with “subject” or “patient.” An individual may be a mammal, for example a human or animal such as a non-human primate, a rodent, a rabbit, a rat, a mouse, a horse, a donkey, a goat, a cat, a dog, a cow, a pig, or a sheep. In embodiments, the individual is a human. In embodiments, the individual is a fetus, an embryo, or a child. In other

embodiments, the individual may be another eukaryotic organism, such as a plant. In some embodiments, the compositions provided herein are administered to a cell *ex vivo*.

[00287] In some embodiments, the compositions provided herein are administered to an individual as a method of treating a disease or disorder. In some embodiments, the individual has a genetic disease, such as any of the diseases described herein. In some embodiments, the individual is at risk of having the disease, such as any of the diseases described herein. In some embodiments, the individual is at increased risk of having a disease or disorder caused by insufficient amount of a protein or insufficient activity of a protein. If an individual is "at an increased risk" of having a disease or disorder caused insufficient amount of a protein or insufficient activity of a protein, the method involves preventative or prophylactic treatment. For example, an individual may be at an increased risk of having such a disease or disorder because of family history of the disease. Typically, individuals at an increased risk of having such a disease or disorder benefit from prophylactic treatment (*e.g.*, by preventing or delaying the onset or progression of the disease or disorder).

[00288] Suitable routes for administration of ASOs of the present invention may vary depending on cell type to which delivery of the ASOs is desired. The ASOs of the present invention may be administered to patients parenterally, for example, by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection. In embodiments, delivery is to the heart or liver. In embodiments, a fetus is treated in utero, e.g., by administering the ASO composition to the fetus directly or indirectly (e.g., via the mother).

[00289] The compositions of the present invention may be provided to muscle cells by any suitable means, including direct administration (e.g., locally by injection or topical administration at a treatment site) or systemically (e.g., parenterally or orally), intranasally, orally, or by intravitreal, subretinal, implantation, inhalational, enteral, topical, intrauterine, vaginal, sublingual, rectal, intramuscular, intrapleural, intraventricular, intraperitoneal, ophthalmic, intravenous, or subcutaneous means.

Methods of identifying additional ASOs that enhance splicing

[00290] Also within the scope of the present invention are methods for identifying (determining) additional ASOs that enhance splicing of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA, specifically at the target intron. ASOs that specifically hybridize to different nucleotides within the target region of the pre-mRNA may be screened to identify (determine) ASOs that improve

the rate and/or extent of splicing of the target intron. In some embodiments, the ASO may block or interfere with the binding site(s) of a splicing repressor(s)/silencer. Any method known in the art may be used to identify (determine) an ASO that when hybridized to the target region of the intron results in the desired effect (*e.g.*, enhanced splicing, protein or functional RNA production). These methods also can be used for identifying ASOs that enhance splicing of the retained intron by binding to a targeted region in an exon flanking the retained intron, or in a non-retained intron. An example of a method that may be used is provided below.

[00291] A round of screening, referred to as an ASO "walk" may be performed using ASOs that have been designed to hybridize to a target region of a pre-mRNA. For example, the ASOs used in the ASO walk can be tiled every 5 nucleotides from approximately 100 nucleotides upstream of the 5' splice site of the retained intron (*e.g.*, a portion of sequence of the exon located upstream of the target/retained intron) to approximately 100 nucleotides downstream of the 5' splice site of the target/retained intron and/or from approximately 100 nucleotides upstream of the 3' splice site of the retained intron to approximately 100 nucleotides downstream of the 3' splice site of the target/retained intron (*e.g.*, a portion of sequence of the exon located downstream of the target/retained intron). For example, a first ASO of 15 nucleotides in length may be designed to specifically hybridize to nucleotides +6 to +20 relative to the 5' splice site of the target/retained intron. A second ASO is designed to specifically hybridize to nucleotides +11 to +25 relative to the 5' splice site of the target/retained intron. ASOs are designed as such spanning the target region of the pre-mRNA. In embodiments, the ASOs can be tiled more closely, *e.g.*, every 1, 2, 3, or 4 nucleotides. Further, the ASOs can be tiled from 100 nucleotides downstream of the 5' splice site, to 100 nucleotides upstream of the 3' splice site.

[00292] One or more ASOs, or a control ASO (an ASO with a scrambled sequence, sequence that is not expected to hybridize to the target region) are delivered, for example by transfection, into a disease-relevant cell line that expresses the target pre-mRNA (e.g., the RIC pre-mRNA described elsewhere herein). The splicing-inducing effects of each of the ASOs may be assessed by any method known in the art, for example by reverse transcriptase (RT)-PCR using primers that span the splice junction, as described herein (see "Identification of intron-retention events"). A reduction or absence of the RT-PCR product produced using the primers spanning the splice junction in ASO-treated cells as compared to in control ASO-treated cells indicates that splicing of the target intron has been enhanced. In some embodiments, the splicing efficiency, the ratio of spliced to unspliced pre-mRNA, the rate of splicing, or the extent of splicing may be improved using the ASOs described herein. The amount of protein or functional RNA that is encoded by the target pre-mRNA can also be assessed to determine whether each

ASO achieved the desired effect (*e.g.*, enhanced protein production). Any method known in the art for assessing and/or quantifying protein production, such as Western blotting, flow cytometry, immunofluorescence microscopy, and ELISA, can be used.

[00293] A second round of screening, referred to as an ASO "micro-walk" may be performed using ASOs that have been designed to hybridize to a target region of a pre-mRNA. The ASOs used in the ASO micro-walk are tiled every 1 nucleotide to further refine the nucleotide acid sequence of the pre-mRNA that when hybridized with an ASO results in enhanced splicing.

[00294] Regions defined by ASOs that promote splicing of the target intron are explored in greater detail by means of an ASO "micro-walk", involving ASOs spaced in 1-nt steps, as well as longer ASOs, typically 18-25 nt.

[00295] As described for the ASO walk above, the ASO micro-walk can be perform by delivering one or more ASOs, or a control ASO (an ASO with a scrambled sequence, sequence that is not expected to hybridize to the target region), for example by transfection, into a disease-relevant cell line that expresses the target pre-mRNA. The splicing-inducing effects of each of the ASOs may be assessed by any method known in the art, for example by reverse transcriptase (RT)-PCR using primers that span the splice junction, as described herein (see "Identification of intron-retention events"). A reduction or absence of the RT-PCR product produced using the primers spanning the splice junction in ASO-treated cells as compared to in control ASO-treated cells indicates that splicing of the target intron has been enhanced. In some embodiments, the splicing efficiency, the ratio of spliced to unspliced pre-mRNA, the rate of splicing, or the extent of splicing may be improved using the ASOs described herein. The amount of protein or functional RNA that is encoded by the target pre-mRNA can also be assessed to determine whether each ASO achieved the desired effect (*e.g.*, enhanced protein production). Any method known in the art for assessing and/or quantifying protein production, such as Western blotting, flow cytometry, immunofluorescence microscopy, and ELISA, can be used.

[00296] ASOs that when hybridized to a region of a pre-mRNA result in enhanced splicing and increased protein production may be tested *in vivo* using animal models, for example transgenic mouse models in which the full-length human gene has been knocked-in or in humanized mouse models of disease. Suitable routes for administration of ASOs may vary depending on the disease and/or the cell types to which delivery of the ASOs is desired. ASOs may be administered, for example, by intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection. Following administration, the cells, tissues, and/or organs of the model animals may be assessed to determine the effect of the ASO treatment

by for example evaluating splicing (efficiency, rate, extent) and protein production by methods known in the art and described herein. The animal models may also be any phenotypic or behavioral indication of the disease or disease severity.

[00297] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

EXAMPLES

[00298] The present invention will be more specifically illustrated by the following Examples. However, it should be understood that the present invention is not limited by these examples in any manner.

Example 1: Identification of intron retention events in ROM1, TEAD1, RDH5, PAX6, FSCN2, MYOC, TCF4, MFSD8, CTNS, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 and IDUA transcripts by RNAseq using next generation sequencing

Whole transcriptome shotgun sequencing was carried out using next generation sequencing to reveal a snapshot of transcripts produced by the ROM1, TEAD1, RDH5, PAX6, FSCN2, TCF4, MFSD8, CTNS, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 and IDUA gene to identify intron-retention events. For this purpose, polyA+ RNA from nuclear and cytoplasmic fractions of cells was isolated from cDNA libraries constructed using Illumina's TruSeq Stranded mRNA library Prep Kit. ARPE-19 cells or astrocytes were used for most analyses, and in certain cases (for RDH8 and RDH12) human retinal transcriptome data was used (Farkas, et al., 2013, "Transcriptome analyses of the human retina identify unprecedented transcript diversity and 3.5 Mb of novel transcribed sequence via significant alternative splicing and novel genes," BMC Genomics 14:486, incorporated herein by reference). The libraries were pair-end sequenced resulting in 100-nucleotide reads that can be mapped to the human genome. The mapped reads were visualized using the UCSC genome browser (operated by the UCSC Genome Informatics Group (Center for Biomolecular Science & Engineering, University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064) and described by, e.g., Rosenbloom, et al., 2015, "The UCSC Genome Browser database: 2015 update," Nucleic Acids Research 43, Database Issue, doi: 10.1093/nar/gku1177) and the coverage and number of reads were inferred by the peak signals. The height of the peaks indicates the level of expression given by the density of the reads in a particular region. A schematic representation of the gene (drawn to scale) was provided by the UCSC genome browser (below the read signals) so that peaks can be matched to the exonic and intronic regions. Based on this display, we identified introns that have high read density in the nuclear fraction of the cells, but have very low to no reads in the cytoplasmic fraction. This indicated that these introns were retained and that the intron-containing transcripts remain in the nucleus, and suggested that these retained RIC pre-mRNAs are non-productive, as they were not exported out to the cytoplasm.

Example 2: Identification of intron retention events in CRX, ABCA4, MYOC, and NXNL1 transcript by RNAseq using next generation sequencing

[00299] Whole transcriptome shotgun sequencing was carried out using next generation sequencing to reveal a snapshot of transcripts produced by the CRX, ABCA4, MYOC, and NXNL1 genes described herein to identify intron-retention events. For this purpose, polyA+ RNA from nuclear and cytoplasmic fractions of THLE-3 (human liver epithelial) cells is isolated and cDNA libraries constructed using Illumina's TruSeq Stranded mRNA library Prep Kit. The libraries are pair-end sequenced resulting in 100-nucleotide reads that were mapped to the human genome. The mapped reads are visualized using the UCSC genome browser (operated by the UCSC Genome Informatics Group (Center for Biomolecular Science & Engineering, University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064) and described by, e.g., Rosenbloom, et al., 2015, "The UCSC Genome Browser database: 2015 update," Nucleic Acids Research 43, Database Issue, doi: 10.1093/nar/gku1177) and the coverage and number of reads were inferred by the peak signals. The height of the peaks indicates the level of expression given by the density of the reads in a particular region. A schematic representation of the gene is provided by the UCSC genome browser so that peaks can be matched to the exonic and intronic regions. Based on this display, we identify introns that have high read density in the nuclear fraction of THLE-3 cells, but have very low to no reads in the cytoplasmic fraction of these cells. This indicates that these introns are retained and that the intron-containing transcripts remain in the nucleus, and suggests that these retained RIC pre-mRNAs are non-productive, as they are not exported out to the cytoplasm.

Example 3: Design of ASO-walk targeting

[00300] An ASO walk was designed to target introns using the method described herein. A region immediately downstream of an intron 5' splice site, *e.g.*, spanning nucleotides +6 to +69 and a region immediately upstream of the intron's 3' splice site, *e.g.*, spanning nucleotides -16 to -68 of the intron was targeted with 2'-O-Me RNA, PS backbone, 18-mer ASOs shifted by 5-nucleotide intervals. Table 1 lists exemplary ASOs that were designed and their target sequences.

Table 1

Gene SEQ ID NO.	Pre-mRNA SEQ ID NO.	ASOs SEQ ID NO.	Retained Intron	Target Sequence SEQ ID NO.
ABCA4 SEQ ID NO. 1	ABCA4:NM_000350 SEQ ID NO. 24	84-315	40	26674
		316-543	38	26706
		544-774	36	26656

		775-1016	44	26681
		1017-1126	39	26664
RPE65 SEQ ID NO. 2	RPE65:NM_000329 SEQ ID NO. 25	1127-1293	9	26691
		1294-1528	10	26671
MYOC SEQ ID NO. 3	MYOC:NM_000261 SEQ ID NO. 26	1529-1855	1	26669
		1856-2318	2	26696
CNGA3 SEQ ID NO. 4	CNGA3:NM_001298 SEQ ID NO. 27	2319-2544	6	26711
	CNGA3:NM_001079878 SEQ ID NO. 28	2545-2770	5	26711
MFSD8 SEQ ID NO. 5	MFSD8:NM_152778 SEQ ID NO. 29	2771-2852	11	26703
		2853-3631	12	26708
IDUA SEQ ID NO. 6	IDUA:NM_000203 SEQ ID NO. 30	3632-3697	3	26668
		3698-3813	4	26679
		3814-3879	5	26700
		3880-3952	6	26655
		3953-4037	7	26663
	IDUA:NR_110313 SEQ ID NO. 31	4038-4103	3	26668
		4104-4219	4	26679
		4220-4285	5	26700
		4286-4358	6	26655
		4359-4443	7	26663

LRAT SEQ ID NO. 7	LRAT:NM_001301645 SEQ ID NO. 32	4444-5545	2	26685
	LRAT:NM_004744 SEQ ID NO. 33	5546-6647	2	26685
OPTN SEQ ID NO. 8	OPTN:NM_001008211 SEQ ID NO. 34	6648-6880	9	26714
	OPTN:NM_001008212 SEQ ID NO. 35	6881-7113	8	26714
	OPTN:NM_001008213 SEQ ID NO. 36	7114-7346	9	26714
	OPTN:NM_021980 SEQ ID NO. 37	7347-7579	7	26714
RGR SEQ ID NO. 9	RGR:NM_002921 SEQ ID No. 38	7580-7806	1	26657
		7807-8040	2	26687
	RGR:NM_001012722 SEQ ID NO. 39	8041-8267	1	26657
		8268-8499	2	26683
	RGR:NM_001012720 SEQ ID NO. 40	8500-8726	1	26657
		8727-8958	2	26683
TEAD1 SEQ ID NO. 10	TEAD1:NM_021961 SEQ ID NO. 41	8959-9163	4	26672
PAX6 SEQ ID NO. 11	PAX6:NM_001310160 SEQ ID NO. 42	9164-9296	2	26697
		9297-9507	3	26677
	PAX6:NM_001310161 SEQ ID NO. 43	9508-9774	1	26707
		9775-9841	3	26678
		9842-10052	4	26713

	PAX6:NM_001258465 SEQ ID NO. 44	10053-10252	3	26694
		10253-10484	4	26659
		10485-10695	5	26713
	PAX6:NM_000280 SEQ ID NO. 45	10696-10895	4	26694
		10896-11127	5	26659
		11128-11338	6	26713
	PAX6:NM_001258464 SEQ ID NO. 46	11339-11538	4	26694
		11539-11770	5	26659
		11771-11981	6	26713
	PAX6:NM_001604 SEQ ID NO. 47	11982-12181	4	26694
		12182-12248	6	26678
		12249-12459	7	26713
	PAX6:NM_001127612 SEQ ID NO. 48	12460-12659	4	26694
		12660-12891	5	26659
		12892-13102	6	26713
	PAX6:NM_001258462 SEQ ID NO. 49	13103-13302	4	26694
		13303-13369	6	26678
		13370-13580	7	26713
	PAX6:NM_001310159 SEQ ID NO. 50	13581-13780	2	26694
		13781-14012	3	26659

		14013-14223	4	26713
	PAX6:NM_001310158 SEQ ID NO. 51	14224-14423	4	26694
		14424-14490	6	26678
		14491-14701	7	26713
	PAX6:NM_001258463 SEQ ID NO. 52	14702-14901	4	26694
		14902-14968	6	26678
		14969-15179	7	26713
ROM1 SEQ ID NO. 12	ROM1:NM_000327 SEQ ID NO. 53	15180-15486	1	26665
RDH5 SEQ ID NO. 13	RDH5:NM_002905 SEQ ID NO. 54	15487-15700	1	26704
		15701-15844	2	26666
	RDH5:NM_001199771 SEQ ID NO. 55	15845-16057	1	26709
		16058-16202	2	26684
RDH12 SEQ ID NO. 14	RDH12:NM_152443 SEQ ID NO. 56	16203-16458	7	26693
NR2E3 SEQ ID NO. 15	NR2E3:NM_014249 SEQ ID NO. 57	16459-16661	1	26702
		16662-16272	2	26660
		16728-16798	3	26705
		16799-16890	4	26698
		16891-17127	5	26658
		17128-17169	6	26676

		17170-17254	7	26712
	NR2E3:NM_016346 SEQ ID NO. 58	17255-17457	1	26702
		17458-17523	2	26660
		17524-17594	3	26705
		17595-17686	4	26698
		17687-17923	5	26658
		17924-17965	6	26676
		17966-18209	7	26701
RLBP1 SEQ ID NO. 16	RLBP1:NM_000326 SEQ ID NO. 59	18210-18383	2	26673
		18384-18638	5	26667
CTNS SEQ ID NO. 17	CTNS:NM_004937 SEQ ID NO. 60	18639-18861	9	26690
		18862-19086	10	26692
	CTNS:NM_001031681 SEQ ID NO. 61	19087-19309	9	26690
		19310-19534	10	26692
PER1 SEQ ID NO. 18	PER1:NM_002616 SEQ ID NO. 62	19535-19782	1	26682
		19783-19845	14	26710
FSCN2 SEQ ID NO. 19	FSCN2:NM_012418 SEQ ID NO. 63	19846-20232	1	26670
		20233-20347	3	26662
	FSCN2:NM_001077182 SEQ ID NO. 64	20348-20734	1	26670
		20735-20849	3	26661

TCF4 SEQ ID NO. 20	TCF4:NM_001243236 SEQ ID NO. 65	20850-21091	9	26688
	TCF4:NM_001243235 SEQ ID NO. 66	21092-21333	9	26688
	TCF4:NM_001243234 SEQ ID NO.67	21334-21577	9	26689
	TCF4:NM_001243233 SEQ ID NO. 68	21578-21819	12	26688
	TCF4:NM_001243232 SEQ ID NO. 69	21820-22063	12	26689
	TCF4:NM_001243231 SEQ ID NO.70	22064-22305	14	26688
	TCF4:NM_003199 SEQ ID NO. 71	22306-22547	16	26688
	TCF4:NM_001306207 SEQ ID NO. 72	22548-22789	15	26688
	TCF4:NM_001306208 SEQ ID NO. 73	22790-23031	12	26688
	TCF4:NM_001243227 SEQ ID NO. 74	23032-23275	15	26689
	TCF4:NM_001243228 SEQ ID NO.75	23276-23519	16	26689
	TCF4:NM_001243230 SEQ ID NO. 76	23520-23761	15	26688
	TCF4:NM_001243226 SEQ ID NO. 77	23762-24005	17	26689
	TCF4:NM_001083962 SEQ ID NO. 78	24006-24249	16	26689
	TCF4:NM_001330605 SEQ ID NO. 79	24250-24493	11	26689
	TCF4:NM_001330604 SEQ ID NO. 80	24494-24737	16	26689

RDH8 SEQ ID NO. 21	RDH8:NM_015725 SEQ ID NO. 81	24738-24873	4	26680
NXNL1 SEQ ID NO. 22	NXNL1:NM_138454 SEQ ID NO. 82	24874-25231	1	26699
CRX SEQ ID NO. 23	CRX:NM_000554 SEQ ID NO. 83	25232-25465	1	26675
		25466-25695	2	26695
		25696-26654	3	26686

Example 4: Improved splicing efficiency via ASO-targeting of a retained intron increases FSCN2 transcript levels

[00301] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 4, FIG. 6, and FIG. 7). Several ASOs were identified that increased the target gene expression, as shown in FIG. 4, FIG. 6, and FIG. 7, implying an increase in splicing at that target

intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 3 and FIG. 5), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 5: Improved splicing efficiency via ASO-targeting of a retained intron increases MFSD8 transcript levels

[00302] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 10). Several ASOs were identified that increased the target gene expression, as shown in FIG. 10, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 8 and FIG. 9), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 6: Improved splicing efficiency via ASO-targeting of a retained intron increases OPTN transcript levels

[00303] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-

well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 12). Several ASOs were identified that increased the target gene expression, as shown in FIG. 12, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 11), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 7: Improved splicing efficiency via ASO-targeting of a retained intron increases RDH5 transcript levels

[00304] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system

(Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 14). Several ASOs were identified that increased the target gene expression, as shown in FIG. 14, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 13 and FIG. 15), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 8: Improved splicing efficiency via ASO-targeting of a retained intron increases RLBP1 transcript levels

[00305] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 17). Several ASOs were identified that increased the target gene expression, as shown in FIG. 17, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 16), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 9: Improved splicing efficiency via ASO-targeting of a retained intron increases ABCA4 transcript levels

[00306] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 29 and FIG. 32). Several ASOs were identified that increased the target gene expression, as shown in FIG. 29 and FIG. 32, implying an increase in splicing at that target intron. These results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 10: Improved splicing efficiency via ASO-targeting of a retained intron increases IDUA transcript levels

[00307] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse

(Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 36). Several ASOs were identified that increased the target gene expression, as shown in FIG. 36, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 35, FIG. 37, FIG. 38, FIG. 39, and FIG. 40), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

Example 11: Improved splicing efficiency via ASO-targeting of a retained intron increases CTNS transcript levels

[00308] To determine an increase in target gene intron splicing efficiency with ASOs we used the method described herein. ARPE-19 cells, a human retinal epithelium cell line (American Type Culture Collection (ATCC), USA) were mock-transfected, or transfected with the targeting ASOs described in Table 1. Cells were transfected using Lipofectamine RNAiMax transfection reagent (Thermo Fisher) according to vendor's specifications. Briefly, ASOs were plated in 96-well tissue culture plates and combined with RNAiMax diluted in Opti-MEM. Cells were detached using trypsin and resuspended in full medium, and approximately 25,000 cells were added the ASO-transfection mixture. Transfection experiments were carried out in triplicate plate replicates. Final ASO concentration was 80 nM. Media was changed 6h post-transfection, and cells harvested at 24h, using the Cells-to-Ct lysis reagent, supplemented with DNAse (Thermo Fisher), according to vendor's specifications. cDNA was generated with Cells-to-Ct RT reagents (Thermo Fisher) according to vendor's specifications. To quantify the amount of splicing at the intron of interest, quantitative PCR was carried out using Taqman assays with probes spanning the corresponding exon-exon junction (Thermo Fisher). Taqman assays were carried out according to vendor's specifications, on a QuantStudio 7 Flex Real-Time PCR system (Thermo Fisher). Target gene assay values were normalized to RPL32 (deltaCt) and plate-matched mock transfected samples (delta-delta Ct), generating fold-change over mock quantitation (2^-(delta-deltaCt). Average fold-change over mock of the three plate replicates is plotted (FIG. 43). Several ASOs were identified that increased the target gene expression, as

shown in FIG. 43, implying an increase in splicing at that target intron. Together with whole transcriptome data confirming retention of the target intron (FIG. 41 and FIG. 42), these results confirm that ASOs can improve the splicing efficiency of a rate limiting intron.

CLAIMS

What is claimed is:

1. A method of treating an eye disease in a subject in need thereof by increasing the expression of a target protein or functional RNA by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site, an exon flanking the 3' splice site, and wherein the RIC pre-mRNA encodes the target protein or functional RNA, the method comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding the target protein or functional RNA, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding the target protein or functional RNA, thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of the target protein or functional RNA in the cells of the subject.
2. The method of claim 1, wherein the eye disease is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome.
3. A method of increasing expression of a target protein, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA, by cells having a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a

retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising contacting the cells with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, thereby increasing the level of mRNA encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, and increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA expression by improving splicing efficiency of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in the cells, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA.

4. The method of claim 1 or 2, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA.

5. The method of claim 1 or 2, wherein the target protein or the functional RNA is a compensating protein or a compensating functional RNA that functionally augments or replaces a target protein or functional RNA that is deficient in amount or activity in the subject.
6. The method of claim 3, wherein the cells are in or from a subject having a condition caused by a deficient amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein.
7. The method of any one of claims 1 to 6, wherein the deficient amount of the target protein is caused by haploinsufficiency of the target protein, wherein the subject has a first allele encoding a functional target protein, and a second allele from which the target protein is not produced, or a second allele encoding a nonfunctional target protein, and wherein the antisense oligomer binds to a targeted portion of a RIC pre-mRNA transcribed from the first allele.
8. The method of any one of claims 1 to 6, wherein the subject has a condition caused by a disorder resulting from a deficiency in the amount or function of the target protein, wherein the subject has

(a) a first mutant allele from which

(i) the target protein is produced at a reduced level compared to production from a wild-type allele,

(ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or

(iii)the target protein is not produced, and

(b) a second mutant allele from which

(i) the target protein is produced at a reduced level compared to production from a wild-type allele,

(ii) the target protein is produced in a form having reduced function compared to an equivalent wild type protein, or

(iii)the target protein is not produced, and

wherein when the subject has a first mutant allele a(iii), the second mutant allele is b(i) or b(ii), and wherein when the subject has a second mutant allele b(iii), the first mutant allele is a(i) or a(ii), and wherein the RIC pre-mRNA is transcribed from either the first mutant allele that is a(i) or a(ii), and/or the second allele that is b(i) or b(ii).

9. The method of claim 8, wherein the target protein is produced in a form having reduced function compared to the equivalent wild-type protein.
10. The method of claim 8, wherein the target protein is produced in a form that is fully-functional compared to the equivalent wild-type protein.
11. The method of any one of claims 1 to 10, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron.
12. The method of any one of claims 1 to 10, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within the region +69 relative to the 5' splice site of the retained intron to –79 relative to the 3' splice site of the retained intron.
13. The method of any one of claims 1 to 12, wherein the target protein is (a) ABCA4, (b) RPE65, (c) MYOC, (d) CNGA3, (e) MFSD8, (f) IDUA, (g) LRAT, (h) OPTN, (i) RGR, (j) TEAD1, (k) PAX6, (l) ROM1, (m) RDH5, (n) RDH12, (o) NR2E3, (p) RLBP1, (q) CTNS, (r) PER1, (s) FSCN2, (t) TCF4, (u) RDH8, (v) NXNL1, or (w) CRX.
14. The method of claim 13, wherein the targeted portion of the RIC pre-mRNA comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to
    (a) any one of SEQ ID NOs 84-1126,
    (b) any one of SEQ ID NOs 1127-1528,
    (c) any one of SEQ ID NOs 1529-2318,
    (d) any one of SEQ ID NOs 2319-2770,
    (e) any one of SEQ ID NOs 2771-3631,
    (f) any one of SEQ ID NOs 3632-4443,
    (g) any one of SEQ ID NOs 4444-6647,
    (h) any one of SEQ ID NOs 6648-7579,
    (i) any one of SEQ ID NOs 7580-8958,
    (j) any one of SEQ ID NOs 8959-9163,
    (k) any one of SEQ ID NOs 9164-15179,
    (l) any one of SEQ ID NOs 15180-15486,
    (m) any one of SEQ ID NOs 15487-16202,
    (n) any one of SEQ ID NOs 16203-16458,
    (o) any one of SEQ ID NOs 16459-18209,
    (p) any one of SEQ ID NOs 18210-18638,
    (q) any one of SEQ ID NOs 18639-19534,
    (r) any one of SEQ ID NOs 19535-19845,

(s) any one of SEQ ID NOs 19846-20849,

(t) any one of SEQ ID NOs 20850-24737,

(u) any one of SEQ ID NOs 24738-24873,

(v) any one of SEQ ID NOs 24874-25231, or

(w) any one of SEQ ID NOs 25232-26654.

15. The method of claim 13 or 14, wherein the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of

(a) SEQ ID NO 26674, SEQ ID NO 26706, SEQ ID NO 26656, SEQ ID NO 26681, or SEQ ID NO 26664,

(b) SEQ ID NO 26691 or SEQ ID NO 26671,

(c) SEQ ID NO 26669 or SEQ ID NO 26696,

(d) SEQ ID NO 26711,

(e) SEQ ID NO 26703 or SEQ ID NO 26708,

(f) SEQ ID NO 26668, SEQ ID NO 26679, SEQ ID NO 26700, SEQ ID NO 26655, or SEQ ID NO 26663,

(g) SEQ ID NO 26685,

(h) SEQ ID NO 26714,

(i) SEQ ID NO 26657, SEQ ID NO 26687, or SEQ ID NO 26683,

(j) SEQ ID NO 26672,

(k) SEQ ID NO 26697, SEQ ID NO 26677, SEQ ID NO 26707, SEQ ID NO 26678, SEQ ID NO 26713, SEQ ID NO 26694, or SEQ ID NO 26659,

(l) SEQ ID NO 26665,

(m) SEQ ID NO 26704, SEQ ID NO 26666, SEQ ID NO 26709, or SEQ ID NO 26684,

(n) SEQ ID NO 26693,

(o) SEQ ID NO 26702, SEQ ID NO 26660, SEQ ID NO 26705, SEQ ID NO 26698, SEQ ID NO 26658, SEQ ID NO 26676, SEQ ID NO 26712 SEQ ID NO 26701,

(p) SEQ ID NO 26673 or SEQ ID NO 26667,

(q) SEQ ID NO 26690 or SEQ ID NO 26692,

(r) SEQ ID NO 26682 or SEQ ID NO 26710,

(s) SEQ ID NO 26670, SEQ ID NO 26662, or SEQ ID NO 26661,

(t) SEQ ID NO 26688 or SEQ ID NO 26689,

(u) SEQ ID NO 26680,

(v) SEQ ID NO 26699, or

(w) SEQ ID NO 26695 or SEQ ID NO 26686.

16. The method of any one of claims 13 to 15, wherein the ASO comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) any one of SEQ ID NOs 84-1126,

(b) any one of SEQ ID NOs 1127-1528,

(c) any one of SEQ ID NOs 1529-2318,

(d) any one of SEQ ID NOs 2319-2770,

(e) any one of SEQ ID NOs 2771-3631,

(f) any one of SEQ ID NOs 3632-4443,

(g) any one of SEQ ID NOs 4444-6647,

(h) any one of SEQ ID NOs 6648-7579,

(i) any one of SEQ ID NOs 7580-8958,

(j) any one of SEQ ID NOs 8959-9163,

(k) any one of SEQ ID NOs 9164-15179,

(l) any one of SEQ ID NOs 15180-15486,

(m) any one of SEQ ID NOs 15487-16202,

(n) any one of SEQ ID NOs 16203-16458,

(o) any one of SEQ ID NOs 16459-18209,

(p) any one of SEQ ID NOs 18210-18638,

(q) any one of SEQ ID NOs 18639-19534,

(r) any one of SEQ ID NOs 19535-19845,

(s) any one of SEQ ID NOs 19846-20849,

(t) any one of SEQ ID NOs 20850-24737,

(u) any one of SEQ ID NOs 24738-24873,

(v) any one of SEQ ID NOs 24874-25231, or

(w) any one of SEQ ID NOs 25232-26654.

17. The method of any one of claims 13 to 16, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) SEQ ID NO 24,

(b) SEQ ID NO 25,

(c) SEQ ID NO 26,

(d) SEQ ID NO 27 or SEQ ID NO 28,

(e) SEQ ID NO 29,

(f) SEQ ID NO 30 or SEQ ID NO 31,

(g) SEQ ID NO 32 or SEQ ID NO 33,

(h) SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, or SEQ ID NO 37,

(i) SEQ ID NO 38, SEQ ID NO 39, or SEQ ID NO 40,

(j) SEQ ID NO 41,

(k) SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, , SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, or SEQ ID NO 52,

(l) SEQ ID NO 53,

(m) SEQ ID NO 54 or SEQ ID NO 55,

(n) SEQ ID NO 56,

(o) SEQ ID NO 57 or SEQ ID NO 58,

(p) SEQ ID NO 59,

(q) SEQ ID NO 60 or SEQ ID NO 61,

(r) SEQ ID NO 62,

(s) SEQ ID NO 63 or SEQ ID NO 64,

(t) SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74, SEQ ID NO 75, SEQ ID NO 76, SEQ ID NO 77, SEQ ID NO 78, SEQ ID NO 79, or SEQ ID NO 80,

(u) SEQ ID NO 81,

(v) SEQ ID NO 82, or

(w) SEQ ID NO 83.

18. The method of any one of claims 13 to 17, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) SEQ ID NO 1,

(b) SEQ ID NO 2,

(c) SEQ ID NO 3,

(d) SEQ ID NO 4,

(e) SEQ ID NO 5,

(f) SEQ ID NO 6,

(g) SEQ ID NO 7,

(h) SEQ ID NO 8,

(i) SEQ ID NO 9,

(j) SEQ ID NO 10,

(k) SEQ ID NO 11,

(l) SEQ ID NO 12,

(m) SEQ ID NO 13,

(n) SEQ ID NO 14,

(o) SEQ ID NO 15,

(p) SEQ ID NO 16,

(q) SEQ ID NO 17,

(r) SEQ ID NO 18,

(s) SEQ ID NO 19,

(t) SEQ ID NO 20,

(u) SEQ ID NO 21,

(v) SEQ ID NO 22,

(w) SEQ ID NO 23.

19. The method of any one of claims 1 to 18, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within:

(a) the region +6 to +100 relative to the 5' splice site of the retained intron; or

(b) the region -16 to -100 relative to the 3' splice site of the retained intron.

20. The composition of any one of claims 1 to 18, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron

21. The method of any one of claims 1 to 18, wherein the targeted portion of the RIC pre-mRNA is within:

(a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or

(b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.

22. The method of any one of claims 1 to 20, wherein the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating alternative splicing of pre-mRNA transcribed from a gene encoding the functional RNA or target protein.

23. The method of any one of claims 1 to 22, wherein the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or the functional RNA.

24. The method of any one of claims 1 to 23, wherein the RIC pre-mRNA was produced by partial splicing of a full-length pre-mRNA or partial splicing of a wild-type pre-mRNA.

25. The method of any one of claims 1 to 24, wherein the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA.
26. The method of any one of claims 1 to 25, wherein the target protein produced is full-length protein, or wild-type protein.
27. The method of any one of claims 1 to 26, wherein the total amount of the mRNA encoding the target protein or functional RNA produced in the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of the mRNA encoding the target protein or functional RNA produced in a control cell.
28. The method of any one of claims 1 to 27, wherein the total amount of target protein produced by the cell contacted with the antisense oligomer is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the total amount of target protein produced by a control cell.
29. The method of any one of claims 1 to 28, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.
30. The method of any of claims 1 to 29, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.
31. The method of any one of claims 1 to 30, wherein the antisense oligomer comprises at least

one modified sugar moiety.

32. The method of claim 31, wherein each sugar moiety is a modified sugar moiety.
33. The method of any one of claims 1 to 32, wherein the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.
34. The method of any one of claims 1 to 33, wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted portion of the RIC pre-mRNA encoding the protein.
35. The method of any one of claims 1 to 34, wherein the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the most abundant retained intron in the population of RIC pre-mRNAs.
36. The method of claim 35, whereby the binding of the antisense oligomer to the most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA.
37. The method of any one of claims 1 to 34, wherein the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the second most abundant retained intron in the population of RIC pre-mRNAs.
38. The method of claim 37, whereby the binding of the antisense oligomer to the second most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA.
39. The method of any of claims 6 to 38, wherein the condition is a disease or disorder.

40. The method of claim 39, wherein the disease or disorder is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome.
41. The method of claim 40, wherein the target protein and the RIC pre-mRNA are encoded by the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene.
42. The method of any of claims 1 to 41, wherein the method further comprises assessing protein expression.
43. The method of any one of claims 1 to 42, wherein the antisense oligomer binds to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA.
44. The method of any one of claims 1 to 43, wherein the subject is a human.
45. The method of any one of claims 1 to 43, wherein the subject is a non-human animal.
46. The method of any one of claims 1 to 44, wherein the subject is a fetus, an embryo, or a child.
47. The method of any one of claims 1 to 45, wherein the cells are *ex vivo*.
48. The method of any one of claims 1 to 45, wherein the antisense oligomer is administered by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject.
49. The method of any one of claims 1 to 48, wherein the 9 nucleotides at -3e to -1e of the exon

flanking the 5' splice site and +1 to +6 of the retained intron, are identical to the corresponding wild-type sequence.

50. The method of any one of claims 1 to 49, wherein the 16 nucleotides at -15 to -1 of the retained intron and +1e of the exon flanking the 3' splice site are identical to the corresponding wild-type sequence.
51. An antisense oligomer as used in a method of any of claims 1 to 50.
52. An antisense oligomer comprising a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs 84-26654.
53. A pharmaceutical composition comprising the antisense oligomer of claim 51 or 52 and an excipient.
54. A method of treating a subject in need thereof by administering the pharmaceutical composition of claim 53 by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.
55. A composition comprising an antisense oligomer for use in a method of increasing expression of a target protein or a functional RNA by cells to treat Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome in a subject in need thereof associated with a deficient protein or deficient functional RNA, wherein the deficient protein or deficient functional RNA is deficient in amount or activity in the subject, wherein the antisense oligomer enhances constitutive splicing of a retained intron-containing pre-mRNA (RIC pre-mRNA) encoding the target protein or the functional RNA, wherein the target protein is:
(a)the deficient protein; or

(b) a compensating protein which functionally augments or replaces the deficient protein or in the subject;

and wherein the functional RNA is:

(a)the deficient RNA; or

(b) a compensating functional RNA which functionally augments or replaces the deficient functional RNA in the subject;

wherein the RIC pre-mRNA comprises a retained intron, an exon flanking the 5' splice site and an exon flanking the 3' splice site, and wherein the retained intron is spliced from the RIC pre-mRNA encoding the target protein or the functional RNA, thereby increasing production or activity of the target protein or the functional RNA in the subject.

56. A composition comprising an antisense oligomer for use in a method of treating a condition associated with ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein in a subject in need thereof, the method comprising the step of increasing expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA) comprising a retained intron, an exon flanking the 5’ splice site of the retained intron, an exon flanking the 3’ splice site of the retained intron, and wherein the RIC pre-mRNA encodes the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising contacting the cells with the antisense oligomer, whereby the retained intron is constitutively spliced from the RIC pre-mRNA transcripts encoding ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, in the cells of the subject.

57. The composition of claim 56, wherein the target protein is ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA.

58. The composition of claim 56 or 57, wherein the condition is a disease or disorder.
59. The composition of claim 58, wherein the disease or disorder is Retinitis pigmentosa-7, Sveinsson chorioretinal atrophy, Fundus Albipunctatus, Retinitis pigmentosa 37, Aniridia, Coloboma of the optic nerve, Ocular coloboma, Foveal hypoplasia-1, Bilateral optic nerve hypoplasia, Cone-rod dystrophy-2, Leber congenital amaurosis-7, Retinitis Pigmentosa 30, Stargardt disease-1, Retinitis pigmentosa-19, Age-related macular degeneration-2, Cone-rod dystrophy-3, Primary open angle glaucoma, Fuchs endothelial corneal dystrophy-3, Macular dystrophy with central cone involvement, Ocular nonnephropathic cystinosis, Leber congenital amaurosis, Primary open angle glaucoma, Amyotrophic lateral sclerosis 12, Bothnia retinal dystrophy, Fundus albipunctatus, Retinitis punctata albescens, Leber congenital amaurosis 2, Retinitis pigmentosa 20, Leber congenital amaurosis 14, Retinitis pigmentosa, Eye diseases with slow clearance or accumulation of all-trans retinal (e.g. STGD1), Leber congenital amaurosis13, Retinitis pigmentosa 44, Achromatopsia-2, Jet lag, Alstrom syndrome, Attenuated MPS-1 (Hurler-scheie syndrome and Scheie syndrome) or Bardet-biedl syndrome.
60. The composition of claim 59, wherein the target protein and RIC pre-mRNA are encoded by the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA gene.
61. The composition of any one of claims 55 to 60, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron.
62. The composition of any one of claims 55 to 60, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within the region +69 relative to the 5' splice site of the retained intron to –79relative to the 3' splice site of the retained intron.
63. The composition of any one of claims 55 to 62, wherein the target protein is (a) ABCA4, (b) RPE65, (c) MYOC, (d) CNGA3, (e) MFSD8, (f) IDUA, (g) LRAT, (h) OPTN, (i) RGR, (j) TEAD1, (k) PAX6, (l) ROM1, (m) RDH5, (n) RDH12, (o) NR2E3, (p) RLBP1, (q) CTNS, (r) PER1, (s) FSCN2, (t) TCF4, (u) RDH8, (v) NXNL1, or (w) CRX.
64. The composition of claim 63, wherein the targeted portion of the RIC pre-mRNA comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to
    (a) any one of SEQ ID NOs 84-1126,
    (b) any one of SEQ ID NOs 1127-1528,
    (c) any one of SEQ ID NOs 1529-2318,

(d) any one of SEQ ID NOs 2319-2770,
(e) any one of SEQ ID NOs 2771-3631,
(f) any one of SEQ ID NOs 3632-4443,
(g) any one of SEQ ID NOs 4444-6647,
(h) any one of SEQ ID NOs 6648-7579,
(i) any one of SEQ ID NOs 7580-8958,
(j) any one of SEQ ID NOs 8959-9163,
(k) any one of SEQ ID NOs 9164-15179,
(l) any one of SEQ ID NOs 15180-15486,
(m) any one of SEQ ID NOs 15487-16202,
(n) any one of SEQ ID NOs 16203-16458,
(o) any one of SEQ ID NOs 16459-18209,
(p) any one of SEQ ID NOs 18210-18638,
(q) any one of SEQ ID NOs 18639-19534,
(r) any one of SEQ ID NOs 19535-19845,
(s) any one of SEQ ID NOs 19846-20849,
(t) any one of SEQ ID NOs 20850-24737,
(u) any one of SEQ ID NOs 24738-24873,
(v) any one of SEQ ID NOs 24874-25231, or
(w) any one of SEQ ID NOs 25232-26654.

65. The composition of claim 63 or 64, wherein the targeted portion of the RIC pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of
(a) SEQ ID NO 26674, SEQ ID NO 26706, SEQ ID NO 26656, SEQ ID NO 26681, or SEQ ID NO 26664,
(b) SEQ ID NO 26691 or SEQ ID NO 26671,
(c) SEQ ID NO 26669 or SEQ ID NO 26696,
(d) SEQ ID NO 26711,
(e) SEQ ID NO 26703 or SEQ ID NO 26708,
(f) SEQ ID NO 26668, SEQ ID NO 26679, SEQ ID NO 26700, SEQ ID NO 26655, or SEQ ID NO 26663,
(g) SEQ ID NO 26685,
(h) SEQ ID NO 26714,
(i) SEQ ID NO 26657, SEQ ID NO 26687, or SEQ ID NO 26683,

(j) SEQ ID NO 26672,

(k) SEQ ID NO 26697, SEQ ID NO 26677, SEQ ID NO 26707, SEQ ID NO 26678, SEQ ID NO 26713, SEQ ID NO 26694, or SEQ ID NO 26659,

(l) SEQ ID NO 26665,

(m) SEQ ID NO 26704, SEQ ID NO 26666, SEQ ID NO 26709, or SEQ ID NO 26684,

(n) SEQ ID NO 26693,

(o) SEQ ID NO 26702, SEQ ID NO 26660, SEQ ID NO 26705, SEQ ID NO 26698, SEQ ID NO 26658, SEQ ID NO 26676, SEQ ID NO 26712 SEQ ID NO 26701,

(p) SEQ ID NO 26673 or SEQ ID NO 26667,

(q) SEQ ID NO 26690 or SEQ ID NO 26692,

(r) SEQ ID NO 26682 or SEQ ID NO 26710,

(s) SEQ ID NO 26670, SEQ ID NO 26662, or SEQ ID NO 26661,

(t) SEQ ID NO 26688 or SEQ ID NO 26689,

(u) SEQ ID NO 26680,

(v) SEQ ID NO 26699, or

(w) SEQ ID NO 26695 or SEQ ID NO 26686.

66. The composition of any one of claims 63 to 65, wherein the ASO comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) any one of SEQ ID NOs 84-1126,

(b) any one of SEQ ID NOs 1127-1528,

(c) any one of SEQ ID NOs 1529-2318,

(d) any one of SEQ ID NOs 2319-2770,

(e) any one of SEQ ID NOs 2771-3631,

(f) any one of SEQ ID NOs 3632-4443,

(g) any one of SEQ ID NOs 4444-6647,

(h) any one of SEQ ID NOs 6648-7579,

(i) any one of SEQ ID NOs 7580-8958,

(j) any one of SEQ ID NOs 8959-9163,

(k) any one of SEQ ID NOs 9164-15179,

(l) any one of SEQ ID NOs 15180-15486,

(m) any one of SEQ ID NOs 15487-16202,

(n) any one of SEQ ID NOs 16203-16458,

(o) any one of SEQ ID NOs 16459-18209,

(p) any one of SEQ ID NOs 18210-18638,

(q) any one of SEQ ID NOs 18639-19534,

(r) any one of SEQ ID NOs 19535-19845,

(s) any one of SEQ ID NOs 19846-20849,

(t) any one of SEQ ID NOs 20850-24737,

(u) any one of SEQ ID NOs 24738-24873,

(v) any one of SEQ ID NOs 24874-25231, or

(w) any one of SEQ ID NOs 25232-26654.

67. The composition of any one of claims 63 to 66, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) SEQ ID NO 24,

(b) SEQ ID NO 25,

(c) SEQ ID NO 26,

(d) SEQ ID NO 27 or SEQ ID NO 28,

(e) SEQ ID NO 29,

(f) SEQ ID NO 30 or SEQ ID NO 31,

(g) SEQ ID NO 32 or SEQ ID NO 33,

(h) SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, or SEQ ID NO 37,

(i) SEQ ID NO 38, SEQ ID NO 39, or SEQ ID NO 40,

(j) SEQ ID NO 41,

(k) SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, , SEQ ID NO 47, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 51, or SEQ ID NO 52,

(l) SEQ ID NO 53,

(m) SEQ ID NO 54 or SEQ ID NO 55,

(n) SEQ ID NO 56,

(o) SEQ ID NO 57 or SEQ ID NO 58,

(p) SEQ ID NO 59,

(q) SEQ ID NO 60 or SEQ ID NO 61,

(r) SEQ ID NO 62,

(s) SEQ ID NO 63 or SEQ ID NO 64,

(t) SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74, SEQ ID NO 75, SEQ ID NO 76, SEQ ID NO 77, SEQ ID NO 78, SEQ ID NO 79, or SEQ ID NO 80,

(u) SEQ ID NO 81,

(v) SEQ ID NO 82, or

(w) SEQ ID NO 83.

68. The composition of any one of claims 63 to 67, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to

(a) SEQ ID NO 1,

(b) SEQ ID NO 2,

(c) SEQ ID NO 3,

(d) SEQ ID NO 4,

(e) SEQ ID NO 5,

(f) SEQ ID NO 6,

(g) SEQ ID NO 7,

(h) SEQ ID NO 8,

(i) SEQ ID NO 9,

(j) SEQ ID NO 10,

(k) SEQ ID NO 11,

(l) SEQ ID NO 12,

(m) SEQ ID NO 13,

(n) SEQ ID NO 14,

(o) SEQ ID NO 15,

(p) SEQ ID NO 16,

(q) SEQ ID NO 17,

(r) SEQ ID NO 18,

(s) SEQ ID NO 19,

(t) SEQ ID NO 20,

(u) SEQ ID NO 21,

(v) SEQ ID NO 22,

(w) SEQ ID NO 23.

69. The composition of any one of claims 55 to 68, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within:

(a) the region +6 to +100 relative to the 5' splice site of the retained intron; or

(b) the region -16 to -100 relative to the 3' splice site of the retained intron.

70. The composition of any one of claims 55 to 68, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of

the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron.

71. The composition of any one of claims 55 to 68, wherein the targeted portion of the RIC pre-mRNA is within:
(a)the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or
(b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.
72. The composition of any one of claims 55 to 71, wherein the antisense oligomer does not increase the amount of target protein or functional RNA by modulating alternative splicing of the pre-mRNA transcribed from a gene encoding the target protein or functional RNA.
73. The composition of any one of claims 55 to 72, wherein the antisense oligomer does not increase the amount of the functional RNA or functional protein by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or functional RNA.
74. The composition of any one of claims 55 to 73, wherein the RIC pre-mRNA was produced by partial splicing from a full-length pre-mRNA or a wild-type pre-mRNA.
75. The composition of any one of claims 55 to 74, wherein the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA.
76. The composition of any one of claims 55 to 75, wherein the target protein produced is full-length protein, or wild-type protein.
77. The composition of any one of claims 55 to 76, wherein the retained intron is a rate-limiting intron.
78. The composition of any one of claims 55 to 77 wherein the retained intron is the most abundant retained intron in the RIC pre-mRNA.
79. The composition of any one of claims 55 to 77, wherein the retained intron is the second most abundant retained intron in the RIC pre-mRNA.
80. The composition of any one of claims 55 to 79, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.
81. The composition of any one of claims 55 to 80 wherein the antisense oligomer is an antisense oligonucleotide.
82. The composition of any one of claims 55 to 81, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.
83. The composition of any one of claims 55 to 82, wherein the antisense oligomer comprises at least one modified sugar moiety.

84. The composition of claim 83, wherein each sugar moiety is a modified sugar moiety.
85. The composition of any one of claims 55 to 84, wherein the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.
86. The composition of any one of claims 55 to 85, wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to the targeted portion of the RIC pre-mRNA encoding the protein.
87. The composition of any one of claims 55 to 86, wherein the antisense oligomer binds to a targeted portion of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA.
88. A pharmaceutical composition comprising the antisense oligomer of any of the compositions of claims 55 to 87, and an excipient.
89. A method of treating a subject in need thereof by administering the pharmaceutical composition of claim 88 by intravitreal injection, subretinal injection, topical application, implantation, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.
90. A pharmaceutical composition comprising: an antisense oligomer that hybridizes to a target sequence of a deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript comprises a retained intron, wherein the antisense oligomer induces splicing out of the retained intron from the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript;

and a pharmaceutical acceptable excipient.

91. The pharmaceutical composition of claim 90, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript.
92. The pharmaceutical composition of claim 90 or 91, wherein the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is in the retained intron within the region +500 relative to the 5' splice site of the retained intron to -500 relative to the 3' spliced site of the retained intron.
93. The pharmaceutical composition of claim 90 or 91, wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 1-23.
94. The pharmaceutical composition of claim 90 or 91, wherein the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 24-83.
95. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.
96. The pharmaceutical composition of claim 90, wherein the antisense oligomer is an antisense oligonucleotide.
97. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.
98. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises at least one modified sugar moiety.
99. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40

nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.

100. The pharmaceutical composition of claim 90 or 91, wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to a targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript.

101. The pharmaceutical composition of claim 90 or 91, wherein the targeted portion of the ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA RIC pre-mRNA transcript is within a sequence selected from SEQ ID NOs: 26655-26714.

102. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises a nucleotide sequence that is at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 84-26654.

103. The pharmaceutical composition of claim 90, wherein the antisense oligomer comprises a nucleotide sequence selected from SEQ ID NOs: 84-26654.

104. The pharmaceutical composition of any one of the claims 90-103, wherein the pharmaceutical composition is formulated for intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

105. A method of inducing processing of a deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript to facilitate removal of a retained intron to produce a fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript that encodes a functional form of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT,

RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein, the method comprising:

(a)contacting an antisense oligomer to a target cell of a subject;

(b) hybridizing the antisense oligomer to the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript is capable of encoding the functional form of a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein and comprises at least one retained intron;

(c)removing the at least one retained intron from the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript to produce the fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript that encodes the functional form of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein; and

(d) translating the functional form of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein from the fully processed ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript.

106. The method of claim 105, wherein the retained intron is an entire retained intron.

107. The method of claim 105 or 106, wherein the deficient ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA mRNA transcript is a ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3,

ALMS1, PER1 or IDUA RIC pre-mRNA transcript.

108. A method of treating a subject having a condition caused by a deficient amount or activity of ROM1, TEAD1, RDH5, NR2E3, PAX6, CRX, FSCN2, ABCA4, MYOC, TCF4, MFSD8, CTNS, NXNL1, OPTN, RLBP1, RPE65, LRAT, RDH8, RDH12, RGR, CNGA3, ALMS1, PER1 or IDUA protein comprising administering to the subject an antisense oligomer comprising a nucleotide sequence with at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 84-26654.

FIG. 1

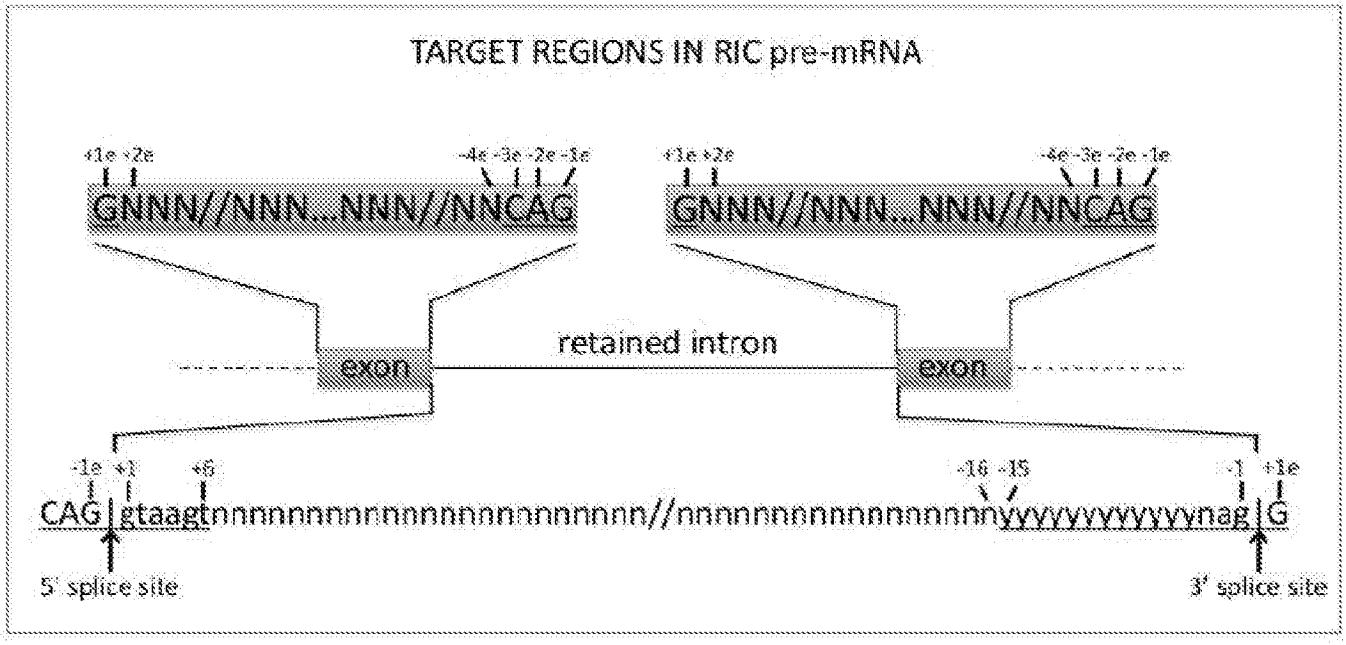

TARGET REGIONS IN RIC pre-mRNA
+1e +2e
-4e -3e -2e -1e
GNNN//NNN..NNN//NNCAG
+1e +2e
-4e -3e -2e -1e
GNNN//NNN..NNN//NNCAG
exon
retained intron
exon
-1e +1 +6
-16 -15
-1 +1e
CAG|gtaagtnnnnnnnnnnnnnnnnnnnnnnnnn//nnnnnnnnnnnnnnnnnnnyyyyyyyyyyyyynag|G
5' splice site
3' splice site

FIG. 2A

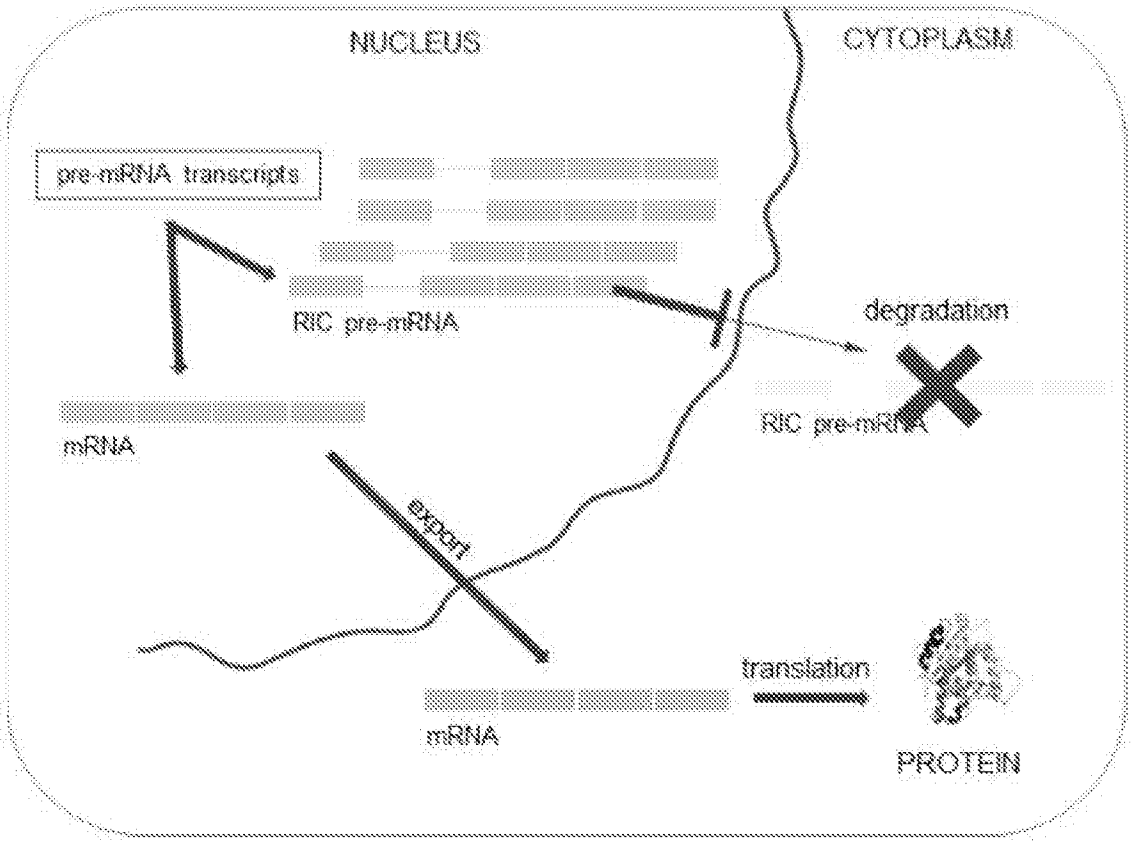

NUCLEUS
CYTOPLASM
pre-mRNA transcripts
RIC pre-mRNA
degradation
RIC pre-mRNA
mRNA
export
translation
mRNA
PROTEIN

FIG. 2B

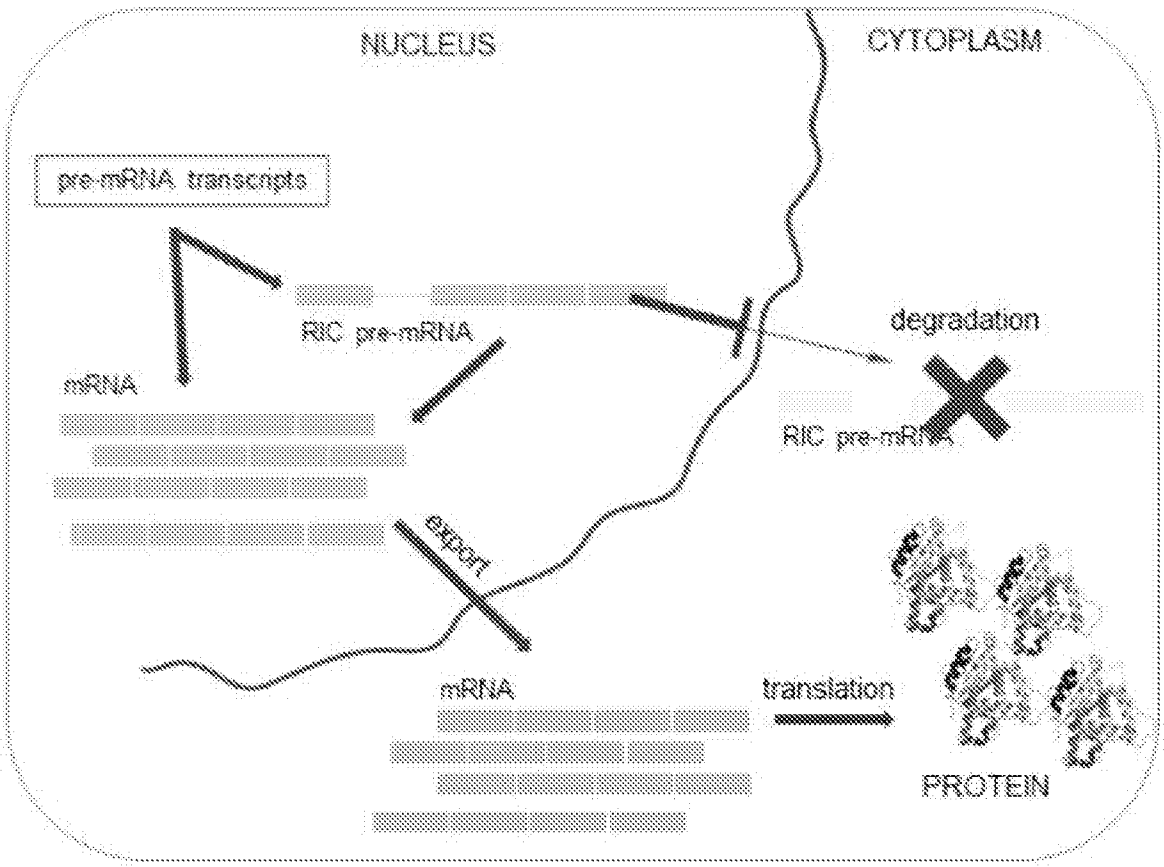

NUCLEUS
CYTOPLASM
pre-mRNA transcripts
RIC pre-mRNA
degradation
RIC pre-mRNA
mRNA
export
mRNA
translation
PROTEIN

FIG. 3

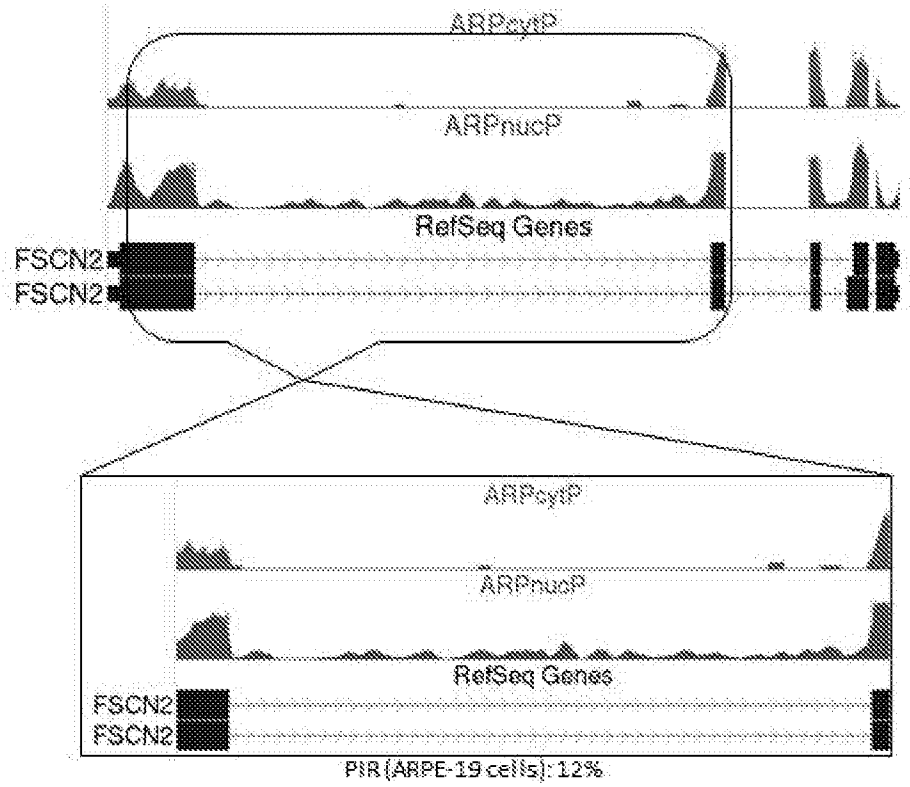

ARPcytP
ARPnucP
RefSeq Genes
FSCN2
FSCN2
ARPcytP
ARPnucP
RefSeq Genes
FSCN2
FSCN2
PIR (ARPE-19 cells): 12%

FIG. 4

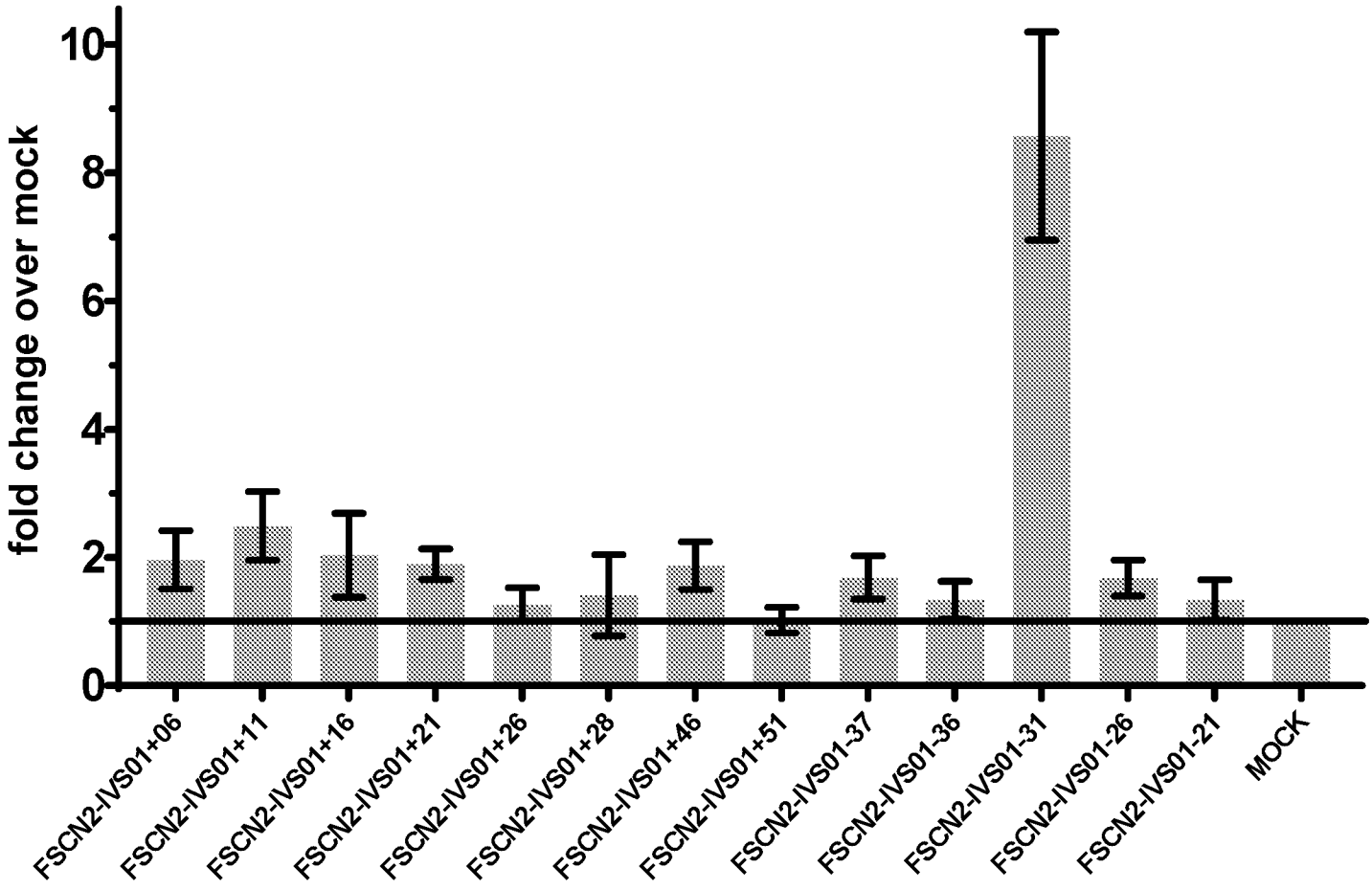

fold change over mock
10
8
6
4
2
0
FSCN2-IVS01+06
FSCN2-IVS01+11
FSCN2-IVS01+16
FSCN2-IVS01+21
FSCN2-IVS01+26
FSCN2-IVS01+28
FSCN2-IVS01+46
FSCN2-IVS01+51
FSCN2-IVS01-37
FSCN2-IVS01-36
FSCN2-IVS01-31
FSCN2-IVS01-26
FSCN2-IVS01-21
MOCK

FIG. 5

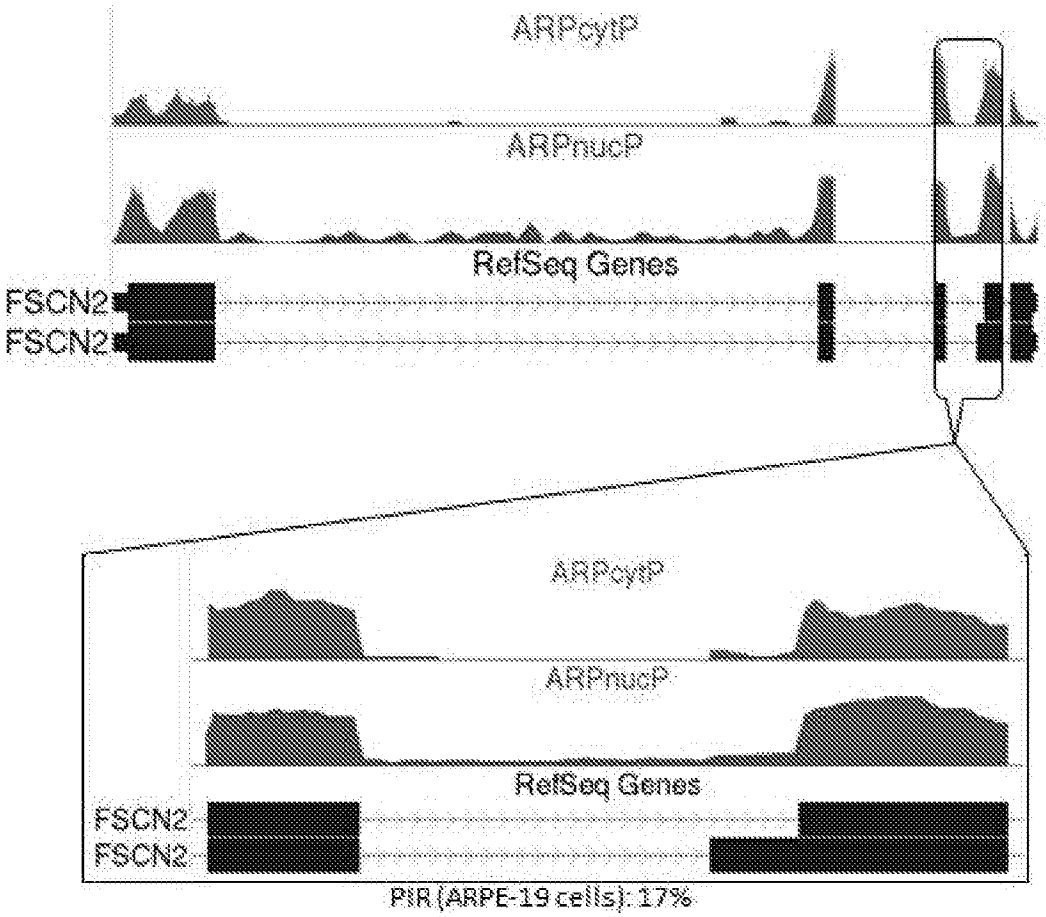

ARPcytP
ARPnucP
RefSeq Genes
FSCN2
FSCN2
ARPcytP
ARPnucP
RefSeq Genes
FSCN2
FSCN2
PIR (ARPE-19 cells): 17%

FIG. 6

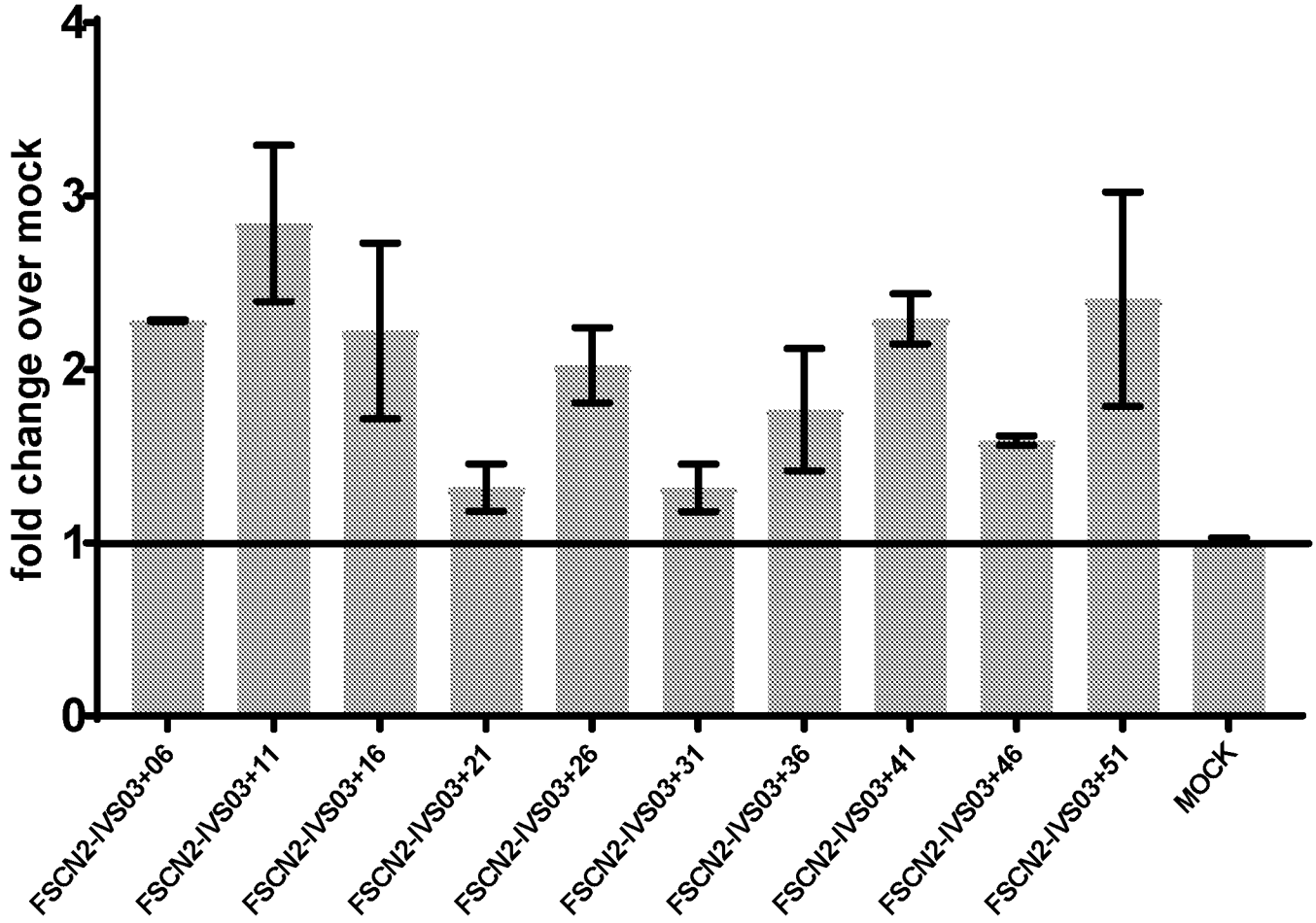

fold change over mock
0
1
2
3
4
FSCN2-IVS03+06
FSCN2-IVS03+11
FSCN2-IVS03+16
FSCN2-IVS03+21
FSCN2-IVS03+26
FSCN2-IVS03+31
FSCN2-IVS03+36
FSCN2-IVS03+41
FSCN2-IVS03+46
FSCN2-IVS03+51
MOCK

FIG. 7

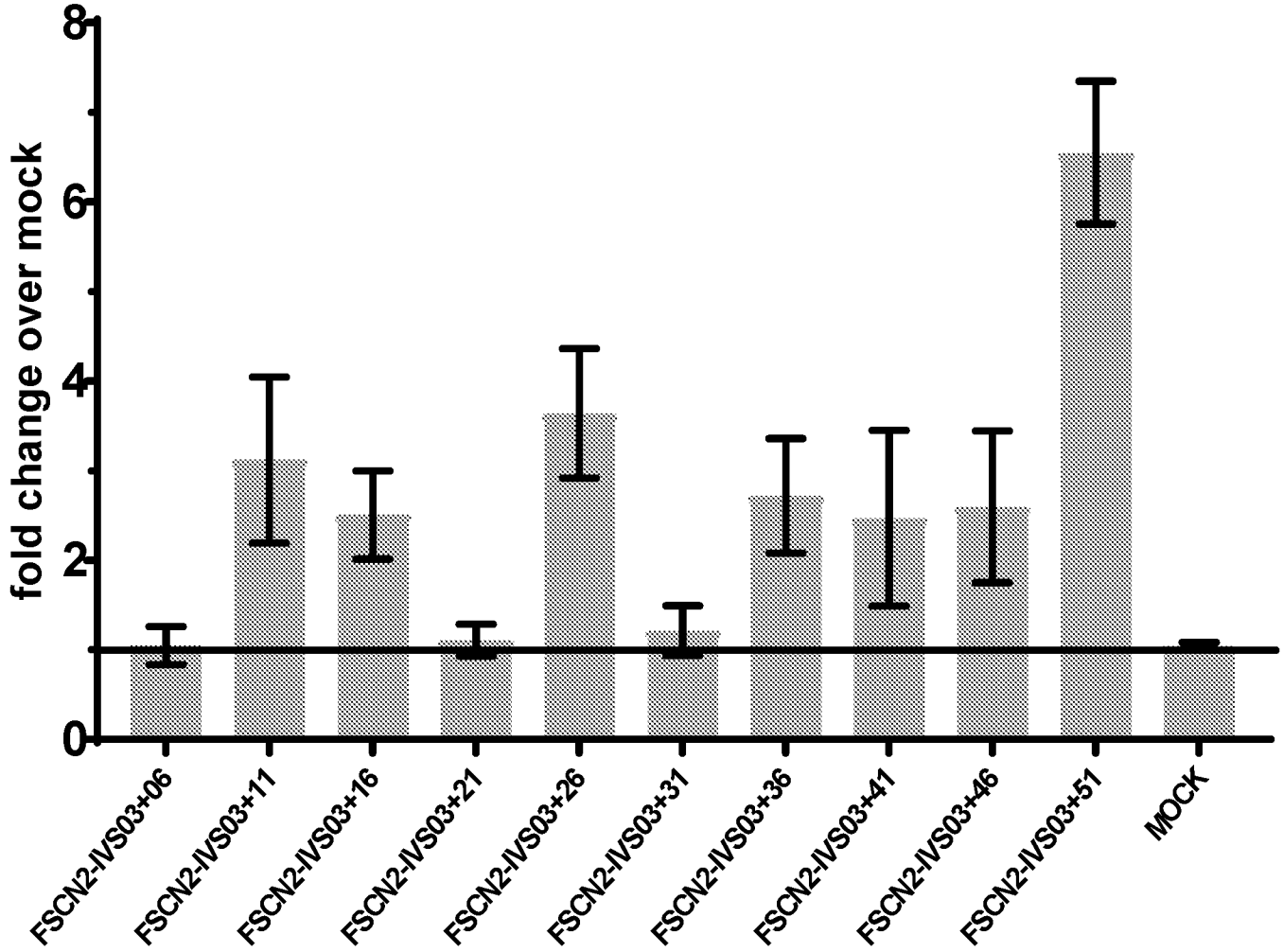

fold change over mock
0
2
4
6
8
FSCN2-IVS03+06
FSCN2-IVS03+11
FSCN2-IVS03+16
FSCN2-IVS03+21
FSCN2-IVS03+26
FSCN2-IVS03+31
FSCN2-IVS03+36
FSCN2-IVS03+41
FSCN2-IVS03+46
FSCN2-IVS03+51
MOCK

FIG. 8

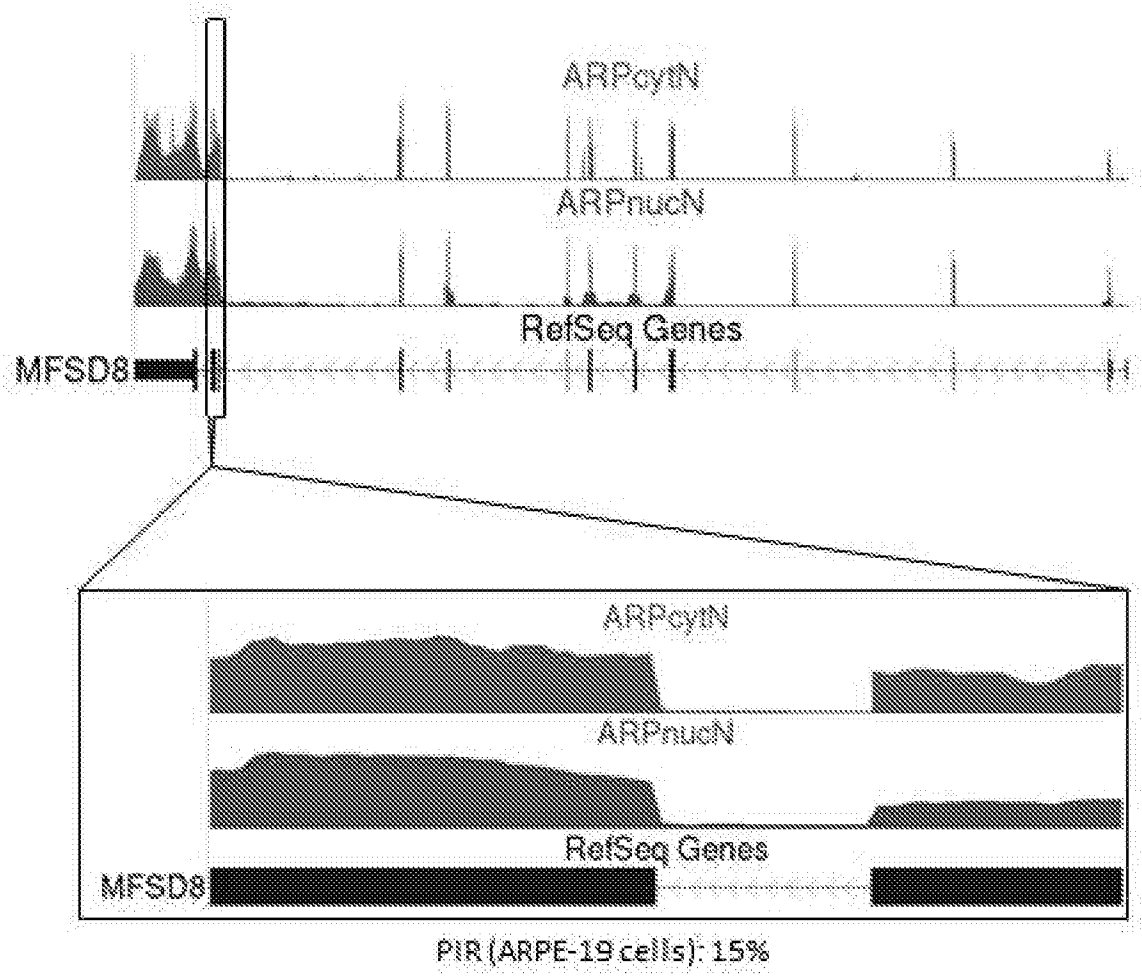

ARPcytN
ARPnucN
RefSeq Genes
MFSD8
ARPcytN
ARPnucN
RefSeq Genes
MFSD8
PIR (ARPE-19 cells): 15%

FIG. 9

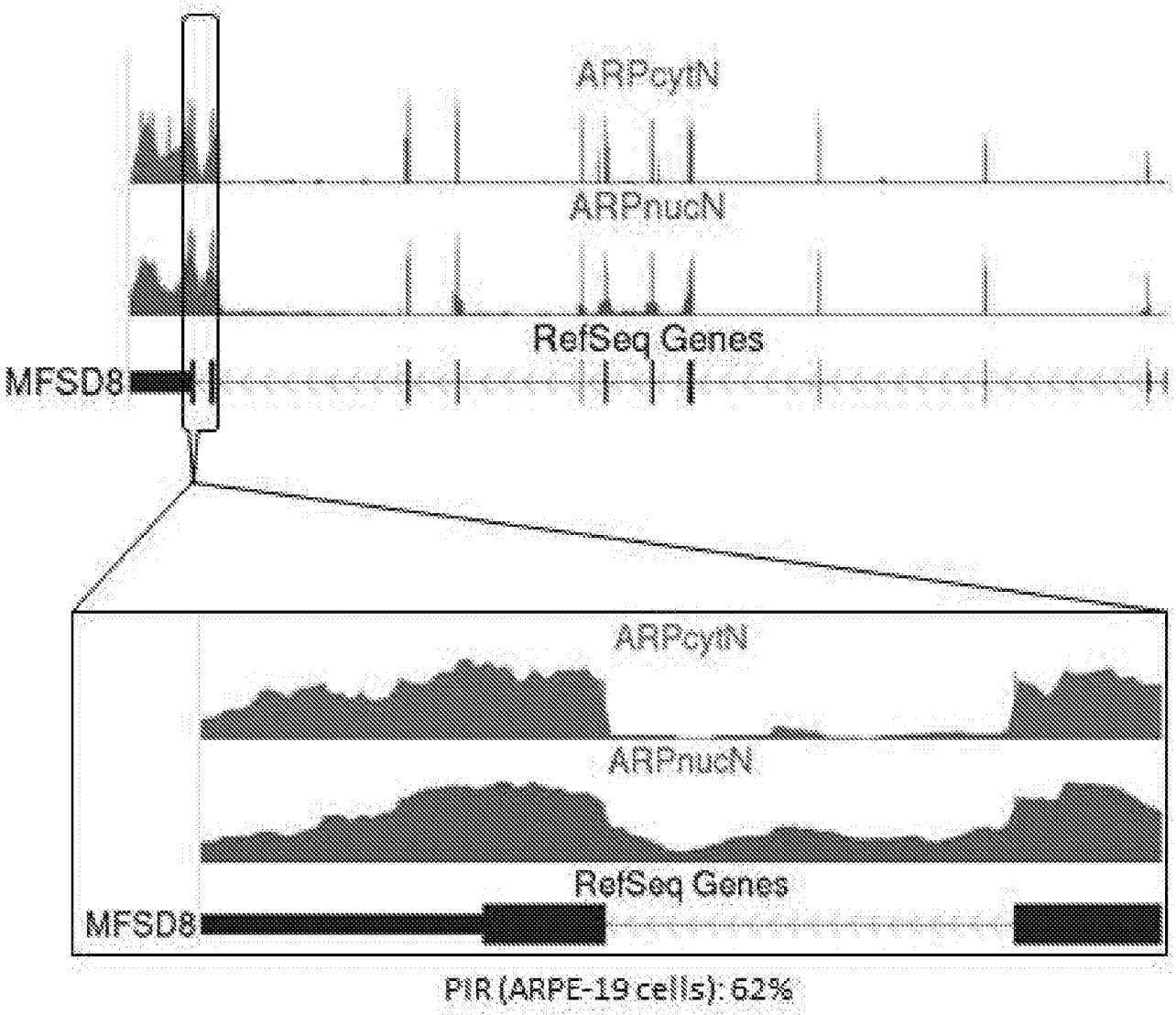

ARPcytN
ARPnucN
RefSeq Genes
MFSD8
ARPcytN
ARPnucN
RefSeq Genes
MFSD8
PIR (ARPE-19 cells): 62%

FIG. 10

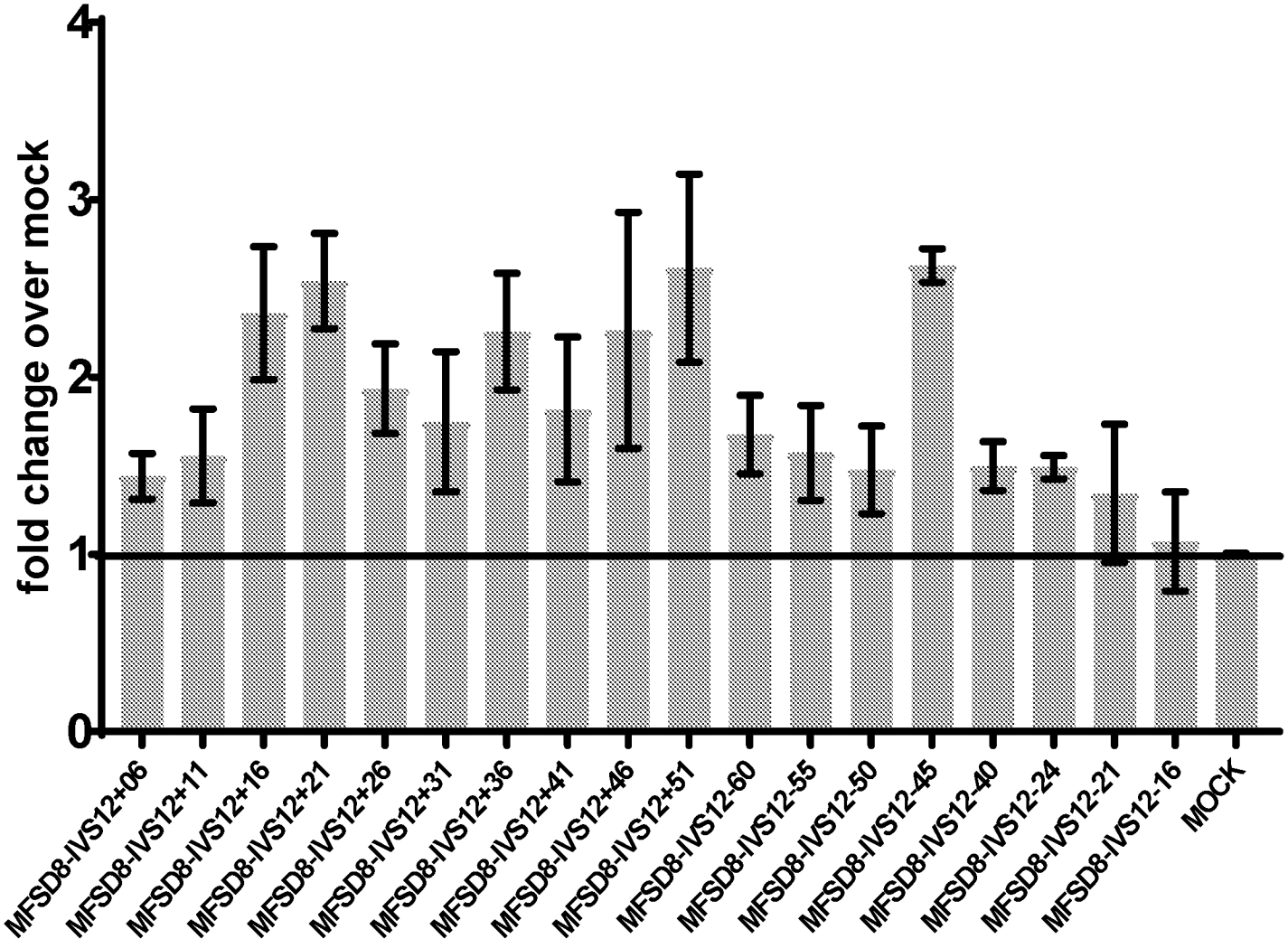

fold change over mock
0
1
2
3
4
MFSD8-IVS12+06
MFSD8-IVS12+11
MFSD8-IVS12+16
MFSD8-IVS12+21
MFSD8-IVS12+26
MFSD8-IVS12+31
MFSD8-IVS12+36
MFSD8-IVS12+41
MFSD8-IVS12+46
MFSD8-IVS12+51
MFSD8-IVS12-60
MFSD8-IVS12-55
MFSD8-IVS12-50
MFSD8-IVS12-45
MFSD8-IVS12-40
MFSD8-IVS12-24
MFSD8-IVS12-21
MFSD8-IVS12-16
MOCK

FIG. 11

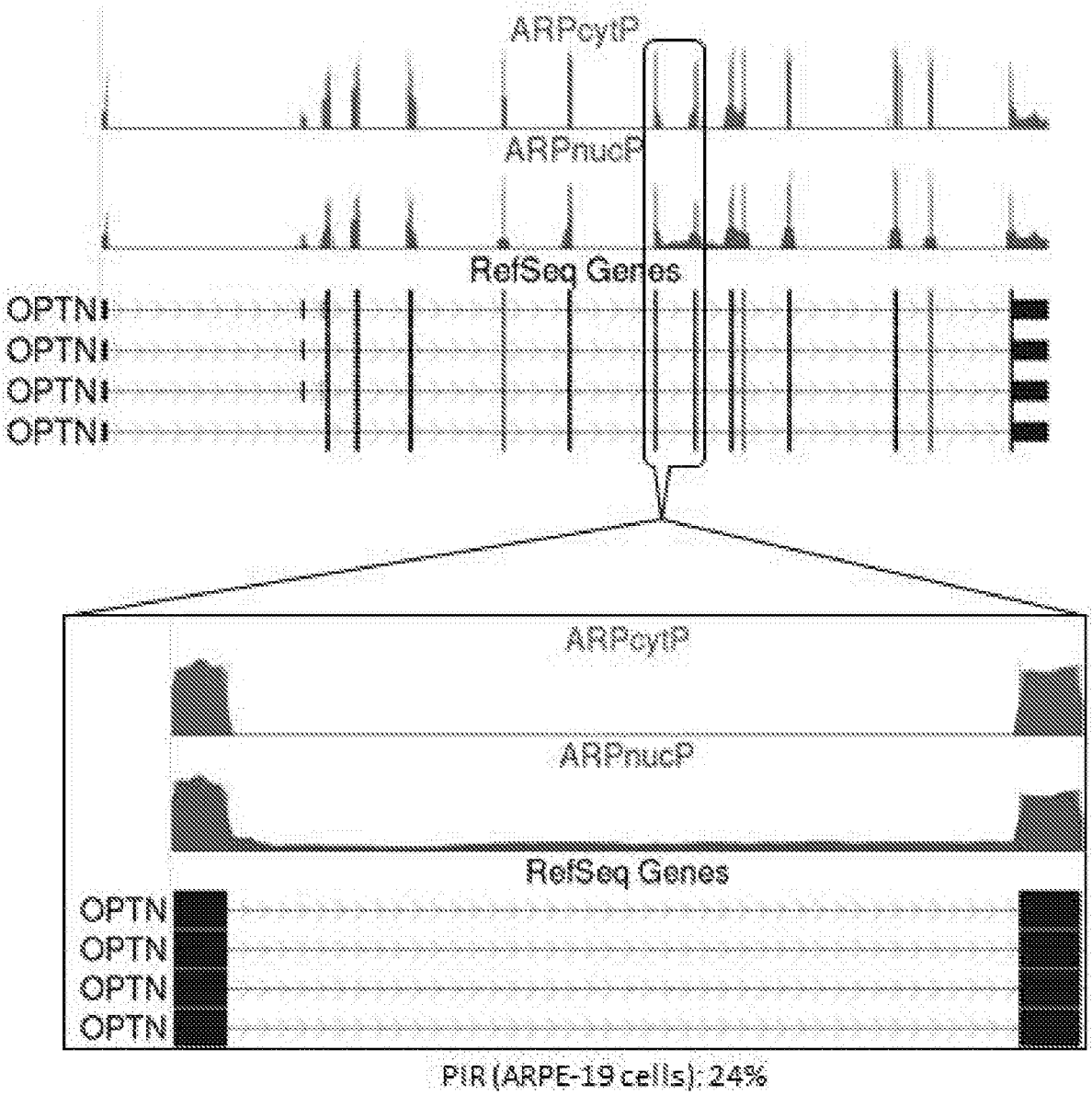

ARPcytP
ARPnucP
RefSeq Genes
OPTN
OPTN
OPTN
OPTN
ARPcytP
ARPnucP
RefSeq Genes
OPTN
OPTN
OPTN
OPTN
PIR (ARPE-19 cells): 24%

FIG. 12

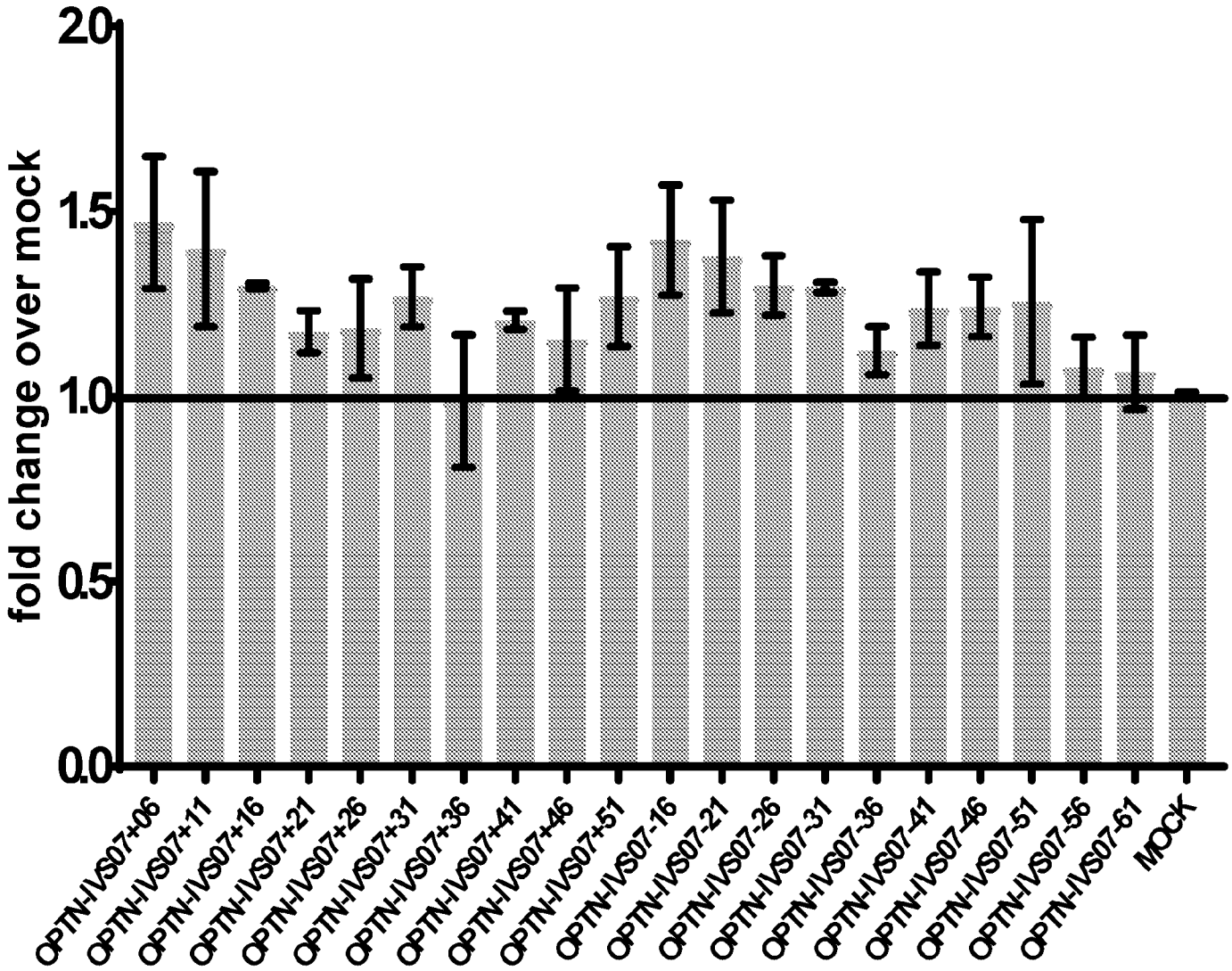
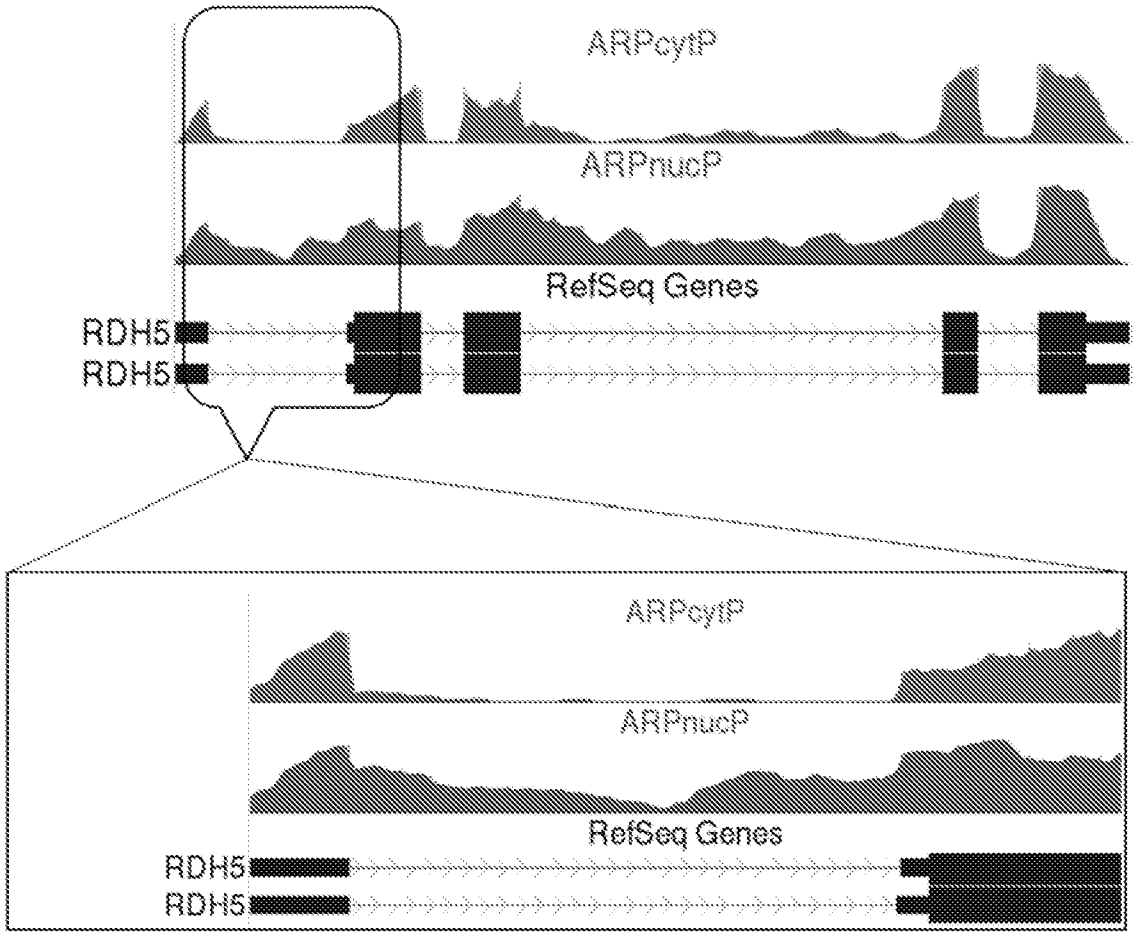

fold change over mock
2.0
1.5
1.0
0.5
0.0
OPTN-IVS07+06
OPTN-IVS07+11
OPTN-IVS07+16
OPTN-IVS07+21
OPTN-IVS07+26
OPTN-IVS07+31
OPTN-IVS07+36
OPTN-IVS07+41
OPTN-IVS07+46
OPTN-IVS07+51
OPTN-IVS07-16
OPTN-IVS07-21
OPTN-IVS07-26
OPTN-IVS07-31
OPTN-IVS07-36
OPTN-IVS07-41
OPTN-IVS07-46
OPTN-IVS07-51
OPTN-IVS07-56
OPTN-IVS07-61
MOCK

FIG. 13



PIR (ARPE-19 cells): 59%

FIG. 14

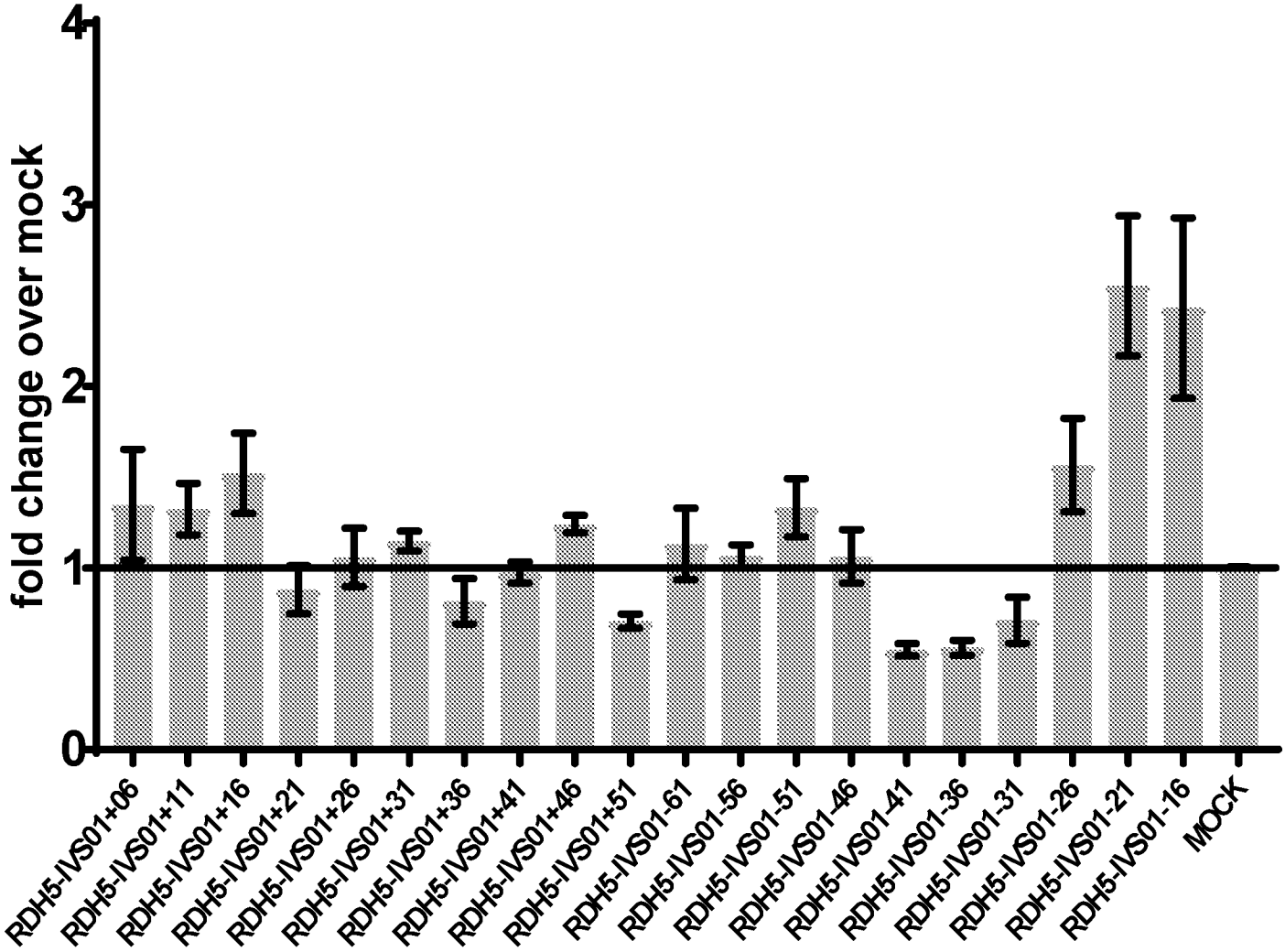
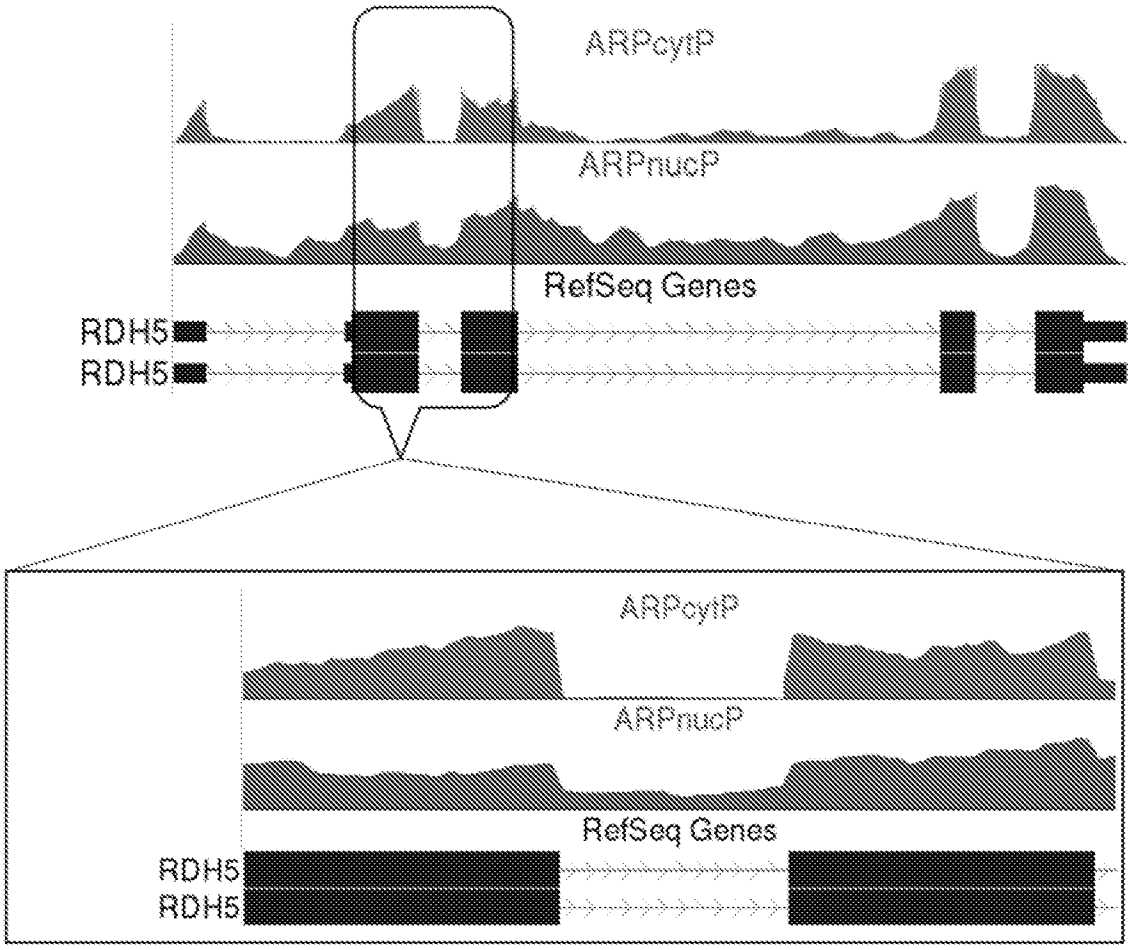

fold change over mock
0
1
2
3
4
RDH5-IVS01+06
RDH5-IVS01+11
RDH5-IVS01+16
RDH5-IVS01+21
RDH5-IVS01+26
RDH5-IVS01+31
RDH5-IVS01+36
RDH5-IVS01+41
RDH5-IVS01+46
RDH5-IVS01+51
RDH5-IVS01-61
RDH5-IVS01-56
RDH5-IVS01-51
RDH5-IVS01-46
RDH5-IVS01-41
RDH5-IVS01-36
RDH5-IVS01-31
RDH5-IVS01-26
RDH5-IVS01-21
RDH5-IVS01-16
MOCK

FIG. 15



PIR (ARPE-19 cells): 59%

FIG. 16

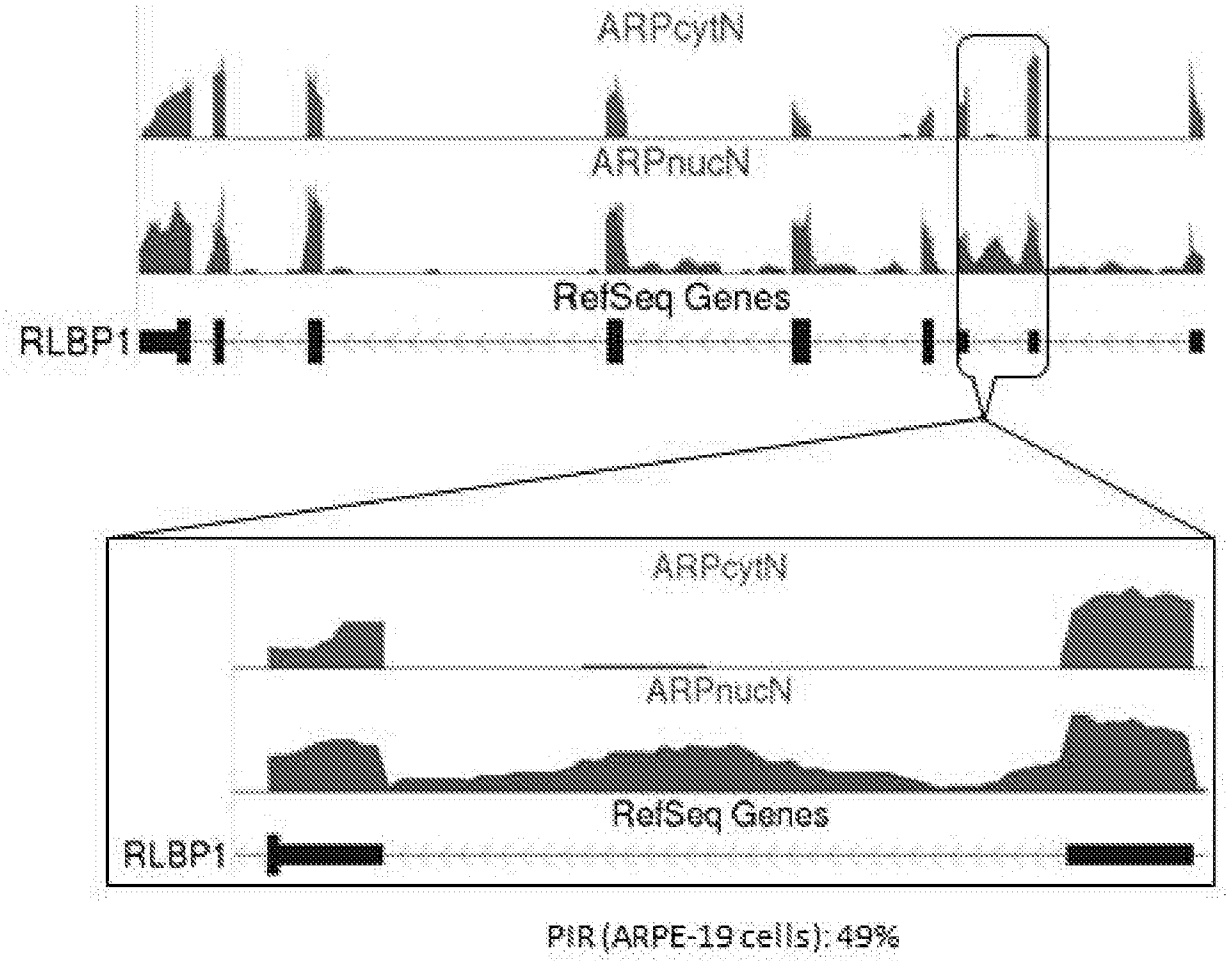

ARPcytN
ARPnucN
RefSeq Genes
RLBP1
ARPcytN
ARPnucN
RefSeq Genes
RLBP1
PIR (ARPE-19 cells): 49%

FIG. 17

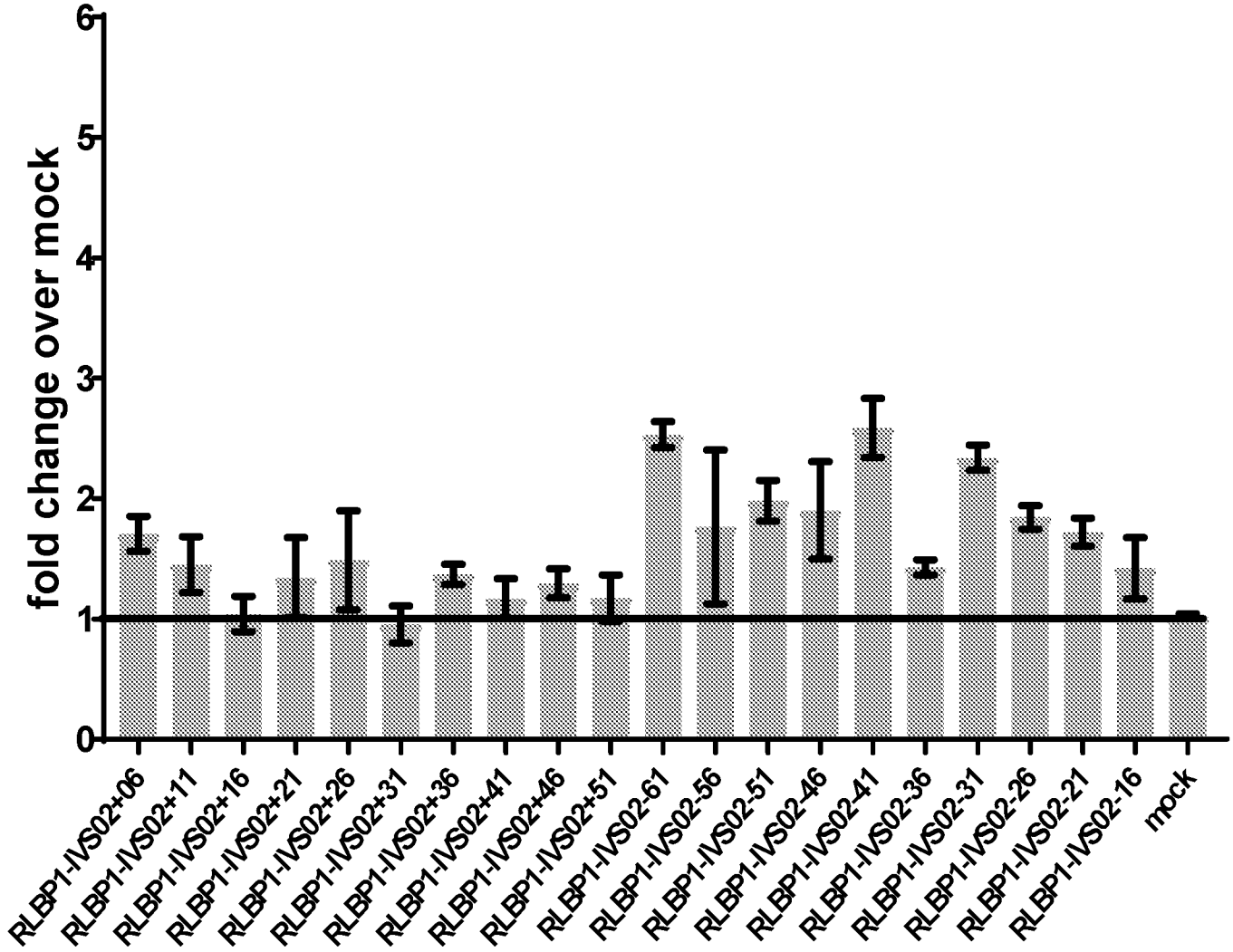

fold change over mock
0
1
2
3
4
5
6
RLBP1-IVS02+06
RLBP1-IVS02+11
RLBP1-IVS02+16
RLBP1-IVS02+21
RLBP1-IVS02+26
RLBP1-IVS02+31
RLBP1-IVS02+36
RLBP1-IVS02+41
RLBP1-IVS02+46
RLBP1-IVS02+51
RLBP1-IVS02-61
RLBP1-IVS02-56
RLBP1-IVS02-51
RLBP1-IVS02-46
RLBP1-IVS02-41
RLBP1-IVS02-36
RLBP1-IVS02-31
RLBP1-IVS02-26
RLBP1-IVS02-21
RLBP1-IVS02-16
mock

FIG. 18

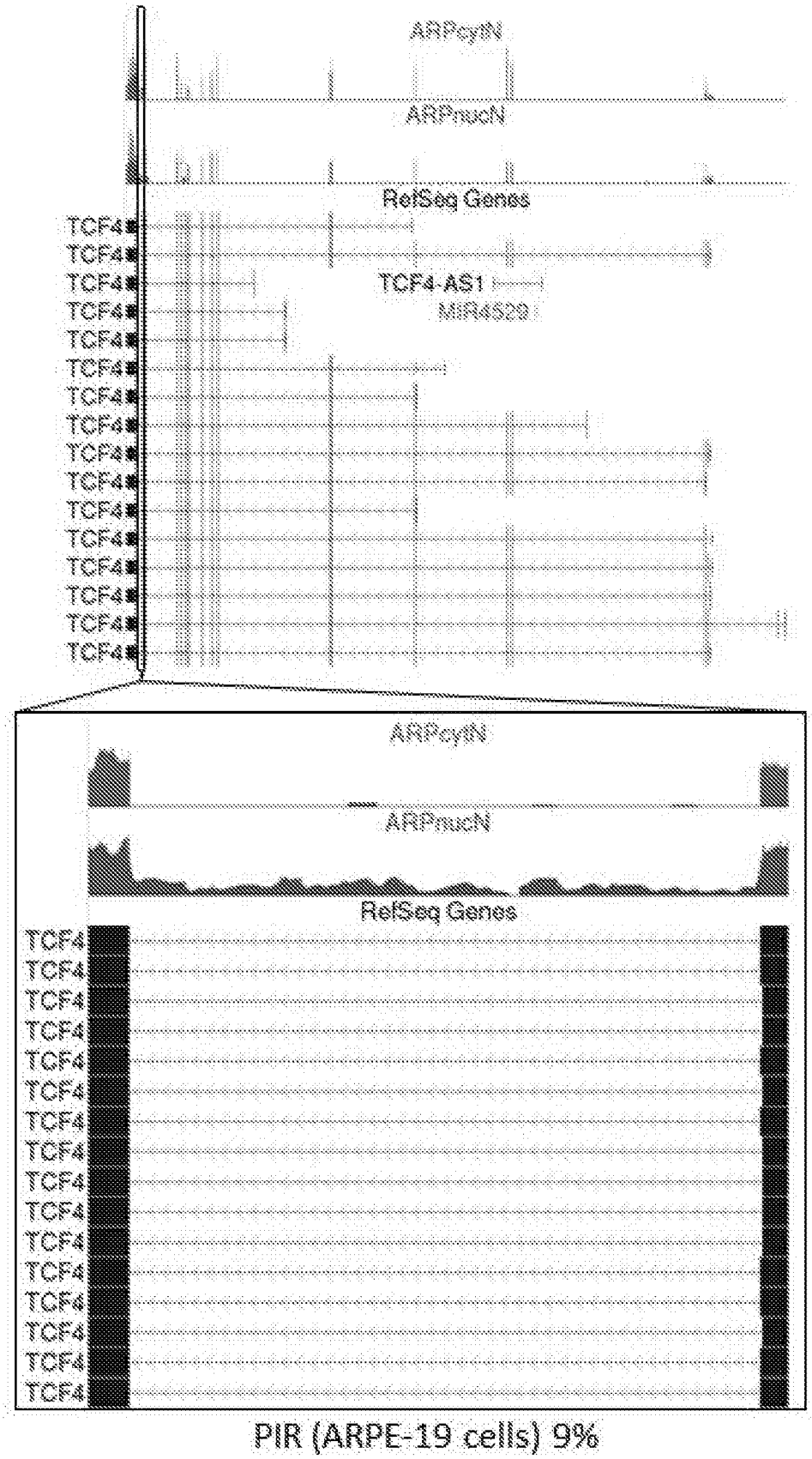
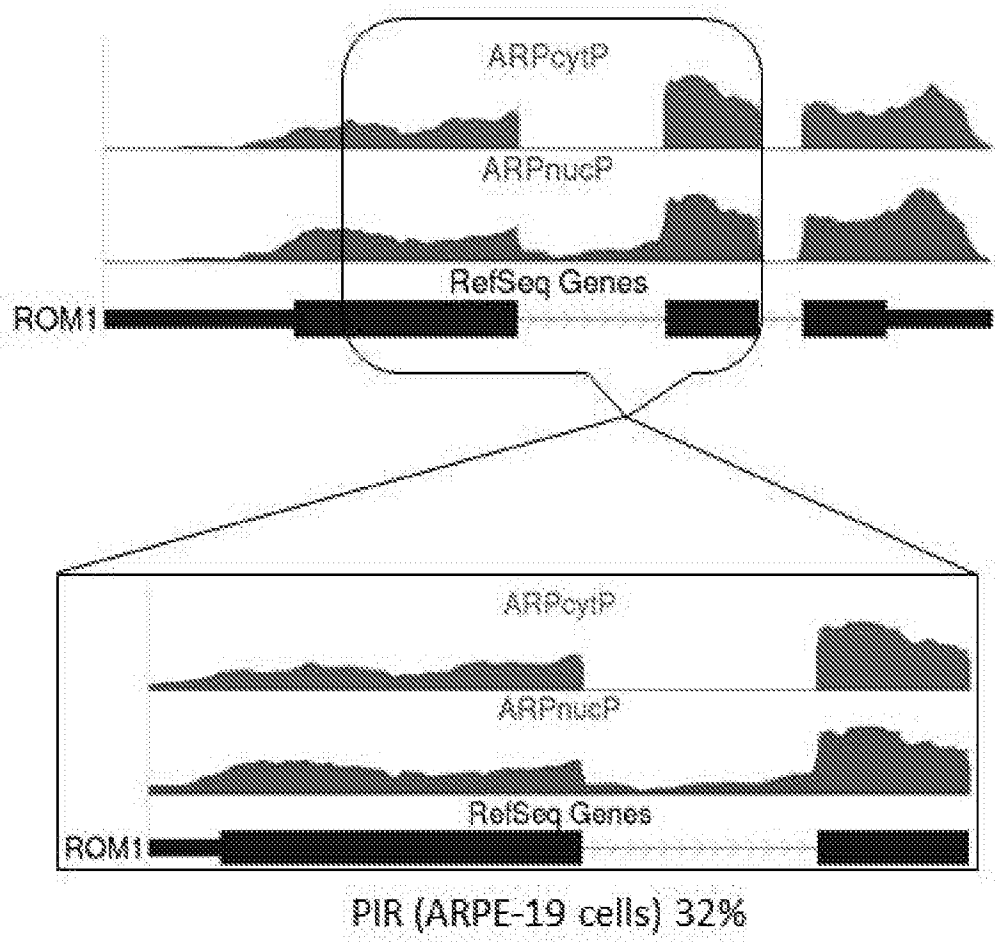

ARPcytN
ARPnucN
RefSeq Genes
TCF4
TCF4-AS1
MIR4529
ARPcytN
ARPnucN
RefSeq Genes
TCF4
PIR (ARPE-19 cells) 9%

FIG. 19



PIR (ARPE-19 cells) 32%

FIG. 20

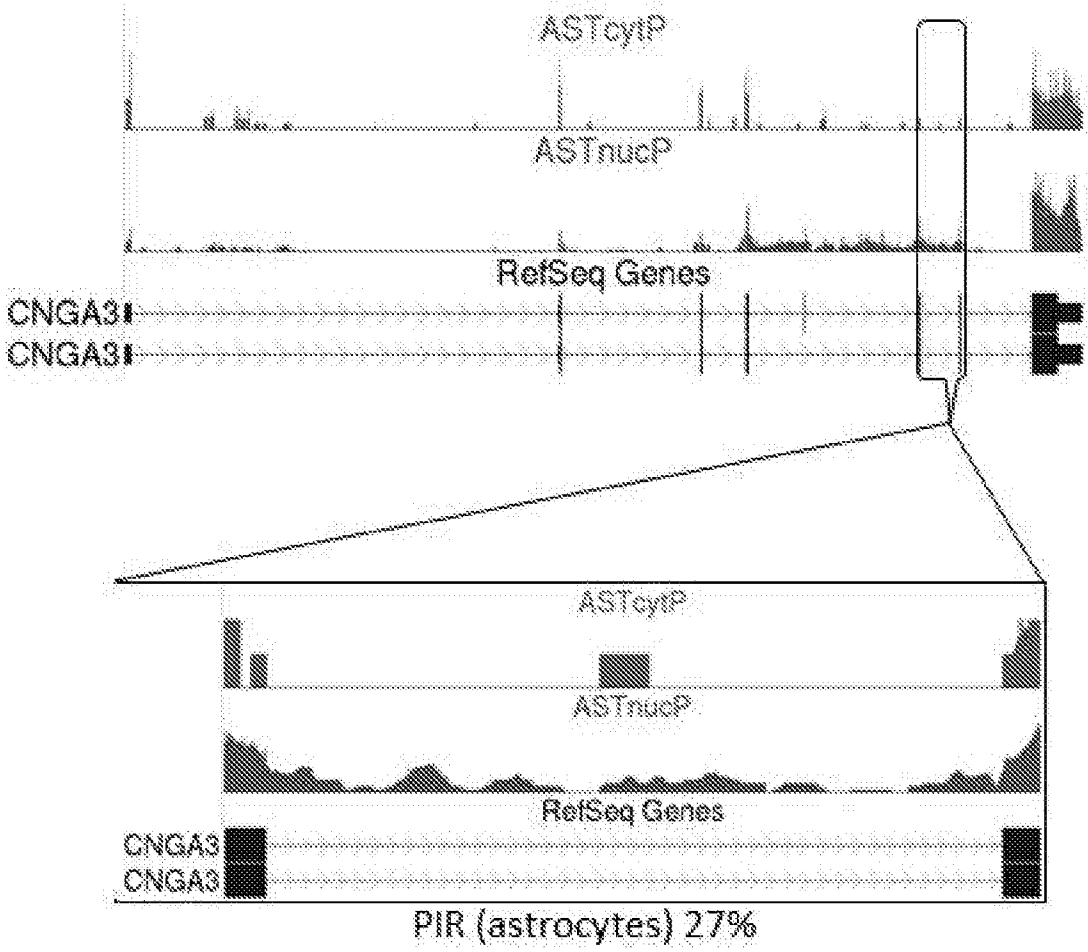

ASTcytP
ASTnucP
RefSeq Genes
CNGA3
CNGA3
ASTcytP
ASTnucP
RefSeq Genes
CNGA3
CNGA3
PIR (astrocytes) 27%

FIG. 21

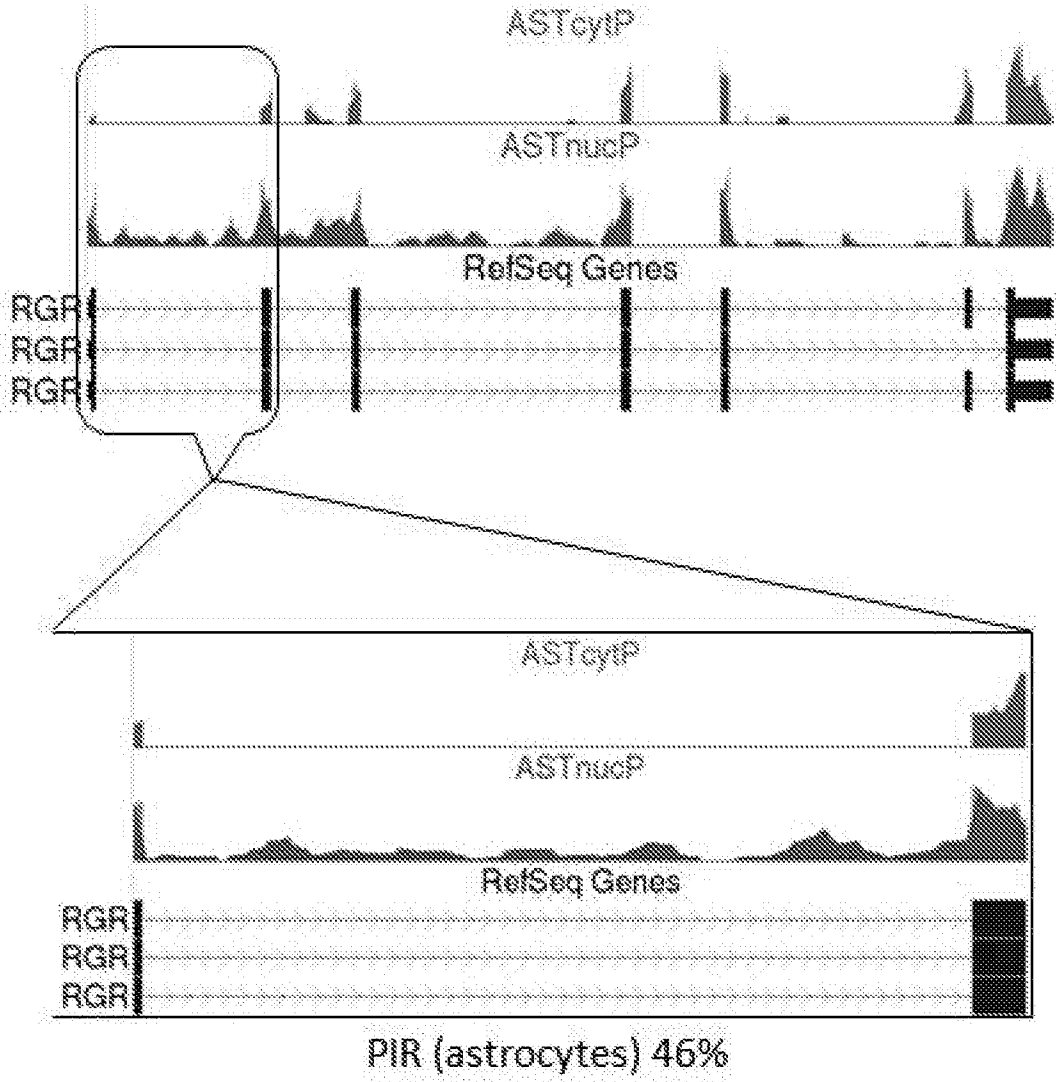

ASTcytP
ASTnucP
RefSeq Genes
RGR
RGR
RGR
ASTcytP
ASTnucP
RefSeq Genes
RGR
RGR
RGR
PIR (astrocytes) 46%

FIG. 22

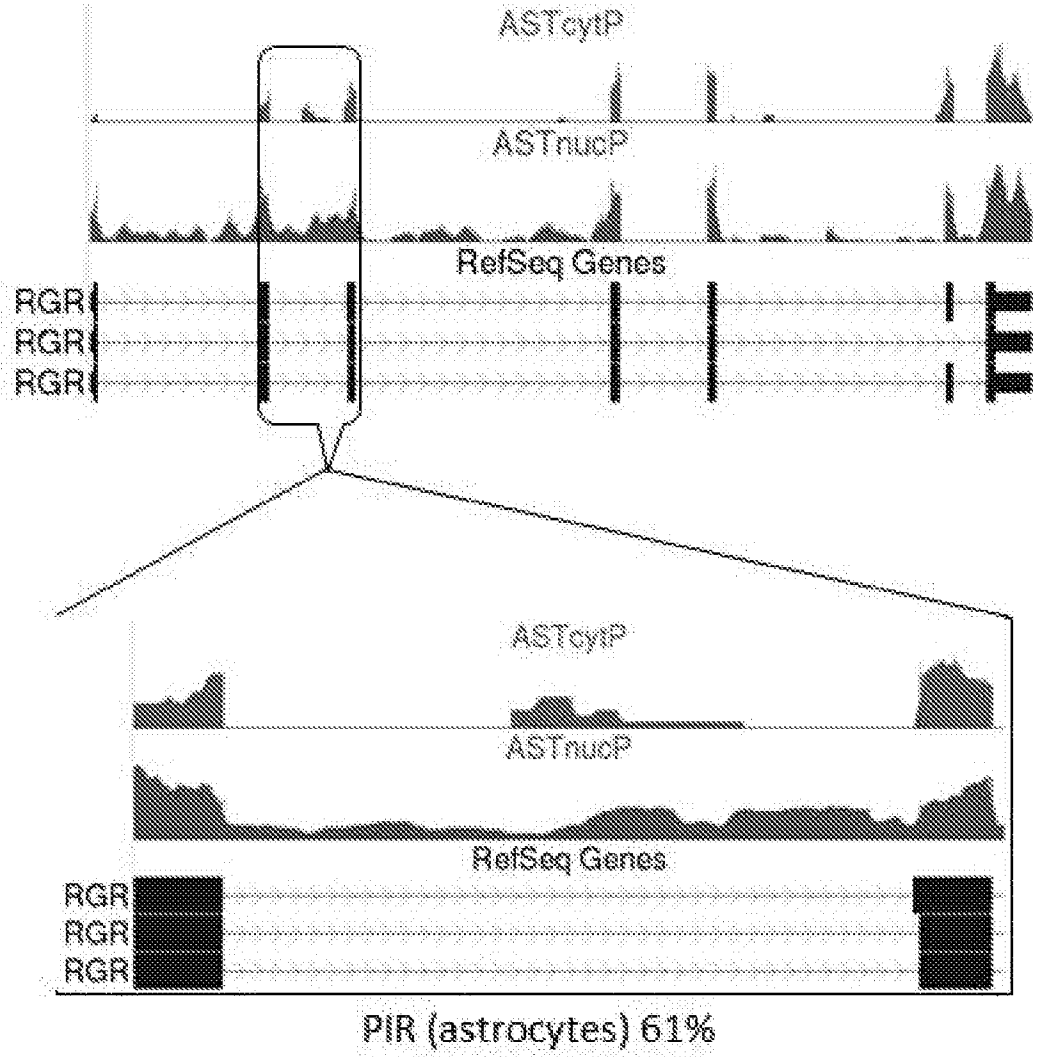

ASTcytP
ASTnucP
RefSeq Genes
RGR
RGR
RGR
ASTcytP
ASTnucP
RefSeq Genes
RGR
RGR
RGR
PIR (astrocytes) 61%

FIG. 23

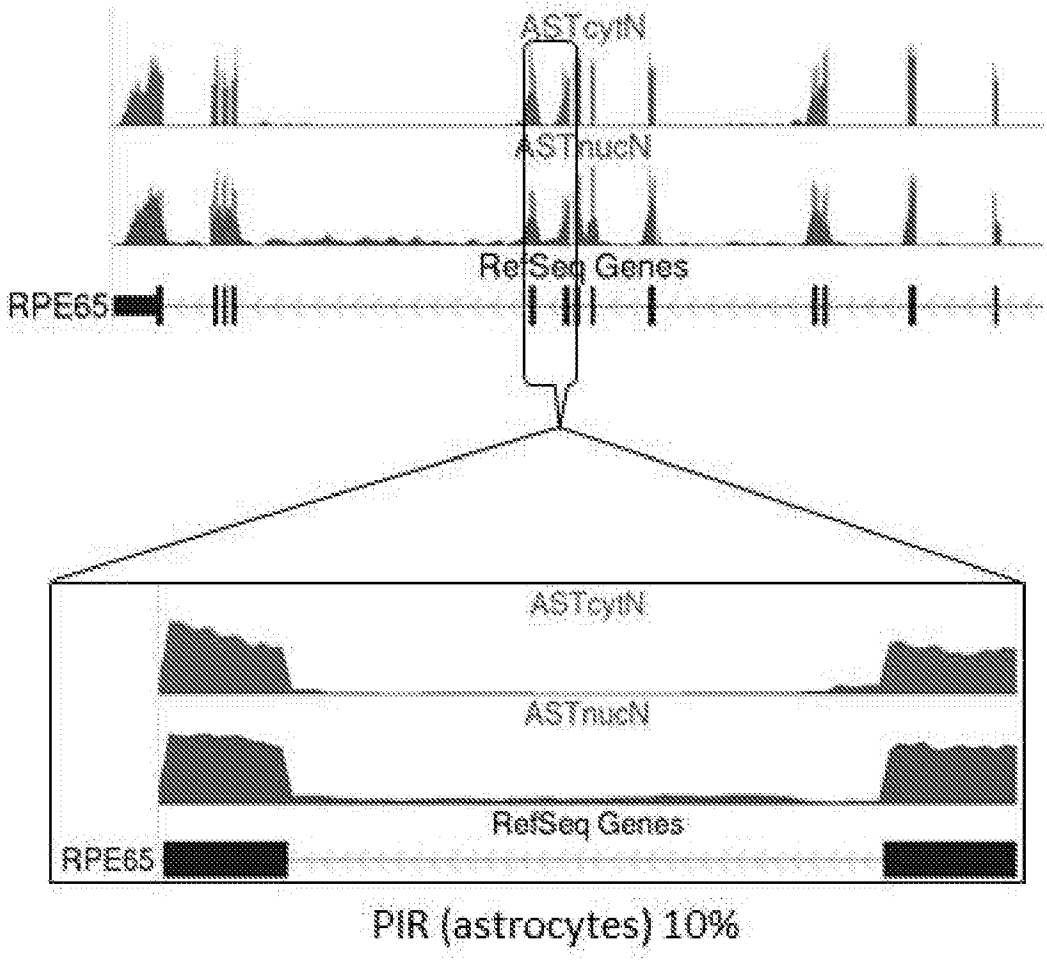
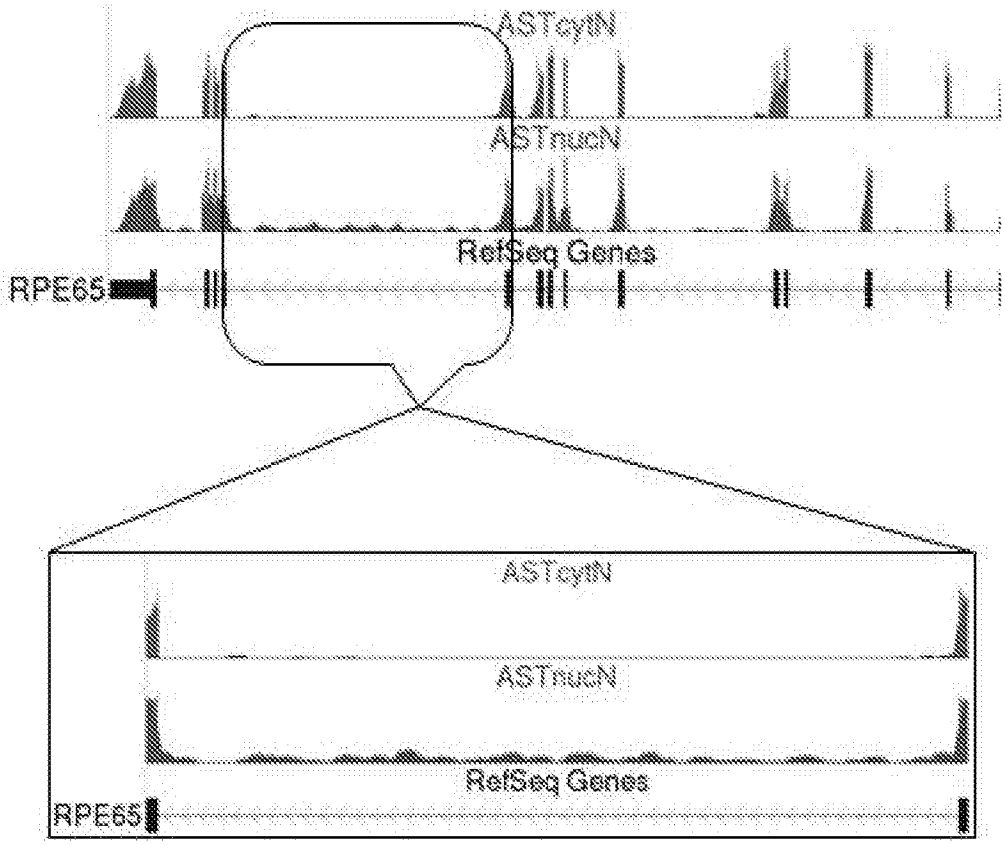

ASTcytN
ASTnucN
RefSeq Genes
RPE65
ASTcytN
ASTnucN
RefSeq Genes
RPE65
PIR (astrocytes) 10%

FIG. 24



PIR (astrocytes) 11%

FIG. 25

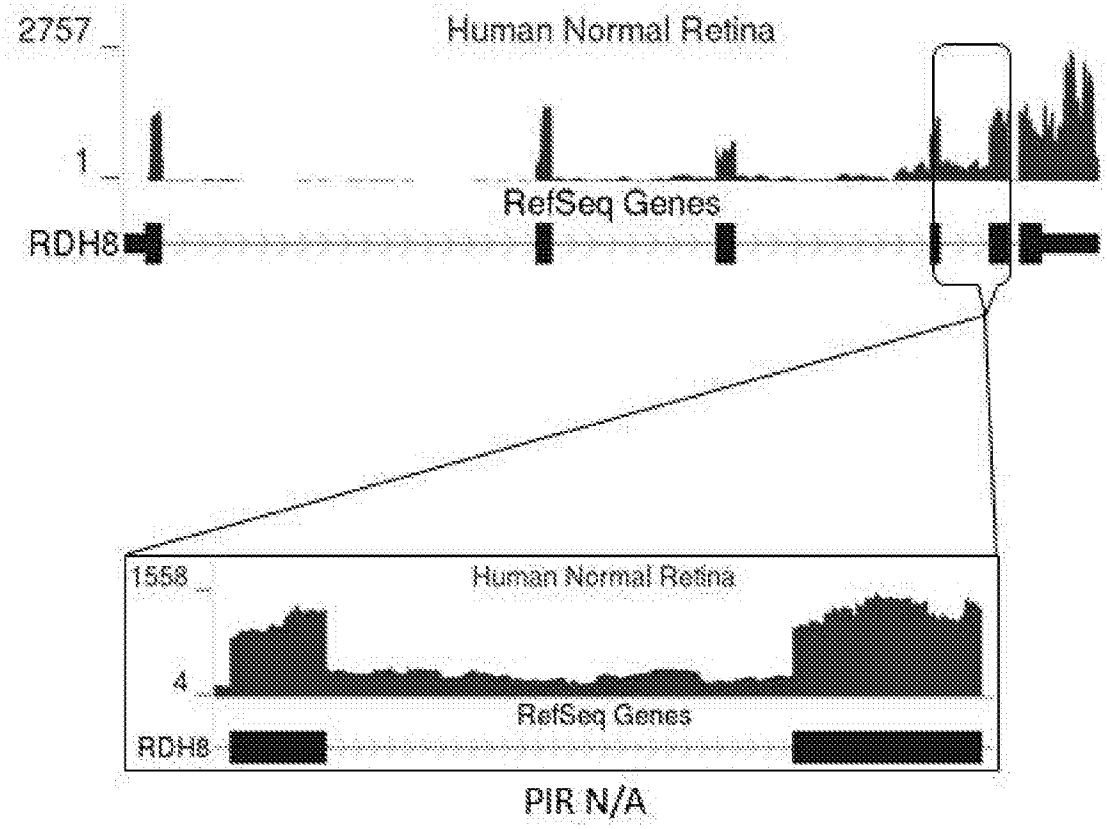

2757
Human Normal Retina
1
RefSeq Genes
RDH8
1558
Human Normal Retina
4
RefSeq Genes
RDH8
PIR N/A

FIG. 26

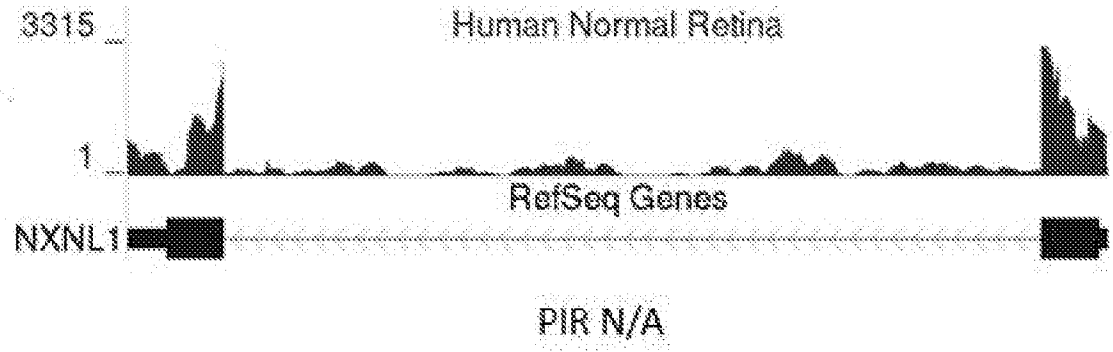


FIG. 27

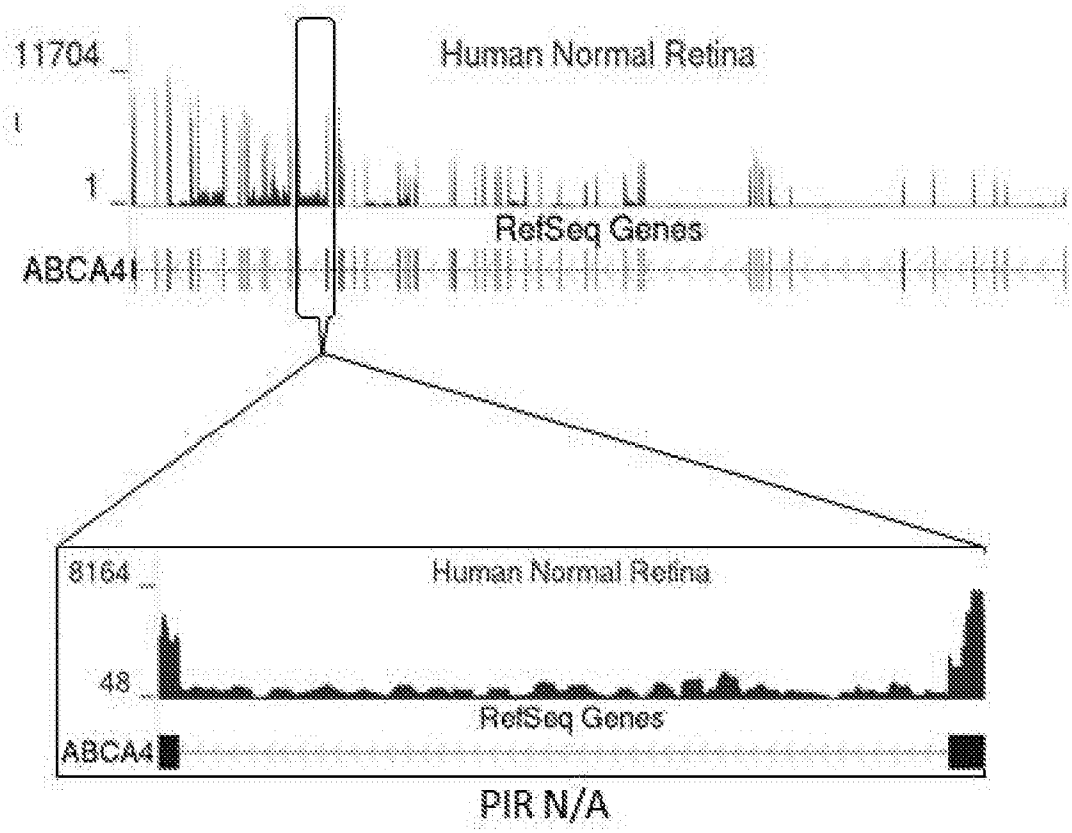

11704
Human Normal Retina
1
RefSeq Genes
ABCA4
8164
Human Normal Retina
48
RefSeq Genes
ABCA4
PIR N/A

FIG. 28

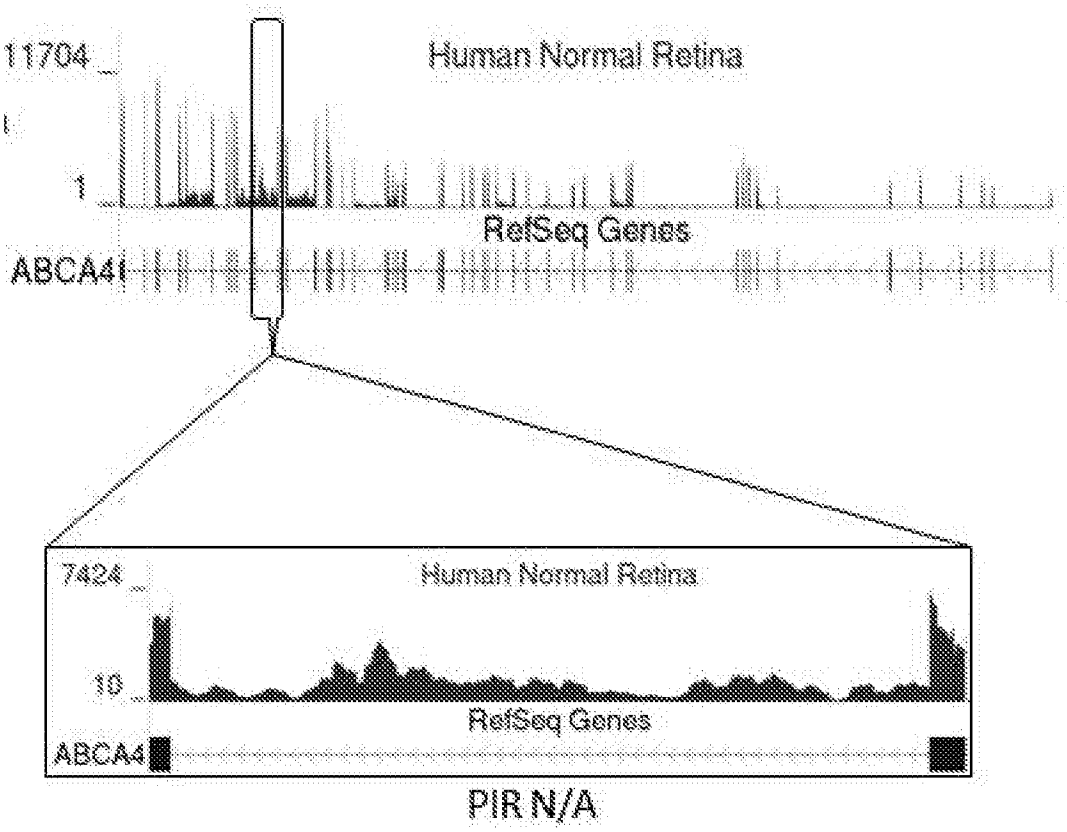

11704
Human Normal Retina
1
RefSeq Genes
ABCA4
7424
Human Normal Retina
10
RefSeq Genes
ABCA4
PIR N/A

FIG. 29

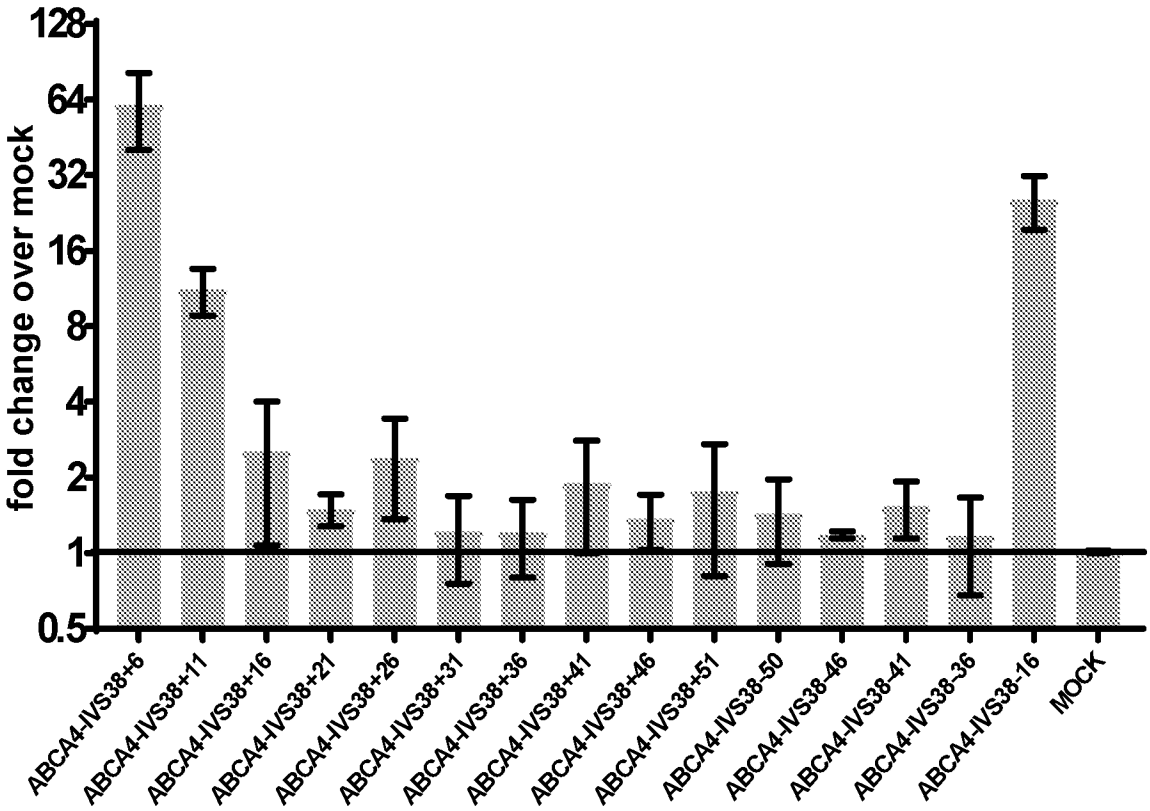

fold change over mock
128
64
32
16
8
4
2
1
0.5
ABCA4-IVS38+6
ABCA4-IVS38+11
ABCA4-IVS38+16
ABCA4-IVS38+21
ABCA4-IVS38+26
ABCA4-IVS38+31
ABCA4-IVS38+36
ABCA4-IVS38+41
ABCA4-IVS38+46
ABCA4-IVS38+51
ABCA4-IVS38-50
ABCA4-IVS38-46
ABCA4-IVS38-41
ABCA4-IVS38-36
ABCA4-IVS38-16
MOCK

FIG. 30

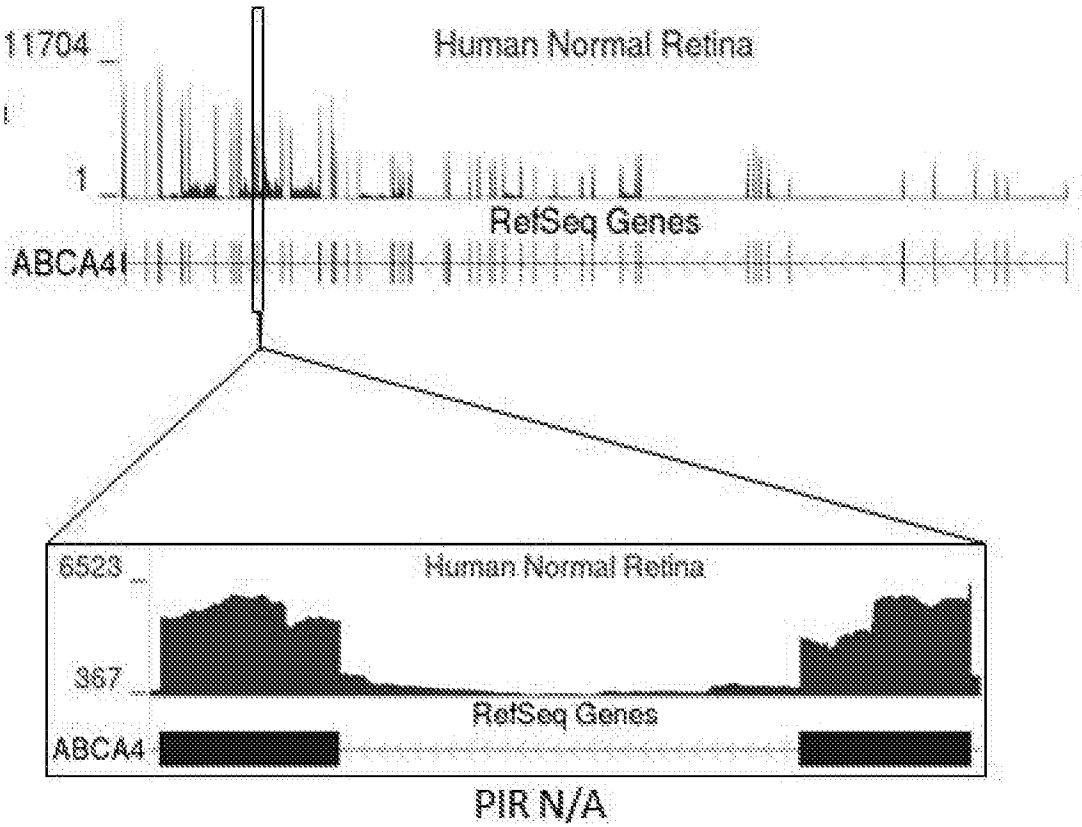

11704
Human Normal Retina
1
RefSeq Genes
ABCA4I
6523
Human Normal Retina
367
RefSeq Genes
ABCA4
PIR N/A

FIG. 31

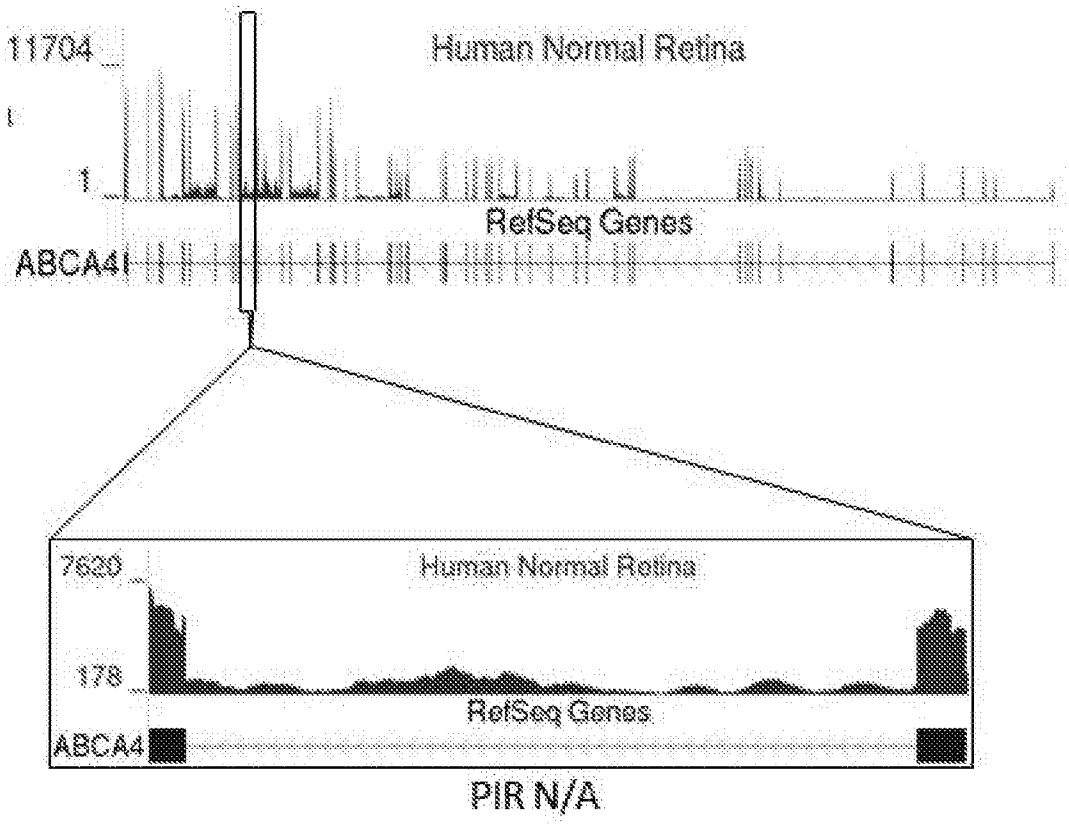

11704
Human Normal Retina
1
RefSeq Genes
ABCA4
7620
Human Normal Retina
178
RefSeq Genes
ABCA4
PIR N/A

FIG. 32

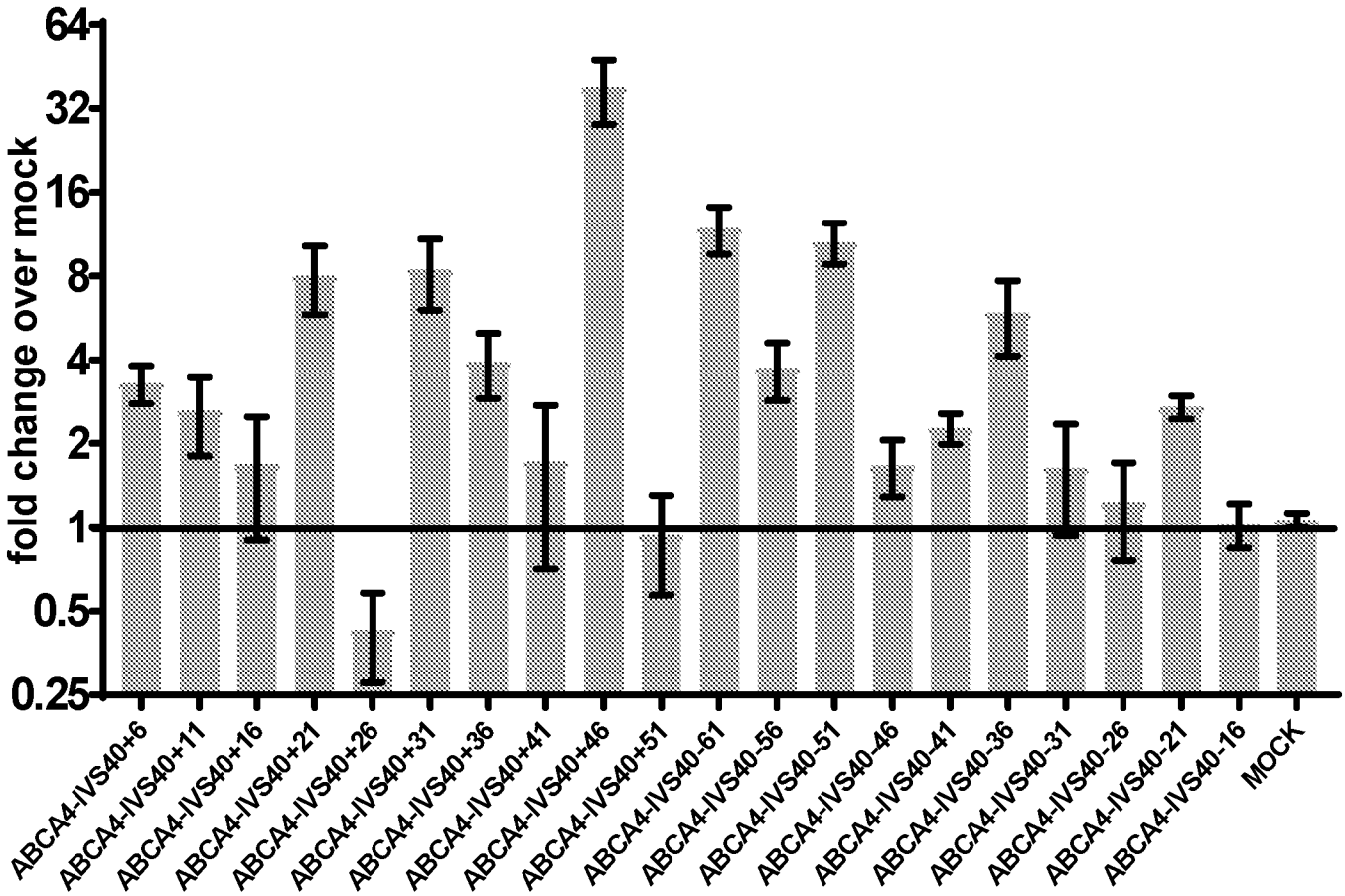

fold change over mock
64
32
16
8
4
2
1
0.5
0.25
ABCA4-IVS40+6
ABCA4-IVS40+11
ABCA4-IVS40+16
ABCA4-IVS40+21
ABCA4-IVS40+26
ABCA4-IVS40+31
ABCA4-IVS40+36
ABCA4-IVS40+41
ABCA4-IVS40+46
ABCA4-IVS40+51
ABCA4-IVS40-61
ABCA4-IVS40-56
ABCA4-IVS40-51
ABCA4-IVS40-46
ABCA4-IVS40-41
ABCA4-IVS40-36
ABCA4-IVS40-31
ABCA4-IVS40-26
ABCA4-IVS40-21
ABCA4-IVS40-16
MOCK

FIG. 33

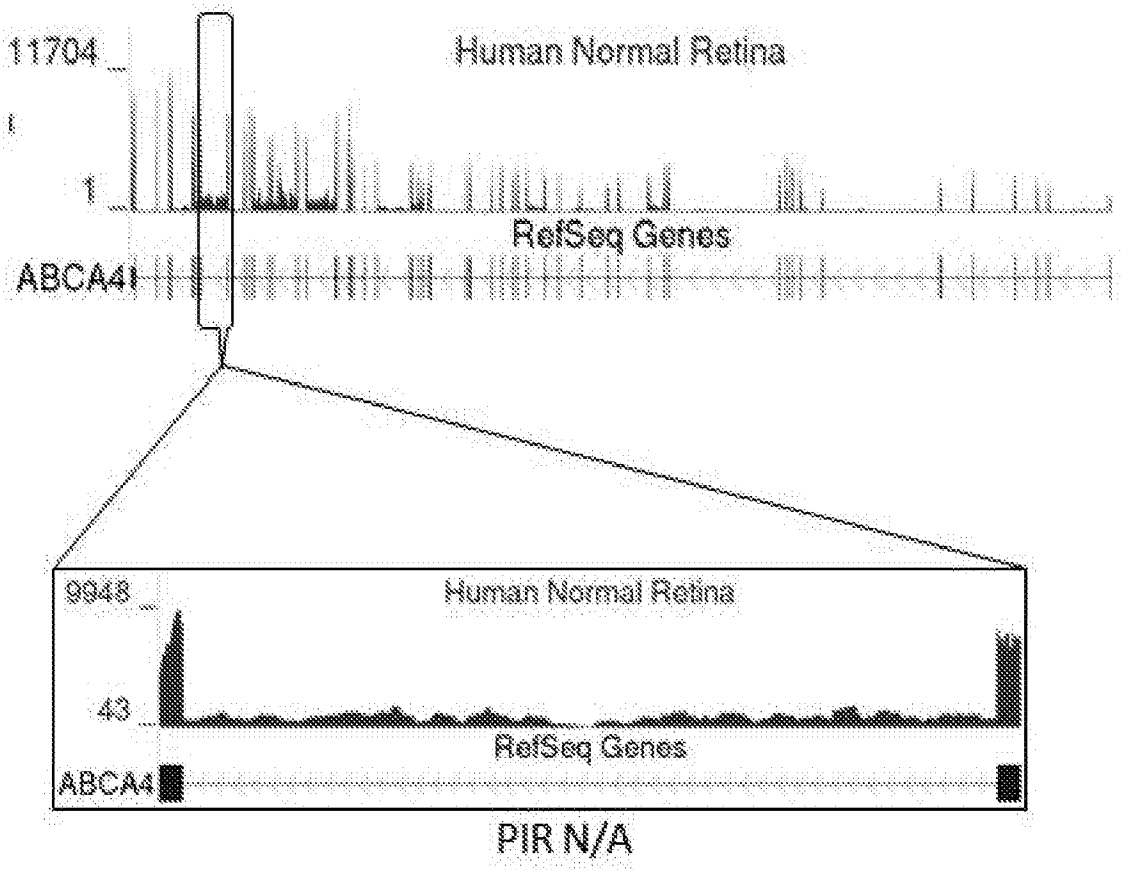

11704
Human Normal Retina
1
RefSeq Genes
ABCA4
9948
Human Normal Retina
43
RefSeq Genes
ABCA4
PIR N/A

FIG. 34

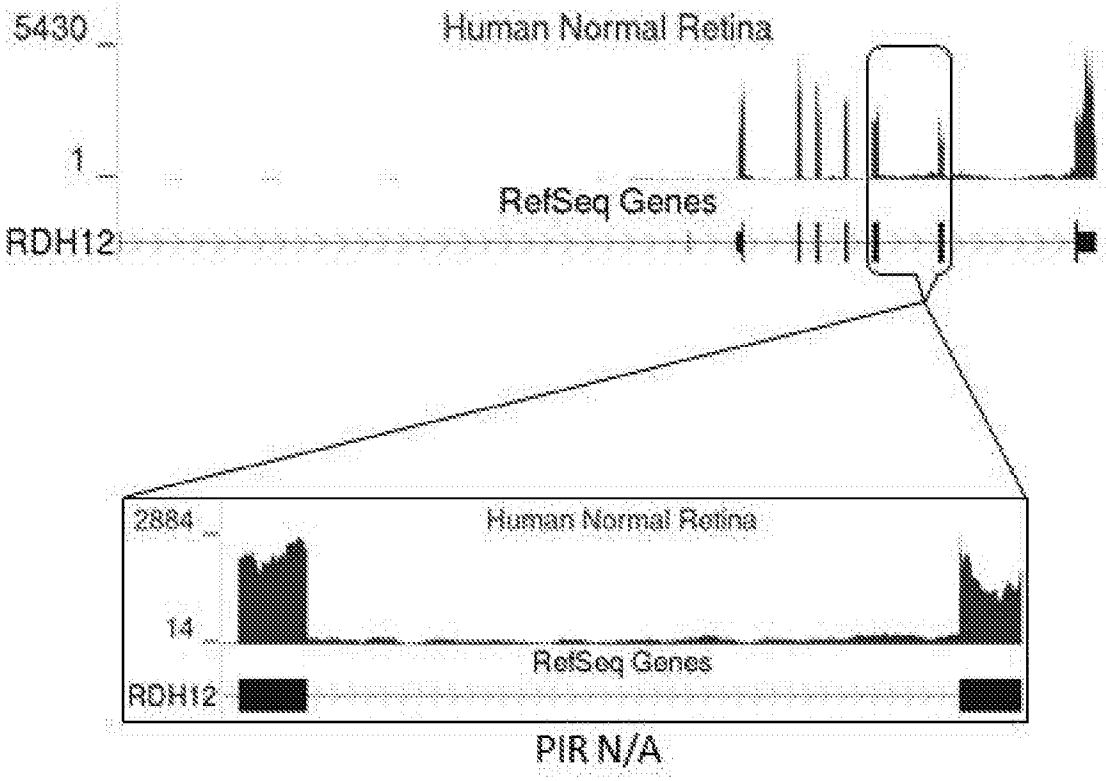

5430
Human Normal Retina
1
RefSeq Genes
RDH12
2884
Human Normal Retina
14
RefSeq Genes
RDH12
PIR N/A

FIG. 35

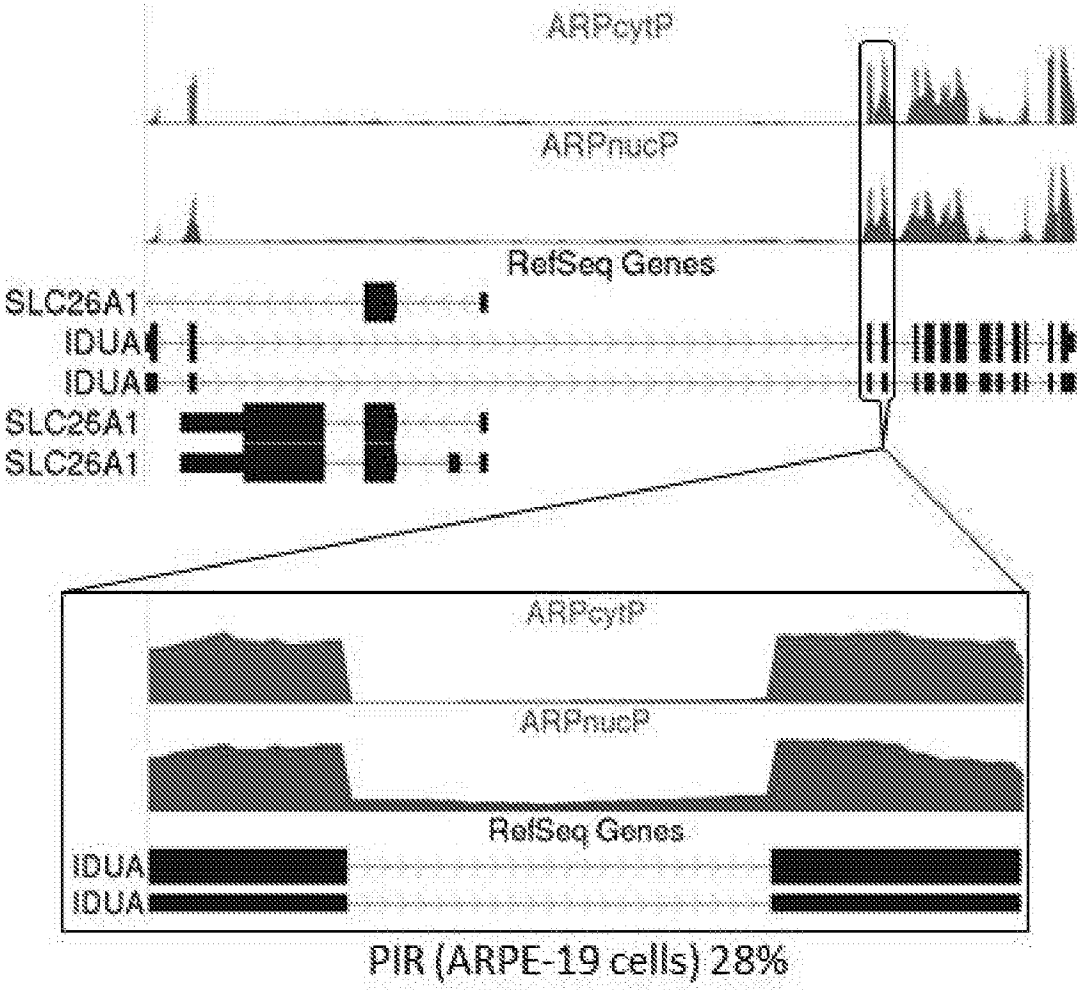

ARPcytP
ARPnucP
RefSeq Genes
SLC26A1
IDUA
IDUA
SLC26A1
SLC26A1
ARPcytP
ARPnucP
RefSeq Genes
IDUA
IDUA
PIR (ARPE-19 cells) 28%

FIG. 36

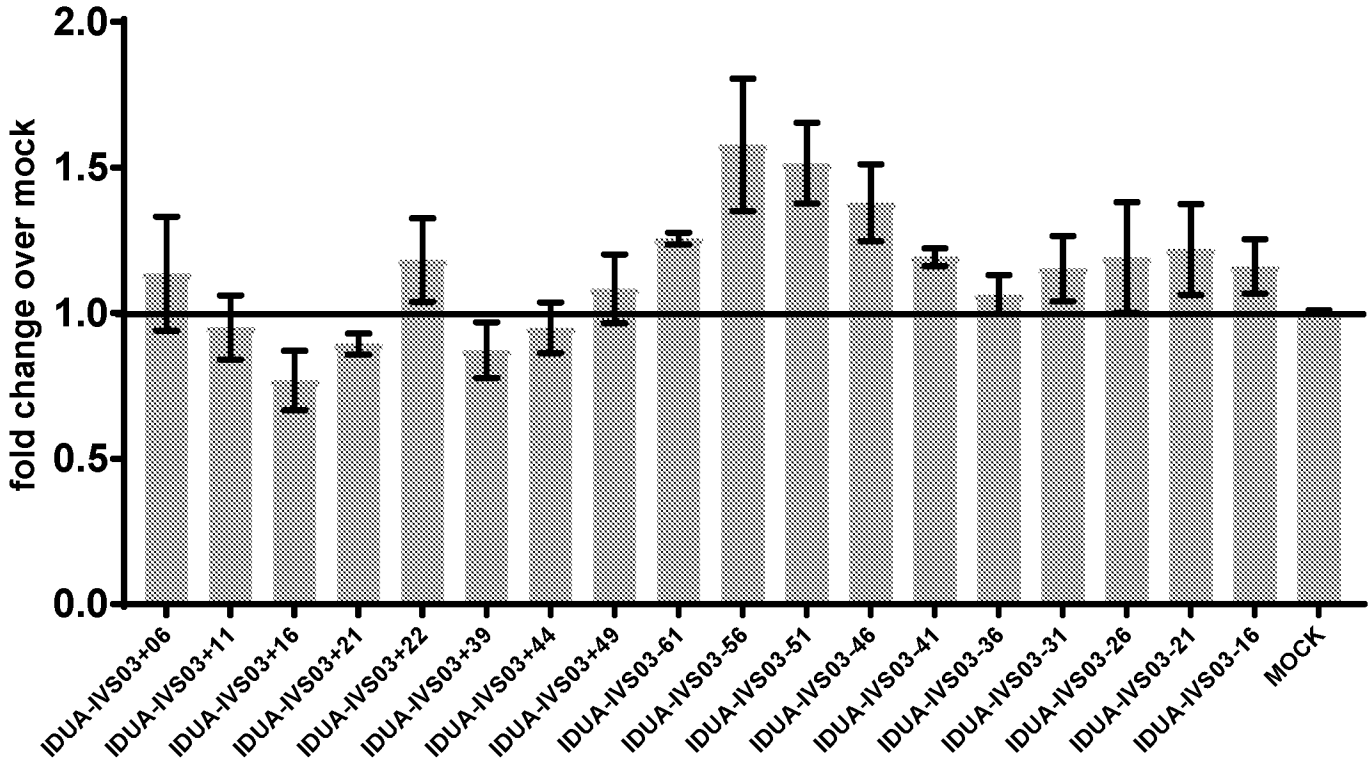

2.0
1.5
1.0
0.5
0.0
fold change over mock
IDUA-IVS03+06
IDUA-IVS03+11
IDUA-IVS03+16
IDUA-IVS03+21
IDUA-IVS03+22
IDUA-IVS03+39
IDUA-IVS03+44
IDUA-IVS03+49
IDUA-IVS03-61
IDUA-IVS03-56
IDUA-IVS03-51
IDUA-IVS03-46
IDUA-IVS03-41
IDUA-IVS03-36
IDUA-IVS03-31
IDUA-IVS03-26
IDUA-IVS03-21
IDUA-IVS03-16
MOCK

FIG. 37

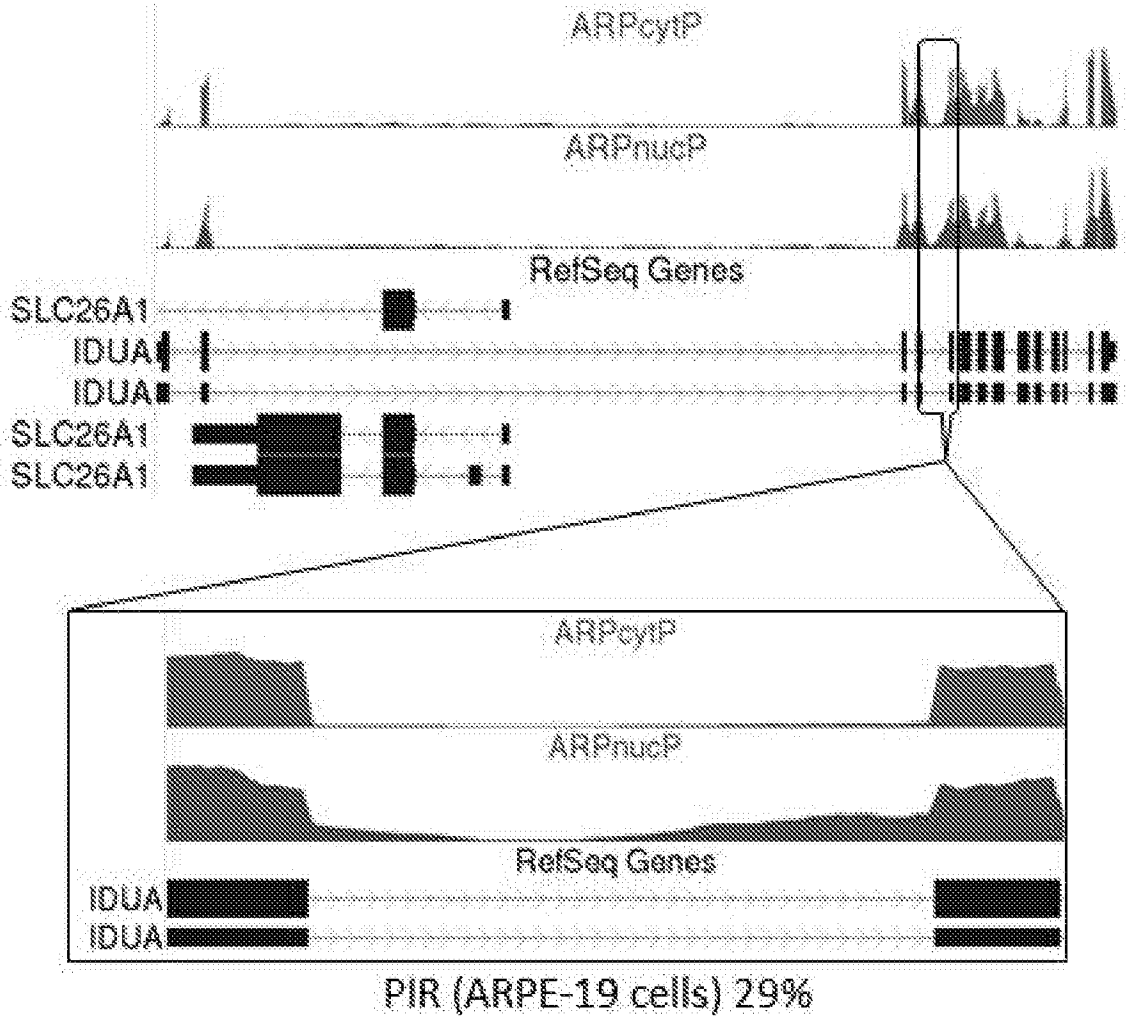

ARPcytP
ARPnucP
RefSeq Genes
SLC26A1
IDUA
IDUA
SLC26A1
SLC26A1
ARPcytP
ARPnucP
RefSeq Genes
IDUA
IDUA
PIR (ARPE-19 cells) 29%

FIG. 38

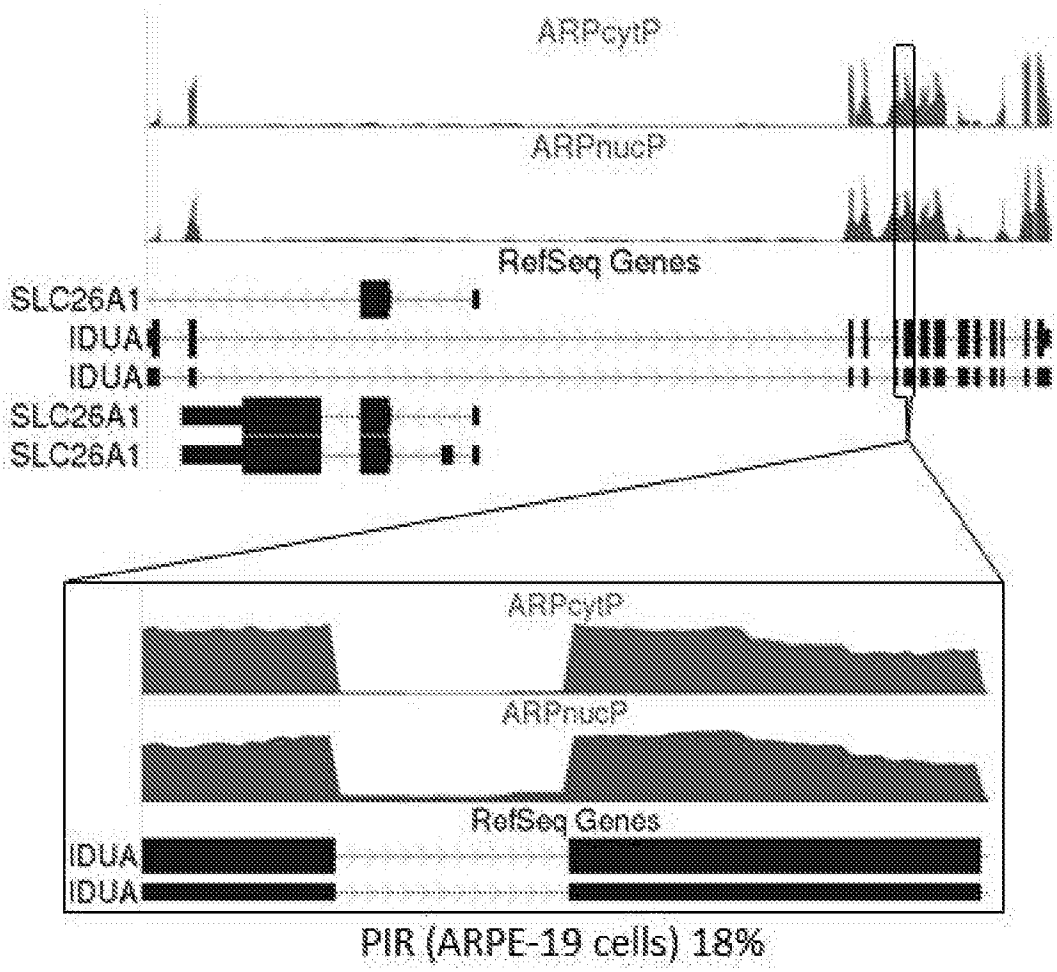

ARPcytP
ARPnucP
RefSeq Genes
SLC26A1
IDUA
IDUA
SLC26A1
SLC26A1
ARPcytP
ARPnucP
RefSeq Genes
IDUA
IDUA
PIR (ARPE-19 cells) 18%

FIG. 39

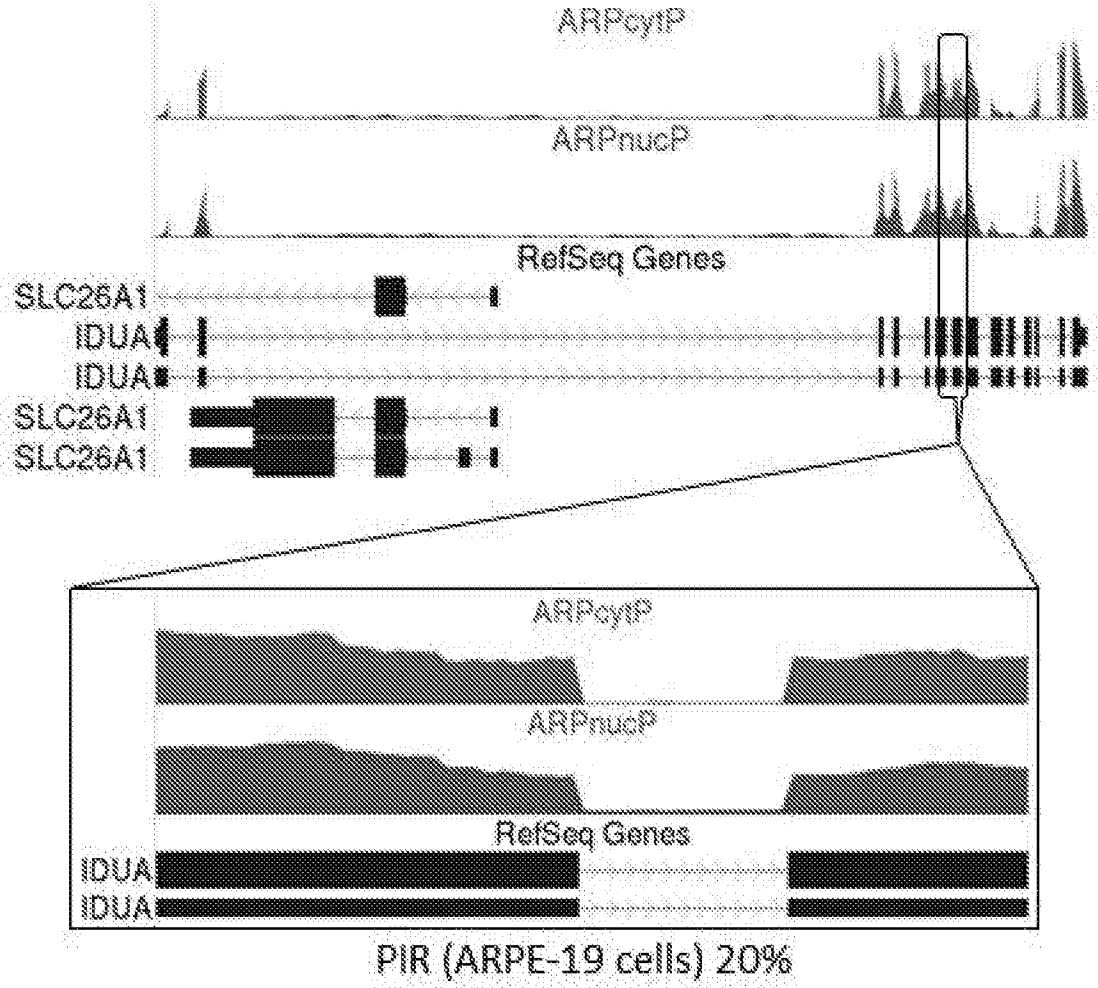

ARPcytP
ARPnucP
RefSeq Genes
SLC26A1
IDUA
IDUA
SLC26A1
SLC26A1
ARPcytP
ARPnucP
RefSeq Genes
IDUA
IDUA
PIR (ARPE-19 cells) 20%

FIG. 40

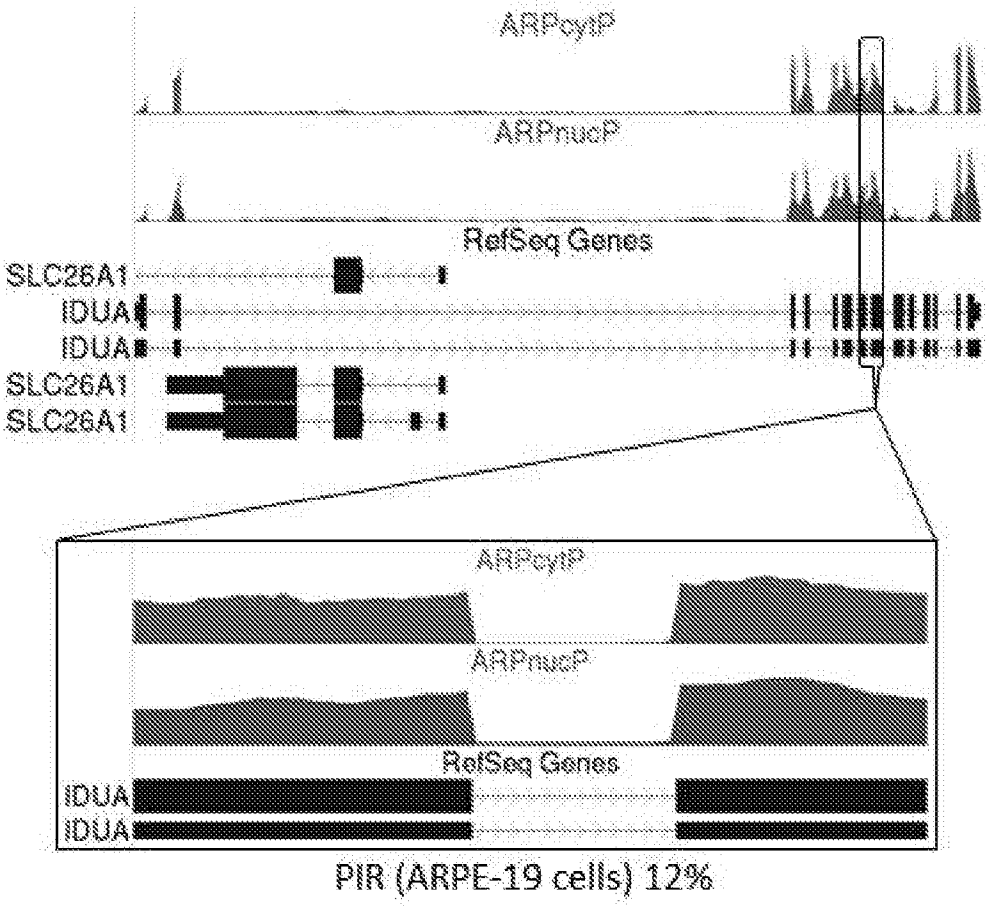
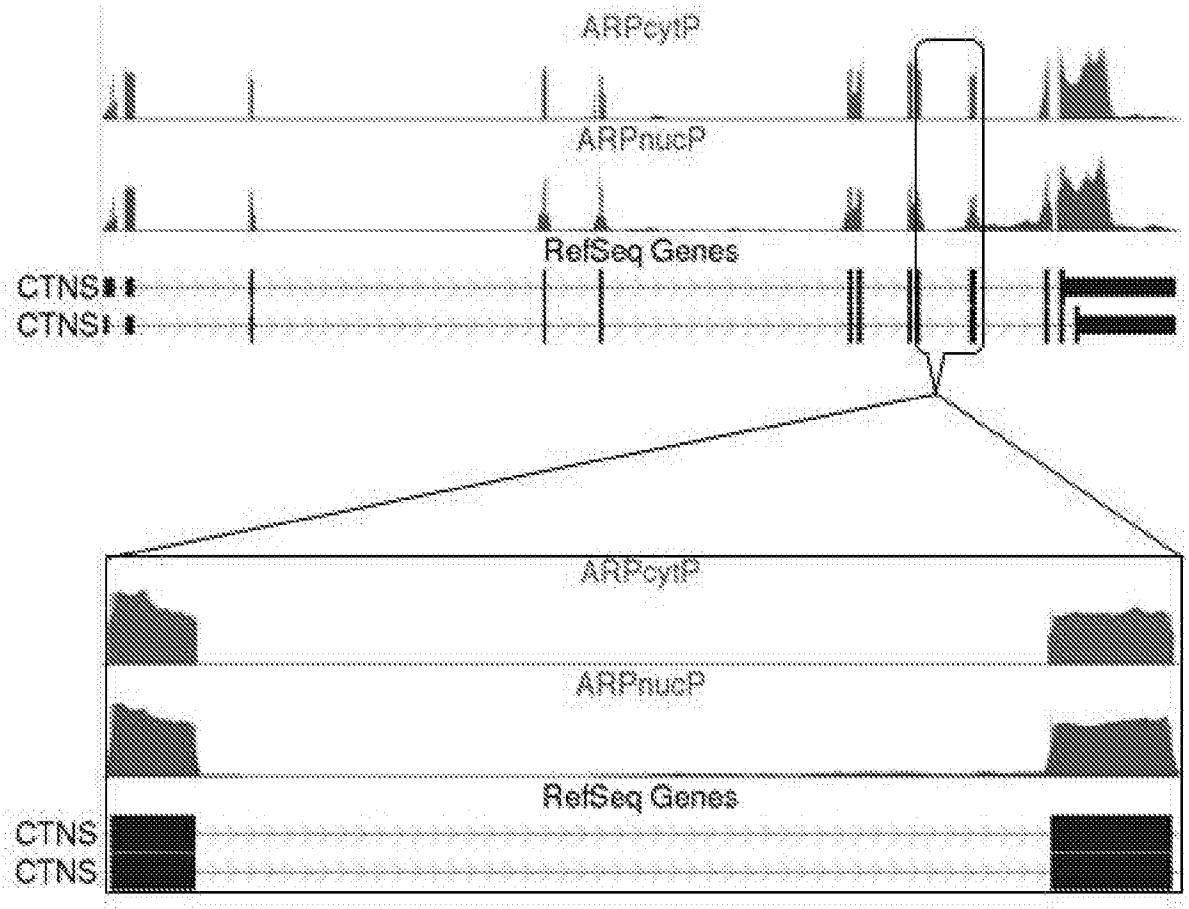
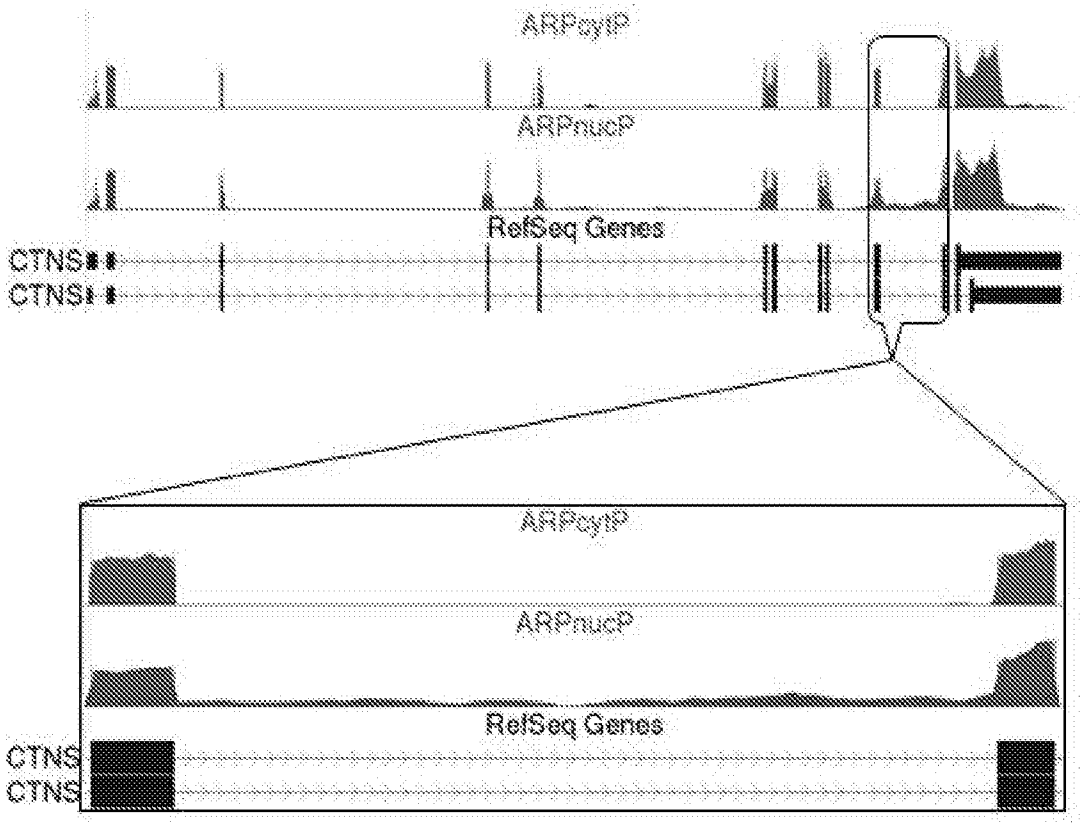

ARPcytP
ARPnucP
RefSeq Genes
SLC26A1
IDUA
IDUA
SLC26A1
SLC26A1
ARPcytP
ARPnucP
RefSeq Genes
IDUA
IDUA
PIR (ARPE-19 cells) 12%

FIG. 41



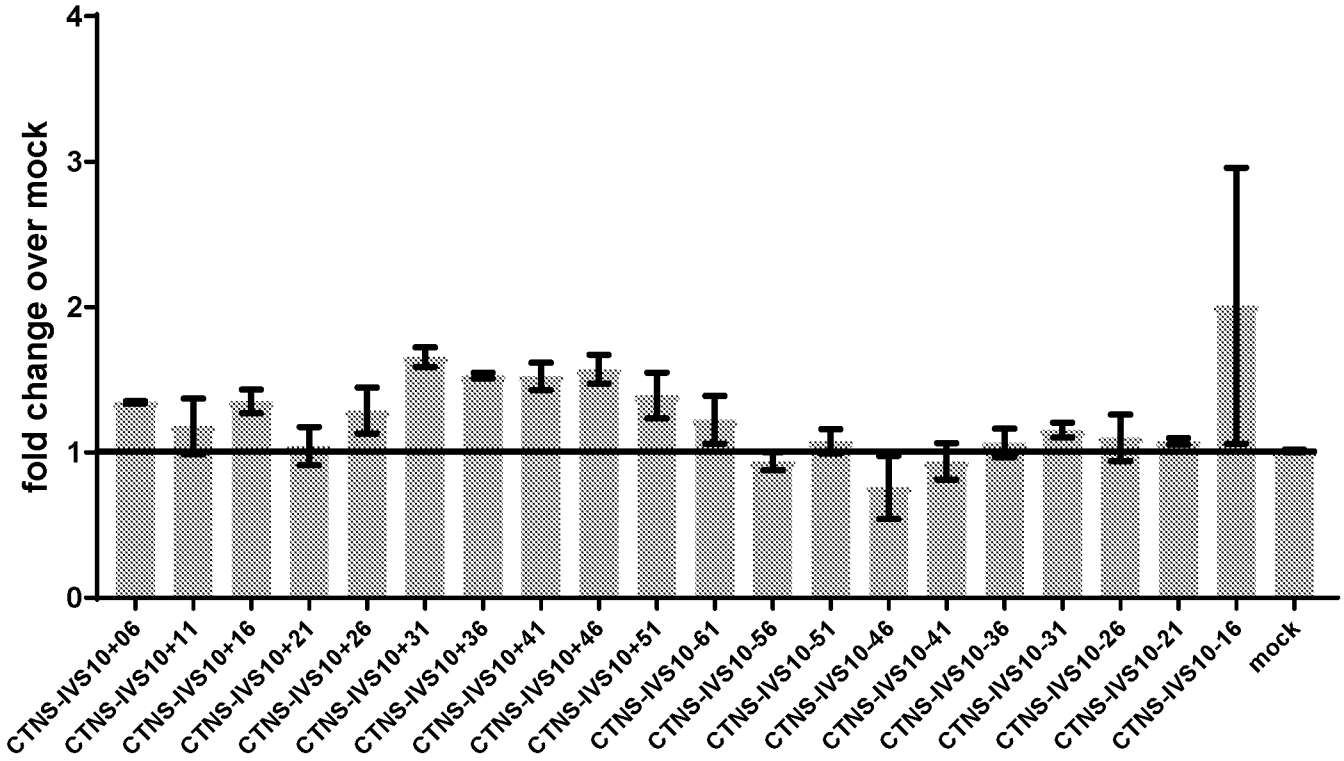
PIR (ARPE-19 cells): 10%

FIG. 42



PIR (ARPE-19 cells): 18%

FIG. 43


fold change over mock
4
3
2
1
0
CTNS-IVS10+06
CTNS-IVS10+11
CTNS-IVS10+16
CTNS-IVS10+21
CTNS-IVS10+26
CTNS-IVS10+31
CTNS-IVS10+36
CTNS-IVS10+41
CTNS-IVS10+46
CTNS-IVS10+51
CTNS-IVS10-61
CTNS-IVS10-56
CTNS-IVS10-51
CTNS-IVS10-46
CTNS-IVS10-41
CTNS-IVS10-36
CTNS-IVS10-31
CTNS-IVS10-26
CTNS-IVS10-21
CTNS-IVS10-16
mock

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/66691

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/113, 15/11; C12Q 1/68 (2017.01)
CPC - C12N 15/113, 15/111, 2320/33, 2310/113; C12Q 1/6883

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SIERAKOWSKA et al. Repair of thalassemic human beta-globin mRNA in mammalian cells by antisense oligonucleotides. Proc Nat Acad Sci 12 November 1996 Vol 93 No 23 Pages 12840-12844. Especially abstract, pg 12841 col 1 para 3-5 and col 2 para 1, pg 12841 fig 1, pg 12843 col 2 para 3.	1-6, 105-108
Y	US 2013/0253036 A1 (COLLARD et al.) 26 September 2013 (26.09.2013). Especially para [0006], [0068], [0070], [0094], [0095], [0099], SEQ ID NO: 1	1-6, 105-108
A	MOSKOWITZ et al. Mutation in Scheie syndrome (MPS IS): a G -->A transition creates new splice site in intron 5 of one IDUA allele. Hum Mutat 1993 Vol 2 No 2 Pages 141-144. Especially pg 141 col 2 para 1, pg 142 col 1 para 3, pg 143 fig 1E	1-3, 105
A	WO 2014/121287 A2 (Isis Pharmaceuticals, Inc.) 7 August 2014 (07.08.2014). Especially pg 23 ln 31-34, pg 70 ln 13-17, pg 73 ln 3-5	1-6, 105-108
Y,P	WO 2015/193651 A1 (University of Southampton) 23 December 2015 (23.12.2015). Especially para [00146], [00280], claims 1-4	1, 3, 105
Y,P	WO 2016/054615 A2 (Cold Spring Harbor Laboratory) 7 April 2016 (07.04.2016). Especially claims 1-9	1-6, 105

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2017	10 MAY 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/66691

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
GenCore ver 6.4.1 SEQ ID NOs: 84, 3814, 15080

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/66691

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 7-51, 53, 54, 61-89, 104
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--------Go to Extra Sheet for continuation----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-6, 105-108, limited to RPE7, ROM1, SEQ ID NO: 15180

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

------continuation of Box III (Lack of Unity of Invention)---------

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-6, 105-108, drawn to a method of treating an eye disease by increasing the expression of a targeted protein or functional RNA associated with the eye disease comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the retained-intron-containing pre-mRNA (RIC pre-mRNA) encoding the target protein or functional RNA.
The method of treating an eye disease will be searched to the extend that the disease and the target protein encompass Retinitis pigmentosa-7 (RPE7) and ROM1, respectively, and the ASO encompasses SEQ ID NO: 15180 [see instant Specification, pg 109, Table 1]. It is believed that claims 1-6, 105-108 read on this first named invention and thus these claims will be searched without fee to the extent that they encompass RPE7, ROM1 and SEQ ID NO: 15180. Additional diseases, target proteins and ASOs will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional diseases, target proteins, or ASOs. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be Stargardt disease-1, ABCA4, and SEQ ID NO: 84 [see instant Specification, pg 105, table 1](claims 1-6, 105-108).

Group II+: Claims 52, 55-60, 90-103, drawn to an antisense oligomer (ASO) composition for treating an eye disease by increasing the expression of a gene associated with the eye disease.
Group II+ will be searched upon payment of additional fee(s). The composition may be searched, for example, to the extent that the disease is RPE7, the target gene is ROM1, and the antisense oligomer comprises SEQ ID NO: 15180, for an additional fee and election as such. It is believed that claims 52, 55-60, 90-103 read on this exemplary invention. Additional diseases, target proteins and ASOs will be searched upon the payment of additional fees. Applicants must indicate, if applicable, which claims read on this named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first named invention to be searched/examined. An exemplary election would Stargardt disease-1, ABCA4, and SEQ ID NO: 84 (claims 52, 55-60, 90-103)

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ inventions have the special technical feature of a method involving specific steps for treating an eye disease by increasing the expression of a target proteins related to the eye disease, not required by Group II+

Group II+ inventions have the special technical feature of an antisense oligomer composition, not required by Group I+

Among the inventions listed as Groups I+ or II+ are the specific antisense oligomer sequences recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among sequences

Common Technical Features:

Groups I+ and II+ share the common technical feature of an eye disease, increasing the expression of a target protein associated with an eye disease, retained-intron-containing pre-mRNA (RIC pre-mRNA), antisense oligomer (ASO).

Group I+ inventions share the common technical feature of claims 1, 3, 105, 108

Group II+ inventions share the common technical features of claims 52, 55, 56, 90

However, said common technical features do not represent a contribution over the prior art, and is obvious over the publication titled "Repair of thalassemic human beta-globin mRNA in mammalian cells by antisense oligonucleotides" by Sierakowska et al. (hereinafter "Sierakowska") [published 12 November 1996 Vol 93 No 23 Pages 12840-12844], in view of US 2013/0253036 A1 to COLLARD et al. (hereinafter "Collard").

------continued on next sheet------

---continued from previous sheet----

As to claims 1 and 3, Sierakowska teaches method of treating a disease in a subject in need thereof, by increasing the expression of a target protein, or functional RNA by cells of the subject (abstract; "In one form of beta-thalassemia, a genetic blood disorder, a mutation in intron 2 of the beta-globin gene (IVS2- 654) causes aberrant splicing of beta-globin pre-mRNA and, consequently, beta-globin deficiency. Treatment of mammalian cells stably expressing the IVS2-654 human beta-globin gene with antisense oligonucleotides targeted at the aberrant splice sites restored correct splicing in a dose-dependent fashion, generating correct human beta-globin mRNA and polypeptide. Both products persisted for up to 72 hr posttreatment. The oligonucleotides modified splicing by a true antisense mechanism without overt unspecific effects on cell growth and splicing of other pre-mRNAs"), wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA) (pg 12841 col 1 para 3; "we have constructed two cell lines stably transformed with the IVS2-654 variant of the thalassemic human beta-globin gene. In a HeLa-based cell line, as in thalassemic patients (1, 3, 4), this mutation created a 5' splice site at nucleotide 652 of intron 2 and activated a 3' cryptic splice site 73 nucleotides upstream, resulting in stably expressed but aberrantly spliced IVS2-654 beta-globin pre-mRNA; pg 12841 fig 1A), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site, an exon flanking the 3' splice site (pg 12841 col 1 para 3; pg 12841 fig 1A), and wherein the RIC pre-mRNA encodes the target protein or functional RNA (pg 12841 col 1 para 3; pg 12841 fig 1A), the method comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding the target protein or functional RNA (pg 12841 col 1 para 3; "To restore correct splicing of the RNA, the cells were treated for 10 hr with a complex of Lipofectamine and the 18-mer phosphorothioate 29-O-methyloligoribonucleotide (5'ss) targeted to the aberrant 5' splice site. The 2'-O-methyl derivatives were chosen since they hybridize well to their target sequences and are very stable in cellular environment") whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding the target protein or functional RNA (pg 12841 fig 1A), thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of the target protein or functional RNA in the cells of the subject (pg 12841 col 1 para 5 continued to pg 12841 col 2 para 1; Analysis of the total protein from oligonucleotide-treated cells by immunoblotting with polyclonal antibody to human hemoglobin showed that the newly generated, correctly spliced beta-globin mRNA was translated into full-length beta-globin. In agreement with the RT-PCR results shown in Fig. 1B, only samples treated with 0.05?0.4 mM oligonucleotide contained significant amounts of full-length beta-globin (Fig. 1C, lanes 3-6); pg 12841 fig 1B and 1C). Sierakowska does not teach the disease is an eye disease or teach a particular target gene related to the eye disease. However, Collard teaches IDUA related to Hurler-Scheie Syndrome [attenuated MPS-1] (para [0070]; "In an embodiment, antisense oligonucleotides are used to prevent or treat diseases or disorders associated with IDUA family members. Exemplary Alpha-L-Iduronidase (IDUA) mediated diseases and disorders which can be treated with the antisense oligonucleotides of the invention...Hurler syndrome; Hurler-Scheie syndrome and Scheie syndrome"), and further teaches splicing defects of pre-mRNA splice junctions (para [0094];" In one embodiment, targeting splice sites, i.e., intron-exon junctions or exon-intron junctions, is particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular splice product is implicated in disease. An aberrant fusion junction due to rearrangement or deletion is another embodiment of a target site. mRNA transcripts produced via the process of splicing of two (or more) mRNAs from different gene sources are known as "fusion transcripts". Introns can be effectively targeted using antisense compounds targeted to, for example, DNA or pre-mRNA."). Based on the teaching of Sierakowska, it would have been obvious to have used the antisense splicing correction strategy to have tried to correct the splicing defect in intronic regions of IDUA, related to Hurler-Scheie syndrome

Collard further teaches antisense oligonucleotides for targeting introns or intron splicing regions (para [0095]; "In an embodiment, the antisense oligonucleotides bind to coding and/or non-coding regions of a target polynucleotide and modulate the expression and/or function of the target molecule"; para [0099]; "Upon excision of one or more exon or intron regions, or portions thereof during splicing, pre-mRNA variants produce smaller "mRNA variants". Consequently, mRNA variants are processed pre-mRNA variants and each unique pre-mRNA variant must always produce a unique mRNA variant as a result of splicing"). Collard further teaches a pharmaceutical composition (para [0193]).

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I+ and II+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note concerning item 4: Claims 7-51, 53, 54, 61-89, 104 are multiple dependent claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a).