

mutations: only very recently a promising research programme was delayed due to a mutation discovered in the ORF15 region of the transgene cassette. In another programme, alternative RPGR splice variants were detected by Western blot (Wu, Z. et al. (2015) Hum. Mol. Genet. 24: 3956-3970).

- 5 There is currently no approved therapy to prevent the development of RP or to improve vision following the onset of the disease. Accordingly, there remains a significant need for treatments of RP, in particular to prevent deterioration in visual function or to enable improvement in the vision of affected individuals.

SUMMARY

- 10 The present inventors have surprisingly found that the sequence of the retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}) gene can be engineered to increase sequence stability, such as by reducing or preventing the occurrence of mutations during replication (i.e. increasing the fidelity of replication). The present inventors have also
15 be mitigated. Moreover, the engineered genes have been demonstrated by the present inventors to successfully treat animal models of retinitis pigmentosa.

Accordingly, in one example, the disclosure provides a polynucleotide comprising a nucleotide sequence encoding the retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}), wherein the RPGR^{ORF15}-encoding nucleotide sequence has been codon
20 optimised to increase fidelity of replication of the sequence.

In one aspect, the present disclosure refers to a composition comprising a nucleic acid comprising

- (a) a sequence encoding a rhodopsin kinase promoter, and
(b) a sequence encoding a retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}) and comprising a nucleotide sequence that has at least 80% identity to the
25 nucleic acid sequence of SEQ ID NO: 3.

Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to reduce the generation of alternative splice variants.

- Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon
30 optimised to minimise or avoid the creation of new CpG sites in comparison to the wild type sequence. In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises less than 220, 210, 200, 190, 170, 165, 160, 150, 140, 130, 120, 110 or 100 CpG sites.

- Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon
35 optimised by replacing some or all GGN codons with GGC codons (when the GGN codons were not originally GGC codons).

Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to minimise or avoid the introduction of new thymine nucleotides in the purine-rich

(i.e. GA-rich) regions of the RPGR^{ORF15}-encoding nucleotide sequence, for example the ORF 15 exon region (which corresponds to nucleotides 1754-3459 of RPGR^{ORF15}, e.g. nucleotides 1754-3459 of SEQ ID NO: 2).

Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to reduce the number of GT sites (i.e. potential splice donor sites) in comparison to the wild type sequence. In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises less than 120, 115, 110, 105, 100, 90, 80, 70, 60, 50, 40, 30, 20 or 10 GT sites. In a preferred example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises less than 105 GT sites.

Preferably, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to avoid the creation of anomalous polyA signals (e.g. AATAAA).

In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to reduce the number of purine nucleotides in comparison to the wild type sequence. The wild type sequence may, for example, be the sequence of SEQ ID NO: 2.

Preferably, the number of purine nucleotides is reduced by replacing purine nucleotides with pyrimidine nucleotides.

In one example, the number of purine nucleotides is reduced in purine-rich (i.e. GA-rich) regions of the RPGR^{ORF15}-encoding nucleotide sequence, for example the ORF 15 exon region (which corresponds to nucleotides 1754-3459 of RPGR^{ORF15}, e.g. nucleotides 1754-3459 of SEQ ID NO: 2).

In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure does not comprise purine nucleotides at positions corresponding to nucleotides 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910, 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361, 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2505, 2520, 2547, 2574, 2622, 2634, 2661, 2673, 2706, 2712, 2763, 2775, 2796, 2811, 2817, 2832, 2838, 2871, 2886, 2892, 2898, 2910, 2922, 2931, 2937, 2958, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 of SEQ ID NO: 2.

Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure does not comprise purine nucleotides at at least 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or all of these nucleotide positions. Preferably, the nucleotide sequence encodes an amino acid

sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 1. More preferably, the nucleotide sequence encodes the amino acid sequence of SEQ ID NO: 1.

In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure is derived from SEQ ID NO: 2 by replacing the purine nucleotides at positions 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910, 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361, 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2505, 2520, 2547, 2574, 2622, 2634, 2661, 2673, 2706, 2712, 2763, 2775, 2796, 2811, 2817, 2832, 2838, 2871, 2886, 2892, 2898, 2910, 2922, 2931, 2937, 2958, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 with pyrimidine nucleotides (e.g. thymine or cytosine). Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. In another example, the purine nucleotides have been replaced at at least 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or all of these nucleotide positions. Preferably, the nucleotide sequence encodes an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 1. More preferably, the nucleotide sequence encodes the amino acid sequence of SEQ ID NO: 1.

According to the disclosure, the number of purine nucleotides may be reduced by at least 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% of the number of purine nucleotides in the wild type sequence (e.g. SEQ ID NO: 2).

According to the disclosure, the number of purine nucleotides may be reduced by 0.5-10%, 0.5-7.5%, 0.5-5%, 0.5-4.5%, 0.5-4%, 0.5-3.5%, 0.5-3%, 1-5%, 1-4.5%, 1-4%, 1-3.5% or 1-3% of the number of purine nucleotides in the wild type sequence (e.g. SEQ ID NO: 2).

In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has been codon optimised to reduce the number of adenine nucleotides in comparison to the wild type sequence. The wild type sequence may, for example, be the sequence of SEQ ID NO: 2. In another example, the number of adenine nucleotides has been reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200. In one example, adenines at positions corresponding to nucleotides 58, 114, 123, 129, 181, 213, 219, 226, 237, 285, 306, 309, 315, 324, 330, 339, 400, 444, 456, 478, 480, 594, 606, 618, 697, 744, 807, 852, 877, 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1194, 1197, 1221, 1249, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1413, 1446,

1452, 1464, 1474, 1482, 1519, 1542, 1584, 1608, 1653, 1674, 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1854, 1881, 1893, 1902, 1909, 1929, 1960, 1987, 1992, 1998, 2020, 2047, 2049, 2062, 2067, 2076, 2167, 2169, 2190, 2208, 2229, 2259, 2298, 2323, 2361, 2373, 2382, 2403, 2410, 2412, 2448, 2457, 2472, 2476, 2622, 2661, 2673, 2712, 2775, 2811, 2832, 2886, 2910, 2931, 2958, 3033, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3306, 3321, 3369, 3405 and/or 3438 of SEQ ID NO: 2 are replaced with pyrimidine nucleotides (e.g. thymine or cytosine). Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure does not comprise a purine nucleotide at at least one position, preferably at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170 or 180 positions, preferably all positions, corresponding to a position where a purine nucleotide in SEQ ID NO: 2 (wtRPGR) aligns with a pyrimidine nucleotide in SEQ ID NO: 3 (coRPGR), for example in the sequence alignment of Figure 2 (wtRPGR, "Original"; coRPGR, "Optimized").

In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure does not comprise purine nucleotides at positions corresponding to nucleotides 33, 58, 59, 114, 123, 129, 181, 182, 213, 219, 226, 227, 237, 267, 285, 306, 309, 315, 324, 330, 339, 400, 401, 444, 456, 478, 480, 510, 594, 606, 618, 639, 697, 726, 744, 777, 807, 852, 877, 879, 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1184, 1194, 1197, 1221, 1249, 1251, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1373, 1413, 1446, 1452, 1464, 1474, 1475, 1482, 1519, 1520, 1542, 1584, 1590, 1599, 1608, 1653, 1668, 1674, 1689, 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910, 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361, 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2505, 2520, 2547, 2574, 2622, 2634, 2661, 2673, 2706, 2712, 2763, 2775, 2796, 2811, 2817, 2832, 2838, 2871, 2886, 2892, 2898, 2910, 2922, 2931, 2937, 2958, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 of SEQ ID NO: 2. Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure does not comprise purine nucleotides at at least 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180 or all of these nucleotide positions. Preferably, the nucleotide sequence encodes an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to

SEQ ID NO: 1. More preferably, the nucleotide sequence encodes the amino acid sequence of SEQ ID NO: 1.

It should be noted that in this application nucleotide positions are identified by those 'corresponding' to a particular position in SEQ ID NO:2. This is not to be interpreted as meaning the sequences of the present disclosure must include sequences present in SEQ ID NO:2. Herein, the nucleotides of the RPGR^{ORF15}-encoding nucleotide sequence are numbered following a convention whereby the 5' adenine of SEQ ID NO: 2 is assigned to be nucleotide 1. Identities of individual nucleotides and positions of mutations are described herein with reference to this numbering convention. A skilled person would readily be able to determine analogous positions in homologous sequences by performing a sequence alignment to SEQ ID NO: 2. An example of such an alignment is shown in Figure 2.

In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure is derived from SEQ ID NO: 2 by replacing the purine nucleotides at positions 33, 58, 59, 114, 123, 129, 181, 182, 213, 219, 226, 227, 237, 267, 285, 306, 309, 315, 324, 330, 339, 400, 401, 444, 456, 478, 480, 510, 594, 606, 618, 639, 697, 726, 744, 777, 807, 852, 877, 879, 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1184, 1194, 1197, 1221, 1249, 1251, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1373, 1413, 1446, 1452, 1464, 1474, 1475, 1482, 1519, 1520, 1542, 1584, 1590, 1599, 1608, 1653, 1668, 1674, 1689, 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910, 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361, 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2505, 2520, 2547, 2574, 2622, 2634, 2661, 2673, 2706, 2712, 2763, 2775, 2796, 2811, 2817, 2832, 2838, 2871, 2886, 2892, 2898, 2910, 2922, 2931, 2937, 2958, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 with pyrimidine nucleotides (e.g. thymine or cytosine). Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. In another example, the purine nucleotides have been replaced at at least 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180 or all of these nucleotide positions. Preferably the purine nucleotides have been replaced at all of these nucleotide positions. Preferably, the nucleotide sequence encodes an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 1. More preferably, the nucleotide sequence encodes the amino acid sequence of SEQ ID NO: 1.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence is such that the nucleotide corresponding to position 33 of SEQ ID NO:2 is T, the nucleotide corresponding to position 58 is T, the nucleotide corresponding to position 59 is C, the nucleotide corresponding to position 114 is C, the nucleotide corresponding to position 123 is T, the nucleotide corresponding to position 129 is C, the nucleotide corresponding to position 181 is T, the nucleotide corresponding to position 182 is C, the nucleotide corresponding to position 213 is C, the nucleotide corresponding to position 219 is T, the nucleotide corresponding to position 226 is T, the nucleotide corresponding to position 227 is C, the nucleotide corresponding to position 237 is C, the nucleotide corresponding to position 267 is C, the nucleotide corresponding to position 285 is C, the nucleotide corresponding to position 306 is C, the nucleotide corresponding to position 309 is C, the nucleotide corresponding to position 315 is C, the nucleotide corresponding to position 324 is C, the nucleotide corresponding to position 330 is C, the nucleotide corresponding to position 339 is C, the nucleotide corresponding to position 400 is T, the nucleotide corresponding to position 401 is C, the nucleotide corresponding to position 444 is C, the nucleotide corresponding to position 456 is T, the nucleotide corresponding to position 478 is C, the nucleotide corresponding to position 480 is C, the nucleotide corresponding to position 510 is C, the nucleotide corresponding to position 594 is C, the nucleotide corresponding to position 606 is C, the nucleotide corresponding to position 618 is C, the nucleotide corresponding to position 639 is C, the nucleotide corresponding to position 697 is C, the nucleotide corresponding to position 726 is T, the nucleotide corresponding to position 744 is C, the nucleotide corresponding to position 777 is T, the nucleotide corresponding to position 807 is C, the nucleotide corresponding to position 852 is C, the nucleotide corresponding to position 877 is C, the nucleotide corresponding to position 879 is C, the nucleotide corresponding to position 888 is T, the nucleotide corresponding to position 891 is C, the nucleotide corresponding to position 921 is C, the nucleotide corresponding to position 930 is C, the nucleotide corresponding to position 960 is C, the nucleotide corresponding to position 1042 is C, the nucleotide corresponding to position 1050 is C, the nucleotide corresponding to position 1116 is T, the nucleotide corresponding to position 1140 is T, the nucleotide corresponding to position 1183 is T, the nucleotide corresponding to position 1184 is C, the nucleotide corresponding to position 1194 is T, the nucleotide corresponding to position 1197 is C, the nucleotide corresponding to position 1221 is T, the nucleotide corresponding to position 1249 is C, the nucleotide corresponding to position 1251 is C, the nucleotide corresponding to position 1257 is T, the nucleotide corresponding to position 1273 is C, the nucleotide corresponding to position 1276 is C, the nucleotide corresponding to position 1281 is C, the nucleotide corresponding to position 1290 is T, the nucleotide corresponding to position 1293 is C, the nucleotide corresponding to position 1357 is C, the

2388 is C, the nucleotide corresponding to position 2403 is C, the nucleotide corresponding to position 2409 is C, the nucleotide corresponding to position 2410 is C, the nucleotide corresponding to position 2412 is C, the nucleotide corresponding to position 2448 is C, the nucleotide corresponding to position 2457 is C, the nucleotide corresponding to position 2472 is C, the nucleotide corresponding to position 2476 is C, the nucleotide corresponding to position 2478 is C, the nucleotide corresponding to position 2505 is C, the nucleotide corresponding to position 2520 is C, the nucleotide corresponding to position 2547 is C, the nucleotide corresponding to position 2574 is C, the nucleotide corresponding to position 2622 is C, the nucleotide corresponding to position 2634 is C, the nucleotide corresponding to position 2661 is C, the nucleotide corresponding to position 2673 is C, the nucleotide corresponding to position 2706 is C, the nucleotide corresponding to position 2712 is C, the nucleotide corresponding to position 2763 is C, the nucleotide corresponding to position 2775 is C, the nucleotide corresponding to position 2796 is C, the nucleotide corresponding to position 2811 is C, the nucleotide corresponding to position 2817 is C, the nucleotide corresponding to position 2832 is C, the nucleotide corresponding to position 2838 is C, the nucleotide corresponding to position 2871 is C, the nucleotide corresponding to position 2886 is C, the nucleotide corresponding to position 2892 is C, the nucleotide corresponding to position 2898 is C, the nucleotide corresponding to position 2910 is C, the nucleotide corresponding to position 2922 is C, the nucleotide corresponding to position 2931 is C, the nucleotide corresponding to position 2937 is C, the nucleotide corresponding to position 2958 is C, the nucleotide corresponding to position 2970 is C, the nucleotide corresponding to position 2997 is C, the nucleotide corresponding to position 3033 is C, the nucleotide corresponding to position 3039 is C, the nucleotide corresponding to position 3069 is C, the nucleotide corresponding to position 3075 is C, the nucleotide corresponding to position 3117 is C, the nucleotide corresponding to position 3129 is C, the nucleotide corresponding to position 3156 is C, the nucleotide corresponding to position 3166 is C, the nucleotide corresponding to position 3235 is C, the nucleotide corresponding to position 3246 is C, the nucleotide corresponding to position 3273 is C, the nucleotide corresponding to position 3285 is C, the nucleotide corresponding to position 3306 is C, the nucleotide corresponding to position 3321 is C, the nucleotide corresponding to position 3369 is T, the nucleotide corresponding to position 3399 is C, the nucleotide corresponding to position 3405 is T and/or the nucleotide corresponding to position 3438 is C.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence does not comprise purine nucleotides at positions corresponding to nucleotides 1689 and/or 3438 of SEQ ID NO: 2. The nucleotide at position 1689 may be replaced with a pyrimidine, preferably a C. The adenine at position 3438 may be replaced with a pyrimidine, preferably a C.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence is derived from SEQ ID NO:2 by replacing the adenine nucleotide at position 3405 with a pyrimidine nucleotide without introducing a CpG dinucleotide.

5 In one example, the RPGR^{ORF15}-encoding nucleotide sequence comprises an adenine nucleotide at the position corresponding to position 3405 of SEQ ID NO:2.

In one example, the encoded RPGR^{ORF15} protein is human RPGR^{ORF15}.

10 In one example, the RPGR^{ORF15}-encoding nucleotide sequence comprises one or more nucleotides selected from: C at the position corresponding to position 30 of SEQ ID NO: 2, T at the position corresponding to position 33 of SEQ ID NO: 2, A at the position corresponding to position 966 of SEQ ID NO: 2, A at the position corresponding to position 969 of SEQ ID NO: 2, T at the position corresponding to position 1011 of SEQ ID NO:2, T at the position corresponding to position 1014 of SEQ ID NO:2, T at the position corresponding to position 1029 of SEQ ID NO:2, A at the position corresponding to position 1299 of SEQ ID NO:2, C at the position corresponding to position 1689 of SEQ ID NO:2, G at the position corresponding to position 3363 of SEQ ID NO:2, T at the position corresponding to position 3405 of SEQ ID NO:2, A at the position corresponding to position 3408 of SEQ ID NO:2, A at the position corresponding to position 3409 of SEQ ID NO:2, G at the position corresponding to position 3410 of SEQ ID NO:2, G at the position corresponding to position 3432 of SEQ ID NO:2, C at the position corresponding to position 3438 of SEQ ID NO:2 and A at the position corresponding to position 3456 of SEQ ID NO:2.

25 In one example, the RPGR^{ORF15}-encoding nucleotide sequence comprises one or more nucleotides selected from: C at the position corresponding to position 30 of SEQ ID NO: 2, T at the position corresponding to position 33 of SEQ ID NO: 2, A at the position corresponding to position 48 of SEQ ID NO: 2, A at the position corresponding to position 57 of SEQ ID NO: 2, T at the position corresponding to position 60 of SEQ ID NO: 2, T at the position corresponding to position 69 of SEQ ID NO: 2, A at the position corresponding to position 72 of SEQ ID NO: 2, C at the position corresponding to position 171 of SEQ ID NO: 2, C at the position corresponding to position 189 of SEQ ID NO: 2, T at the position corresponding to position 441 of SEQ ID NO: 2, T at the position corresponding to position 537 of SEQ ID NO: 2, C at the position corresponding to position 546 of SEQ ID NO: 2, T at the position corresponding to position 786 of SEQ ID NO: 2, T at the position corresponding to position 792 of SEQ ID NO: 2, A at the position corresponding to position 966 of SEQ ID NO: 2, A at the position corresponding to position 969 of SEQ ID NO: 2, A at the position corresponding to position 990 of SEQ ID NO: 2, T at the position corresponding to position

1011 of SEQ ID NO: 2, T at the position corresponding to position 1014 of SEQ ID NO: 2, T at the position corresponding to position 1029 of SEQ ID NO: 2, A at the position corresponding to position 1299 of SEQ ID NO: 2, C at the position corresponding to position 1689 of SEQ ID NO: 2, A at the position corresponding to position 3355 of SEQ ID NO: 2, G at the position corresponding to position 3357 of SEQ ID NO: 2, G at the position corresponding to position 3363 of SEQ ID NO: 2, T at the position corresponding to position 3403 of SEQ ID NO: 2, C at the position corresponding to position 3404 of SEQ ID NO: 2, T at the position corresponding to position 3405 of SEQ ID NO: 2, A at the position corresponding to position 3408 of SEQ ID NO: 2, A at the position corresponding to position 3409 of SEQ ID NO: 2, G at the position corresponding to position 3410 of SEQ ID NO: 2, G at the position corresponding to position 3432 of SEQ ID NO: 2, C at the position corresponding to position 3438 of SEQ ID NO: 2 and A at the position corresponding to position 3456 of SEQ ID NO: 2.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises a sequence selected from the group consisting of:

- (a) a nucleotide sequence encoding an amino acid sequence that has at least 80% identity to SEQ ID NO: 1;
- (b) a nucleotide sequence that has at least 80% identity to SEQ ID NO: 3; and
- (c) the nucleotide sequence of SEQ ID NO: 3,

preferably wherein the protein encoded by the nucleotide sequence substantially retains the natural function of the protein represented by SEQ ID NO: 1.

In another example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises a nucleotide sequence encoding an amino acid sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 1, preferably wherein the amino acid sequence substantially retains the natural function of the protein represented by SEQ ID NO: 1.

The present disclosure further provides a polynucleotide comprising a nucleotide sequence encoding the retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}) or a functional variant thereof having at least 80% identity to SEQ ID NO: 1, wherein the nucleotide sequence comprises one or more, preferably all, of the nucleotides selected from: C at the position corresponding to position 30 of SEQ ID NO: 2, T at the position

corresponding to position 33 of SEQ ID NO: 2, A at the position corresponding to position 966 of SEQ ID NO: 2, A at the position corresponding to position 969 of SEQ ID NO: 2, T at the position corresponding to position 1011 of SEQ ID NO:2, T at the position corresponding to position 1014 of SEQ ID NO:2, T at the position corresponding to position 1029 of SEQ ID NO:2, A at the position corresponding to position 1299 of SEQ ID NO:2, C at the position corresponding to position 1689 of SEQ ID NO:2, G at the position corresponding to position 3363 of SEQ ID NO:2, T at the position corresponding to position 3405 of SEQ ID NO:2, A at the position corresponding to position 3408 of SEQ ID NO:2, A at the position corresponding to position 3409 of SEQ ID NO:2, G at the position corresponding to position 3410 of SEQ ID NO:2, G at the position corresponding to position 3432 of SEQ ID NO:2, C at the position corresponding to position 3438 of SEQ ID NO:2 and A at the position corresponding to position 3456 of SEQ ID NO:2. The polynucleotide may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 of said nucleotides

The disclosure also provides a polynucleotide comprising a nucleotide sequence encoding the retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}) or a functional variant thereof having at least 80% identity to SEQ ID NO: 1, wherein the nucleotide sequence is selected from the group consisting of:

(a) nucleotide sequence that has at least 80% identity to SEQ ID NO: 3, wherein said sequence comprises one or more, preferably all, of the nucleotides selected from: C at the position corresponding to position 30 of SEQ ID NO: 2, T at the position corresponding to position 33 of SEQ ID NO: 2, A at the position corresponding to position 48 of SEQ ID NO: 2, A at the position corresponding to position 57 of SEQ ID NO: 2, T at the position corresponding to position 60 of SEQ ID NO: 2, T at the position corresponding to position 69 of SEQ ID NO: 2, A at the position corresponding to position 72 of SEQ ID NO: 2, C at the position corresponding to position 171 of SEQ ID NO: 2, C at the position corresponding to position 189 of SEQ ID NO: 2, T at the position corresponding to position 441 of SEQ ID NO: 2, T at the position corresponding to position 537 of SEQ ID NO: 2, C at the position corresponding to position 546 of SEQ ID NO: 2, T at the position corresponding to position 786 of SEQ ID NO: 2, T at the position corresponding to position 792 of SEQ ID NO: 2, A at the position corresponding to position 966 of SEQ ID NO: 2, A at the position corresponding to position 969 of SEQ ID NO: 2, A at the position corresponding to position 990 of SEQ ID NO: 2, T at the position corresponding to position 1011 of SEQ ID NO: 2, T at the position corresponding to position 1014 of SEQ ID NO: 2, T at the position corresponding to position 1029 of SEQ ID NO: 2, A at the position corresponding to position 1299 of SEQ ID NO: 2, C at the position corresponding to position 1689 of SEQ ID NO: 2, A at the position

corresponding to position 3355 of SEQ ID NO: 2, G at the position corresponding to position 3357 of SEQ ID NO: 2, G at the position corresponding to position 3363 of SEQ ID NO: 2, T at the position corresponding to position 3403 of SEQ ID NO: 2, C at the position corresponding to position 3404 of SEQ ID NO: 2, T at the position corresponding to position 3405 of SEQ ID NO: 2, A at the position corresponding to position 3408 of SEQ ID NO: 2, A at the position corresponding to position 3409 of SEQ ID NO: 2, G at the position corresponding to position 3410 of SEQ ID NO: 2, G at the position corresponding to position 3432 of SEQ ID NO: 2, C at the position corresponding to position 3438 of SEQ ID NO: 2 and A at the position corresponding to position 3456 of SEQ ID NO: 2; or (b) the nucleotide sequence of SEQ ID NO: 3. The polynucleotide may comprises 2, 3, 4, 5, 6, 7, 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 or 34 of said nucleotides.

Preferably the functional variant substantially retains the natural function of the protein represented by SEQ ID NO:1.

15 In one example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises a nucleotide sequence that has at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 3, preferably wherein the protein encoded by the nucleotide sequence substantially retains the natural function of the protein represented by SEQ ID NO: 1.

20 Preferably, the protein encoded by the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure provides for the same or improved functioning of the cells of the retina and/or visual function as provided for by the protein represented by SEQ ID NO: 1.

In a preferred example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure encodes a protein of SEQ ID NO: 1.

25 The polynucleotide of the disclosure may have substantially the same or increased fidelity of replication relative to an equivalent polynucleotide comprising the human wild type RPGR^{ORF15} of SEQ ID NO: 2.

The polynucleotide of the disclosure may have increased stability and/or be less prone to mutations occurring during cycles of polynucleotide replication relative to an equivalent polynucleotide comprising the human wild type RPGR^{ORF15} of SEQ ID NO: 2.

30 The polynucleotide of the disclosure may confer higher rates of translation and/or protein expression relative to an equivalent polynucleotide comprising the human wild type RPGR^{ORF15} of SEQ ID NO: 2.

The polynucleotide of the disclosure may reduce or avoid the generation of alternatively spliced variants and/or truncated proteins relative to an equivalent polynucleotide comprising the human wild type RPGR^{ORF15} of SEQ ID NO: 2.

5 In a preferred example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure has substantially the same or increased fidelity of replication as SEQ ID NO: 3. Fidelity of replication can be measured by any of a number of methods known to the skilled person, for example the methods described herein.

In a preferred example, the RPGR^{ORF15}-encoding nucleotide sequence of the disclosure comprises the nucleotide sequence of SEQ ID NO: 3.

10 The RPGR^{ORF15}-encoding nucleotide sequence may comprise fewer than 165 CpG dinucleotides and/or comprises no more than two CpG islands. CpG islands can readily be identified using routine methods, for example, using EMBOSS Cpgplot (http://www.ebi.ac.uk/Tools/seqstats/emboss_cpgplot/help/).

15 The polynucleotide of the disclosure may encode an RPGR^{orf15} that has been shortened relative to the wild type sequence. In this regard, the codon optimization described herein is applied to the corresponding portions of the shortened sequence. Preferably, the shortened RPGR^{orf15} has the ability to rescue loss of RPGR function.

The RPGR^{orf15} encoding sequence of the disclosure may encode the shortened RPGR^{orf15} disclosed in WO2016/001693.

20 In one example, the RPGR^{orf15} encoding sequence of the disclosure is shortened by removal of some or all of the nucleotides corresponding to positions 2485 to 2940 of SEQ ID NO:2. According to this example, the RPGR^{ORF15}-encoding nucleotide sequence preferably does not comprise purine nucleotides at positions corresponding to nucleotides 33, 58, 59, 114, 123, 129, 181, 182, 213, 219, 226, 227, 237, 267, 285, 306, 309, 315, 324, 330, 339, 400,
25 401, 444, 456, 478, 480, 510, 594, 606, 618, 639, 697, 726, 744, 777, 807, 852, 877, 879, 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1184, 1194, 1197, 1221, 1249, 1251, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1373, 1413, 1446, 1452, 1464, 1474, 1475, 1482, 1519, 1520, 1542, 1584, 1590, 1599, 1608, 1653, 1668, 1674, 1689, 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910,
30 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361, 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2958, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273,

3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 of SEQ ID NO: 2. Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. A preferred RPGR^{ORF15}-encoding nucleotide sequence according to this example comprises or consists of the sequence shown in SEQ ID NO:9.

The polynucleotide of the disclosure may comprise:

(a) a nucleotide sequence shown in SEQ ID NO:9;

(b) a nucleotide sequence comprising the sequence of SEQ ID NO:3 but with a deletion corresponding to (i) the sequence of SEQ ID NO: 10, (ii) the sequence of SEQ ID NO: 10 and up to 75 additional nucleotides flanking SEQ ID NO: 10 on one or both sides of SEQ ID NO:10 in the sequence of SEQ ID NO: 3, or (iii) 390 or more contiguous nucleotides from within SEQ ID NO:10; or

(c) a nucleotide sequence according to (a) or (b) but truncated at one or both of its 5' and 3' ends by up to 150 nucleotides per end.

Preferably the deletion comprises at least 400, 420 or 450 contiguous nucleotides of SEQ ID NO:10.

ATGAGAGAGCCAGAGGAGCTGATGCCAGACAGTGGAGCAGTGTTTACATTTCGGAAAATCTAAGTTCGCTGAAAAT
AACCCAGGAAAGTTCTGGTTTAAAAACGACGTGCCCGTCCACCTGTCTTGTGGCGATGAGCATAGTCCCGTGGTC
ACTGGGAACAATAAGCTGTACATGTTTCGGGTCCAACAACCTGGGGACAGCTGGGGCTGGGATCCAAATCTGCTATC
TCTAAGCCAACCTGCGTGAAGGCACTGAAACCCGAGAAGGTCAAACCTGGCCGCTTGTGGCAGAAACCACACTCTG
GTGAGCACCGAGGGCGGGAATGTCTATGCCACCGGAGGCAACAATGAGGGACAGCTGGGACTGGGGGACACTGAG
GAAAGGAATACCTTTTCAGTGATCTCCTTCTTTACATCTGAGCATAAGATCAAGCAGCTGAGCGCTGGCTCCAAC
ACATCTGCAGCCCTGACTGAGGACGGGCGCCTGTTTCATGTGGGGAGATAATTTCAGAGGGCCAGATTGGGCTGAAA
AACGTGAGCAATGTGTGCGTCCCTCAGCAGGTGACCATCGGAAAGCCAGTCAGTTGGATTTCATGTGGCTACTAT
CATAGCGCCTTCGTGACCACAGATGGCGAGCTGTACGTCTTTGGGGAGCCCGAAAAACGGAAAACTGGGCCCTGCCT
AACCAGCTGCTGGGCAATCACCGGACACCCAGCTGGTGTCCGAGATCCCTGAAAAAGTGATCCAGGTCGCCTGC
GGGGGAGAGCATAACAGTGGTCTGACTGAGAATGCTGTGTATACCTTCGGACTGGGCCAGTTTGGCCAGCTGGGG
CTGGGAACCTTCCTGTTTGTAGACATCCGAACCAAAAAGTGATCGAGAACATTTCGCGACCAGACTATCAGCTACATT
TCCTGCGGAGAGAATCACACCGCACTGATCACAGACATTGGCCTGATGTATACCTTTGGCGATGGACGACACGGG
AAGCTGGGACTGGGACTGGAGAATTCACCTAATCATTTTATCCCCACCCTGTGTTCTAACTTCCTGCGGTTTCATC
GTGAAACTGGTCGCTTTCGGCGGGTGTACATGGTGGTCTTCGCTGCACCTCATAGGGGCGTGGCTAAGGAGATC
GAATTTGACGAGATTAACGATACATGCCTGAGCGTGGCAACTTTCCTGCCATACAGCTCCCTGACTTCTGGCAAT
GTGCTGCAGAGAACCCTGAGTGCAAGGATGCGGAGAAGGGAGAGGGAACGCTCTCCTGACAGTTTCTCAATGCGA
CGAACCTGCCACCTATCGAGGGAACACTGGGACTGAGTGCTGCTTCCTGCCTAACTCAGTGTTTCCACGATGT
AGCGAGCGGAATCTGCAGGAGTCTGTCTGAGTGAGCAGGATCTGATGCAGCCAGAGGAACCCGACTACCTGCTG
GATGAGATGACCAAGGAGGCCGAAATCGACAACCTCTAGTACAGTGGAGTCCCTGGGCGAGACTACCGATATCCTG
AATATGACACACATTATGTCACTGAACAGCAATGAGAAGAGTCTGAACTGTCAACAGTGCGAGAAGCAGAAGAAA
CAGCAGACTATTGGCGAGCTGACTCAGGACACCGCCCTGACAGAGAACGACGATAGCGATGAGTATGAGGAAATG
TCCGAGATGAAGGAAGGCAAAGCTTGTAAGCAGCATGTCAGTCAGGGGATCTTCATGACACAGCCAGCCACAAC
ATTGAGGCTTTTTTCAGACGAGGAAGTGGAGATCCCCGAGGAAAAAGAGGGCGCAGAAGATTCCAAGGGGAATGGA
ATTGAGGAACAGGAGGTGGAAGCCAACGAGGAAAAATGTGAAAGTCCACGGAGGCAGGAAGGAGAAAAACAGAAATC
CTGTCTGACGATCTGACTGACAAGGCCGAGGTGTCCGAAGGCAAGGCAAAATCTGTGCGAGAGGCAGAAGACGGA

CCAGAGGGACGAGGGGATGGAACCTGCGAGGAAGGCTCAAGCGGGGCTGAGCATTGGCAGGACGAGGAACGAGAG
AAGGGCGAAAAGGATAAAGGCCGCGGGGAGATGGAACGACCTGGAGAGGGCGAAAAAGAGCTGGCAGAGAAGGAG
GAATGGAAGAAAAGGGACGGCGAGGAACAGGAGCAGAAAAGAAAGGGAGCAGGGCCACCAGAAGGAGCGCAACCAG
GAGATGGAAGAGGGCGCGAGGAAGAGCATGGCGAGGGAGAAGAGGAAAGAGGGCGATAGAGAAGAGGAAGAGGAA
5 AAAGAAGGCGAAGGGAAGGAGGAAGGAGAGGGCGAGGAAGTGAAGGCGAGAGGGAAAAGGAGGAAGGAGAACGG
AAGAAAGAGGAAAGAGCCGGCAAAGAGGAAAAGGGCGAGGAAGAGGGCGATCAGGGCGAAGGCGAGGAGGAAGAG
ACCGAGGGCCGCGGGGAAGAGAAAGAGGAGGGAGGAGAGGTGGAGGGCGGAGAGGTGCAAGAGGGAAAGGGCGAG
CGCGAAGAGGGGGAGGAAGAGGAAGGCGAAGGAGAAGGCGAGGAAGAAGAGGGAGAGGAGGAAGGCGAGGAGGAA
GGAGAGGGGGAGGAGGAGGGAGAAGGCGAGGGCGAAGAAGAAGAGGGAGAAAGTGGAGGGCGAAGTTCAGGGGG
10 GAGGAGGGAGAAGGGGAAGGGGAGGAAGAAGAGGGCGAAGAAGAAGGCGAGGAAAGAGAAAAAGAGGGAGAAGGC
GAGGAAAACCGGAGAAATAGGGAAGAGGAGGAAGAGGAAGAGGGAAAAGTACCAGGAGACAGGCGAAGAGGAAAAC
GAGCGGCAGGATGGCGAGGAATATAAGAAAGTGAGCAAGATCAAAGGATCCGTCAAGTACGGCAAGCACAAAACC
TATCAGAAGAAAAGCGTGACCAACACACAGGGGAATGGAAGAGAGCAGAGGAGTAAGATGCCTGTGCAGTCAAAA
CGGCTGCTGAAGAATGGCCCATCTGGAAGTAAAAAATTCTGGAACAATGTGCTGCCCCACTATCTGGAAGTAAAA
15 TAA (SEQ ID NO:9)

GAAGAGGAAGAGGGCGAGGGCGAGGAAGAAGAGGGCGAGGGGGAAAGAAGAGGAGGGAGAGGGCGAAGAGGAAGAG
GGGGAGGGAAAAGGGCGAAGAGGAAGGAGAGGAAGGGGAGGGAGAGGAAGAGGGGGAGGAGGGCGAGGGGGAAGGC
GAGGAGGAAGAAGGAGAGGGGGAAGGCGAAGAGGAAGGCGAGGGGGAAGGAGAGGAGGAAGAAGGGGAAGGCGAA
20 GGCGAAGAGGAGGGAGAAGGAGAGGGGGAGGAAGAGGAAGGAGAAGGGAAGGGCGAGGAGGAAGGCGAAGAGGGGA
GAGGGGGAAGGCGAGGAAGAGGAAGGCGAGGGCGAAGGAGAGGACGGCGAGGGCGAGGGAGAAGAGGAGGAAGGG
GAATGGGAAGGCGAAGAAGAGGAAGGCGAAGGCGAAGGCGAAGAAGAGGGCGAAGGGGAGGGCGAGGAGGGCGAA
GGCGAA (SEQ ID NO: 10)

The RPGR^{orf15} encoding sequence of the disclosure may encode the shortened RPGR^{orf15} disclosed in WO2016/014353.

25 In one example, the RPGR^{orf15} encoding sequence of the disclosure is shortened by removal of some or all of the nucleotides corresponding to positions 2086 to 3027 of SEQ ID NO:2.

According to this example, the RPGR^{ORF15}-encoding nucleotide sequence preferably does not comprise purine nucleotides at positions corresponding to nucleotides 33, 58, 59, 114, 123, 129, 181, 182, 213, 219, 226, 227, 237, 267, 285, 306, 309, 315, 324, 330, 339, 400,
30 401, 444, 456, 478, 480, 510, 594, 606, 618, 639, 697, 726, 744, 777, 807, 852, 877, 879, 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1184, 1194, 1197, 1221, 1249, 1251, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1373, 1413, 1446, 1452, 1464, 1474, 1475, 1482, 1519, 1520, 1542, 1584, 1590, 1599, 1608, 1653, 1668, 1674, 1689, 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910,
35 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246, 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 of SEQ ID NO: 2. Preferably the nucleotides at these positions correspond to those found in SEQ ID NO:3. A preferred RPGR^{ORF15}-encoding

nucleotide sequence according to this example comprises or consists of the sequence shown in SEQ ID NO:11.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence comprises SEQ ID NO:3 but with a deletion corresponding to some or all of the sequence of SEQ ID NO: 12.

5 ATGAGAGAGCCAGAGGAGCTGATGCCAGACAGTGGAGCAGTGTTTACATTTCGGAAAAATCTAAGTTCGCTGAAAAAT
AACCCAGGAAAAGTTCTGGTTTAAAAACGACGTGCCCCGTCCACCTGTCTTGTGGCGATGAGCATAGTGCCGTGGTC
ACTGGGAACAATAAGCTGTACATGTTTCGGGTCCAACAACCTGGGGACAGCTGGGGCTGGGATCCAAATCTGCTATC
TCTAAGCCAACCTGCGTGAAGGCACTGAAACCCGAGAAGGTCAAACCTGGCCGCTTGTGGCAGAAACCACACTCTG
10 GTGAGCACCGAGGGCGGGAATGTCTATGCCACCGGAGGCAACAATGAGGGACAGCTGGGACTGGGGGACACTGAG
GAAAGGAATACCTTTCACGTGATCTCCTTCTTTACATCTGAGCATAAGATCAAGCAGCTGAGCGCTGGCTCCAAC
ACATCTGCAGCCCTGACTGAGGACGGGCGCCTGTTTCATGTGGGGAGATAATTTCAGAGGGCCAGATTGGGCTGAAA
AACGTGAGCAATGTGTGCGTCCCTCAGCAGGTGACCATCGGAAAAGCCAGTCAGTTGGATTTCATGTGGCTACTAT
CATAGCGCCTTCGTGACCACAGATGGCGAGCTGTACGTCTTTGGGGAGCCCCGAAAACGAAAACTGGGCCTGCCT
15 AACCAGCTGCTGGGCAATCACCGGACACCCAGCTGGTGTCCGAGATCCCTGAAAAAGTGATCCAGGTGCGCTGC
GGGGGAGAGCATAACAGTGGTCTGACTGAGAATGCTGTGTATACCTTCGGACTGGGCCAGTTTGGCCAGCTGGGG
CTGGGAACCTTCCTGTTTGTAGACATCCGAACCAAAAAGTGATCGAGAACATTTCGCGACCAGACTATCAGCTACATT
TCCTGCGGAGAGAATCACACCGCACTGATCACAGACATTGGCCTGATGTATACCTTTGGCGATGGACGACACGGG
AAGCTGGGACTGGGACTGGGAGAACTTCACTAATCATTTTTATCCCCACCCTGTGTTCTAACTTCCTGCGGTTTCATC
GTGAAACTGGTTCGCTTTCGCGCGGGTGTACATGGTGGTCTTCGCTGCACCTCATAGGGGCGTGGCTAAGGAGATC
20 GAATTTGACGAGATTAACGATACATGCCTGAGCGTGGCAACTTTCCTGCCATACAGCTCCCTGACTTCTGGCAAT
GTGCTGCAGAGAACCTGAGTGCAAGGATGCGGAGAAAGGAGAGGGAACGCTCTCCTGACAGTTTCTCAATGCGA
CGAACCTTCCACCTATCGAGGGAACACTGGGACTGAGTGCTGCTTCCTGCCTAACTCAGTGTTTCCACGATGT
AGCGAGCGGAATCTGCAGGAGTCTGTCTGAGTGAGCAGGATCTGATGCAGCCAGAGGAACCCGACTACCTGCTG
GATGAGATGACCAAGGAGGCCGAAAATCGACAACCTCTAGTACAGTGGAGTCCCTGGGCGAGACTACCGATATCCTG
25 AATATGACACACATTATGTCACTGAACAGCAATGAGAAGAGTCTGAAACTGTCACCAGTGCAGAAGCAGAAGAAA
CAGCAGACTATTGGCGAGCTGACTCAGGACACCGCCCTGACAGAGAACGACGATAGCGATGAGTATGAGGAAATG
TCCGAGATGAAGGAAGGCAAAGCTTGTAAGCAGCATGTCAGTCAGGGGATCTTCATGACACAGCCAGCCACAACCT
ATTGAGGCTTTTTTCAGACGAGGAAGTGAGATCCCCGAGGAAAAAGAGGGCGCAGAAGATTCCAAGGGGAATGGA
ATTGAGGAACAGGAGGTGGAAGCCAACGAGGAAAAATGTGAAAAGTCCACGGAGGCAGGAAGGAGAAAAACAGAAATC
30 CTGTCTGACGATCTGACTGACAAGGCCGAGGTGTCCGAAGGCAAGGCAAAATCTGTGCGAGAGGCAGAAGACGGA
CCAGAGGGACGAGGGGATGGAACCTGCGAGGAAGGCTCAAGCGGGGCTGAGCATTGGCAGGACGAGGAACGAGAG
AAGGGCGAAAAGGATAAAGGCCGCGGGGAGATGGAACGACCTGGAGAGGGCGAAAAAGAGGAAGGCGAGGGCGAA
GAAGAAGAAGAGGGAGAAGTGAGGGGCGAAGTCGAGGGGGAGGAGGGAGAAGGGGAAGGGGAGGAAGAAGAGGGC
GAAGAAGAAGGCGAGGAAAGAGAAAAAGAGGGAGAAGGCGAGGAAAAACCGAGAAAAATAGGGAAGAGGAGGAAGAG
35 GAAGAGGGAAAGTACCAGGAGACAGGCGAAGAGGAAAAACGAGCGGCAGGATGGCGAGGAATATAAGAAAGTGAGC
AAGATCAAAGGATCCGTCAAAGTACGGCAAGCACAAAACCTATCAGAAGAAAAAGCGTGACCAACACACAGGGGAAT
GGAAAAGAGCAGAGGAGTAAGATGCCTGTGCAGTCAAAACGGCTGCTGAAGAATGGCCCATCTGGAAGTAAAAAA
TTCTGGAACAATGTGCTGCCCCACTATCTGGAACCTGAAATAA (SEQ ID NO:11)

40 CTGGCAGAGAAGGAGGAATGGAAGAAAAGGGACGGCGAGGAACAGGAGCAGAAAAGAAAGGGAGCAGGGCCACCAG
AAGGAGCGCAACCAGGAGATGGAAGAGGGCGGCGAGGAAGAGCATGGCGAGGGAGAAGAGGAAGAGGGCGATAGA
GAAGAGGAAGAGGAAAAAGAAAGGCGAAGGGAAGGAGGAAGGAGAGGGCGAGGAAGTGAAGGCGAGAGGGAAAAAG
GAGGAAGGAGAACGGAAGAAAGAGGAAAGAGCCGGCAAAGAGGAAAAAGGGCGAGGAAGAGGGCGATCAGGGCGAA
45 GGCGAGGAGGAAGAGACCGAGGGCCGCGGGGAAGAGAAAGAGGAGGGAGGAGAGGTGGAGGGCGGAGAGGTCGAA
GAGGGAAAGGGCGAGCGCGAAGAGGAAGAGGAAGAGGGCGAGGGCGAGGAAGAAGAGGGCGAGGGGGAAGAAGAG
GAGGGAGAGGGCGAAGAGGAAGAGGGGGAGGGGAAAGGGCGAAGAGGAAGGAGAGGAAGGGGAGGGAGAGGAAGAG

GGGGAGGAGGGCGAGGGGGAAGGCCAGGAGGAAGAAGGAGAGGGGGAAGGCCAAGAGGAAGGCCAGGGGGAAGGA
 GAGGAGGAAGAAGGGGAAGGCCAAGGCCAAGAGGAGGGAGAAGGAGAGGGGGAGGAAGAGGAAGGAGAAGGGGAAG
 GGCGAGGAGGAAGGCCAAGAGGGAGAGGGGGAAGGCCAGGAAGAGGAAGGCCAGGGCGAAGGAGAGGACGGCGAG
 GGCGAGGGAGAAGAGGAGGAAGGGGAATGGGAAGGCCAAGAAGAGGAAGGCCAAGGCCAAGGCCAAGAAGAGGGC
 5 GAAGGGGAGGGCGAGGAGGGCGAAGGCCAAGGGGAGGAAGAGGAAGGCCAAGGAGAAGGCCAGGAAGAAGAGGGGA
 GAGGAGGAAGGCCAGGAGGAAGGAGAGGGGGAGGAGGAGGGA (SEQ ID NO: 12)

In another example, the RPGR^{ORF15} encoding sequence of the disclosure is shortened by
 removal of some or all of the nucleotides corresponding to positions 2584 – 2961 of SEQ ID
 10 NO:2.

According to this example, the RPGR^{ORF15}-encoding nucleotide sequence preferably does
 not comprise purine nucleotides at positions corresponding to nucleotides 33, 58, 59, 114,
 123, 129, 181, 182, 213, 219, 226, 227, 237, 267, 285, 306, 309, 315, 324, 330, 339, 400,
 401, 444, 456, 478, 480, 510, 594, 606, 618, 639, 697, 726, 744, 777, 807, 852, 877, 879,
 15 888, 891, 921, 930, 960, 1042, 1050, 1116, 1140, 1183, 1184, 1194, 1197, 1221, 1249,
 1251, 1257, 1273, 1276, 1281, 1290, 1293, 1357, 1372, 1373, 1413, 1446, 1452, 1464,
 1474, 1475, 1482, 1519, 1520, 1542, 1584, 1590, 1599, 1608, 1653, 1668, 1674, 1689,
 1692, 1734, 1761, 1776, 1788, 1803, 1824, 1845, 1854, 1881, 1893, 1902, 1909, 1910,
 1929, 1932, 1960, 1987, 1988, 1992, 1998, 2020, 2031, 2047, 2049, 2062, 2067, 2076,
 20 2121, 2167, 2169, 2190, 2193, 2208, 2229, 2259, 2283, 2298, 2323, 2343, 2346, 2361,
 2373, 2382, 2388, 2403, 2409, 2410, 2412, 2448, 2457, 2472, 2476, 2478, 2505, 2520,
 2547, 2574, 2970, 2997, 3033, 3039, 3069, 3075, 3117, 3129, 3156, 3166, 3235, 3246,
 3273, 3285, 3306, 3321, 3369, 3399, 3405 and/or 3438 of SEQ ID NO: 2. Preferably the
 nucleotides at these positions correspond to those found in SEQ ID NO:3. A preferred
 25 RPGR^{ORF15}-encoding nucleotide sequence according to this example comprises or consists
 of the sequence shown in SEQ ID NO:13.

In one example, the RPGR^{ORF15}-encoding nucleotide sequence comprises SEQ ID NO:3 but
 with a deletion corresponding to some or all of the sequence of SEQ ID NO:14.

ATGAGAGAGCCAGAGGAGCTGATGCCAGACAGTGGAGCAGTGTTTACATTTCGGAAAATCTAAGTTCGCTGAAAAT
 30 AACCCAGGAAAGTTCTGGTTTAAAAACGACGTGCCCCGTCCACCTGTCTTGTGGCGATGAGCATAGTGCCGTGGTC
 ACTGGGAACAATAAGCTGTACATGTTTCGGGTCCAACAACCTGGGGACAGCTGGGGCTGGGATCCAAATCTGCTATC
 TCTAAGCCAACCTGCGTGAAGGCACTGAAACCCGAGAAGGTCAAACCTGGCCGCTTGTGGCAGAAACCACACTCTG
 GTGAGCACCGAGGGCGGGAATGTCTATGCCACCGGAGGCAACAATGAGGGACAGCTGGGACTGGGGGACACTGAG
 35 GAAAGGAATACCTTTCACGTGATCTCCTTCTTTACATCTGAGCATAAGATCAAGCAGCTGAGCGCTGGCTCCAAC
 ACATCTGCAGCCCTGACTGAGGACGGGCGCCTGTTTCATGTGGGGAGATAATTTCAGAGGGCCAGATTGGGCTGAAA
 AACGTGAGCAATGTGTGCGTCCCTCAGCAGGTGACCATCGGAAAGCCAGTCAGTTGGATTTCATGTGGCTACTAT
 CATAGCGCCTTCGTGACCACAGATGGCGAGCTGTACGTCTTTGGGGAGCCCCGAAAACGGAAAACCTGGGCCTGCCT
 AACCAGCTGCTGGGCAATCACCAGACACCCAGCTGGTGTCCGAGATCCCTGAAAAAGTGATCCAGGTCGCCTGC
 40 GGGGAGAGCATACAGTGGTCTCTGACTGAGAATGCTGTGTATACCTTCGGACTGGGCCAGTTTGGCCAGCTGGGG
 CTGGGAACCTTCCTGTTTGAGACATCCGAACCAAAAAGTGATCGAGAACATTTCGCGACCAGACTATCAGCTACATT

TCCTGCGGAGAGAATCACACCGCACTGATCACAGACATTGGCCTGATGTATACCTTTGGCGATGGACGACACGGG
 AAGCTGGGACTGGGACTGGGAGAACTTCACTAATCATTTTATCCCCACCCTGTGTTCTAACTTCCTGCGGTTTCATC
 GTGAAACTGGTTCGCTTGGCGGGGTGTCACATGGTGGTCTTCGCTGCACCTCATAGGGGCGTGGCTAAGGAGATC
 5 GAATTTGACGAGATTAACGATACATGCCTGAGCGTGCCAACCTTTCTGCCATACAGCTCCCTGACTTCTGGCAAT
 GTGCTGCAGAGAACCCTGAGTGCAAGGATGCGGAGAAAGGAGAGGGAACGCTCTCCTGACAGTTTCTCAATGCGA
 CGAACCTTGCACCTATCGAGGGAACACTGGGACTGAGTGCTTCTTCTGCTAACTCAGTGTTCACGATGT
 AGCGAGCGGAATCTGCAGGAGTCTGTCTGAGTGAGCAGGATCTGATGCAGCCAGAGGAACCCGACTACCTGCTG
 GATGAGATGACCAAGGAGGCCGAAATCGACAACCTCTAGTACAGTGAGTCCCTGGGCGAGACTACCGATATCCTG
 10 AATATGACACACATTATGTCACTGAACAGCAATGAGAAGAGTCTGAAACTGTCACCAGTGCAGAAGCAGAAGAAA
 CAGCAGACTATTGGCGAGCTGACTCAGGACACCGCCCTGACAGAGAACGACGATAGCGATGAGTATGAGGAAATG
 TCCGAGATGAAGGAAGGCAAAGCTTGTAAAGCAGCATGTCACTCAGGGGATCTTCATGACACAGCCAGCCACAAC
 ATTGAGGCTTTTTTTCAGACGAGGAAGTGGAGATCCCCGAGGAAAAAGAGGGCGCAGAAGATTCCAAGGGGAATGGA
 ATTGAGGAACAGGAGGTGGAAGCCAACGAGGAAAATGTGAAAGTCCACGGAGGCAGGAAGGAGAAAAACAGAAAATC
 CTGTCTGACGATCTGACTGACAAGGCCGAGGTGTCCGAAGGCAAGGCCAAAATCTGTGCGAGAGGCAGAAGACGGA
 15 CCAGAGGGACGAGGGGATGGAACCTGCGAGGAAGGCTCAAGCGGGGCTGAGCATTGGCAGGACGAGGAACGAGAG
 AAGGGCGAAAAGGATAAAAGGCCGCGGGGAGATGGAACGACCTGGAGAGGGCGAAAAAGAGCTGGCAGAGAAGGAG
 GAATGGAAGAAAAGGGACGGCGAGGAACAGGAGCAGAAAAGAAAGGGAGCAGGGCCACCAGAAGGAGCGCAACCAG
 GAGATGGAAGAGGGCGCGCAGGAAGAGCATGGCGAGGGAGAAGAGGAAGAGGGCGATAGAGAAGAGGAAGAGGAA
 AAAGAAGGCGAAGGGAAGGAGGAAGGAGAGGGCGAGGAAGTGAAGGCGAGAGGGAAAAGGAGGAAGGAGAACGG
 20 AAGAAAGAGGAAAGAGCCGGCAAAGAGGAAAAGGGCGAGGAAGAGGGCGATCAGGGCGAAGGCGAGGAGGAAGAG
 ACCGAGGGCCGCGGGGAAGAGAAAGAGGAGGGAGGAGAGGTGGAGGGCGAGAGGTGCAAGAGGGAAAGGGCGAG
 CGCGAAGAGGAAGAGGAAGAGGGCGAGGGCGAGGAAGAAGAGGGCGAGGGGGAAGAAGAGGAGGGAGAGGGCGAA
 GAGGAAGAGGGGGAGGGGAAAGGGCGAAGAGGAAGGAGAAGGCGAGGAAGAAGAGGGAGAGGAGGAAGGCGAGGAG
 GAAGGAGAGGGGGAGGAGGAGGGAGAAGGCGAGGGCGAAGAAGAAGAGGGAGGAAGTGGAGGGCGAAGTCGAG
 25 GGGGAGGAGGGGAGAAGGGGAAGGGGAGGAAGAAGAGGGCGAAGAAGAAGGCGAGGAAAGAGAAAAAGAGGGAGAA
 GGCGAGGAAAACCGGAGAAATAGGGAAGAGGAGGAAGAGGAAGAGGGGAAAGTACCAGGAGACAGGCCAAGAGGAA
 AACGAGCGGCAGGATGGCGAGGAATATAAGAAAGTGAGCAAGATCAAAGGATCCGTCAAGTACGGCAAGCACAAA
 ACCTATCAGAAGAAAAGCGTGACCAACACACAGGGGAATGGAAGAAGAGCAGAGGAGTAAGATGCCTGTGCAGTCA
 AAACGGCTGCTGAAGAATGGCCCATCTGGAAGTAAAAAATTCTGGAACAATGTGCTGCCCCACTATCTGGAACCTG
 30 AAATAA (SEQ ID NO:13)

35 GGAGAGGAAGGGGAGGGAGAGGAAGAGGGGGAGGAGGGCGAGGGGGAAGGCGAGGAGGAAGAAGGAGAGGGGGAA
 GGCGAAGAGGAAGGCGAGGGGGAAGGAGAGGAGGAAGAAGGGGAAGGCGAAGGCGAAGAGGAGGGAGAAGGAGAG
 GGGGAGGAAGAGGAAGGAGAAGGGGAAGGGCGAGGAGGAAGGCGAAGAGGGAGAGGGGGAAGGCGAGGAAGAGGAA
 GGCGAGGGCGAAGGAGAGGACGGCGAGGGCGAGGGAGAAGAGGAGGAAGGGGAATGGGAAGGCGAAGAAGAGGAA
 GGCGAAGGCGAAGGCGAAGAAGAGGGCGAAGGGGAGGGCGAGGAGGGCGAAGGCGAAGGGGAGGAAGAGGAAGGC
 GAA (SEQ ID NO: 14)

40

The RPGR^{ORF15}-encoding nucleotide sequence of the disclosure may be operably linked to a
 polynucleotide comprising a promoter element capable of driving expression of RPGR^{ORF15}
 or a functional variant thereof in human rod and cone photoreceptor cells.

45 The RPGR^{ORF15}-encoding nucleotide sequence of the disclosure may be operably linked to
 the rhodopsin kinase (GRK1) promoter, preferably the human GRK1 promoter.

Preferably, aside from the promoter, no additional enhancer elements are used to control
 expression of RPGR^{ORF15}. Thus, in one example, the nucleotide sequence of the disclosure
 does not comprise an enhancer element. In one example, the nucleotide sequence does
 not comprise a woodchuck hepatitis postregulatory element (WPRE) element.

In another example, the disclosure provides a viral vector comprising the polynucleotide of the disclosure.

In one example, the viral vector is an adeno-associated viral (AAV), retroviral, lentiviral or adenoviral vector.

- 5 In a preferred example, the viral vector is in the form of a viral particle.

In a preferred example, the viral vector is an AAV vector.

The AAV vector may be of any serotype (e.g. comprise any AAV serotype genome and/or capsid protein), provided that the vector is capable of infecting or transducing cells of the eye.

- 10 In one example, the AAV vector comprises an AAV serotype 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 genome. In another example, the AAV vector comprises an AAV serotype 2, 4, 5 or 8 genome. Preferably, the AAV vector comprises an AAV serotype 2 genome.

- In one example, the AAV vector particle comprises an AAV serotype 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 capsid protein. In another example, the AAV vector particle comprises an AAV serotype 2, 4, 5 or 8 capsid protein. Preferably, the AAV vector particle comprises an AAV serotype 8 capsid protein. The AAV serotype 8 capsid protein may, for example, be a AAV8/Y733F mutant capsid protein.
- 15

- In one example, the AAV vector particle comprises an AAV2 genome and AAV2 capsid proteins (AAV2/2); an AAV2 genome and AAV5 capsid proteins (AAV2/5); or an AAV2 genome and AAV8 capsid proteins (AAV2/8). Preferably, the AAV vector particle comprises an AAV2 genome and AAV8 capsid proteins (AAV2/8).
- 20

- The AAV vector particle of the disclosure may be a chimeric, shuffled or capsid-modified derivative of one or more naturally occurring AAVs. In particular, the AAV vector particle may comprise capsid protein sequences from different serotypes, clades, clones or isolates of AAV within the same vector (i.e. a pseudotyped vector). Thus, in one example the AAV vector is in the form of a pseudotyped AAV vector particle.
- 25

In another example, the disclosure provides a viral vector production system comprising a set of polynucleotides encoding the components required for production of the viral vector, wherein the viral vector genome comprises the polynucleotide of the disclosure.

- 30 In one example, the viral vector is an adeno-associated viral (AAV), retroviral, lentiviral or adenoviral vector. Preferably, the viral vector is an AAV vector.

In another example, the disclosure provides a DNA construct for use in the viral vector production system of the disclosure comprising the polynucleotide of the disclosure.

5 In another example, the disclosure provides a viral vector production cell comprising the polynucleotide, viral vector production system or DNA construct of the disclosure. The viral vector production cell may, for example, be a HEK293, HEK293T, Sf9, C12 or HeLa cell. Preferably, the viral vector production cell is a HEK293 or HEK293T cell.

In another example, the disclosure provides a process for producing a viral vector comprising introducing the polynucleotide of the disclosure into a cell and culturing the cell under conditions suitable for the production of the viral vector.

10 In another example, the disclosure provides a viral vector obtainable using the viral vector production cell of the disclosure or by the process of the disclosure.

In another example, the disclosure provides a cell transfected with the polynucleotide of the disclosure or transduced by the viral vector of the disclosure.

15 In another example, the disclosure provides a pharmaceutical composition comprising the polynucleotide, viral vector or cell of the disclosure in combination with a pharmaceutically acceptable carrier, diluent or excipient.

20 In another example, the disclosure provides the polynucleotide or viral vector of the disclosure for use in treating or preventing retinitis pigmentosa. The disclosure also provides the polynucleotide or viral vector of the disclosure for use in reducing photoreceptor cell death in a subject suffering from or at risk of developing retinitis pigmentosa.

In one example, the retinitis pigmentosa is X-linked retinitis pigmentosa.

25 In one example, the polynucleotide or viral vector is administered to the eye of a subject by subretinal, direct retinal or intravitreal injection. Preferably, the polynucleotide or viral vector is administered to the eye of a subject by subretinal injection. The subretinal injection may be performed using the two-step subretinal injection method described herein.

The subretinal injection preferably comprises the steps:

- (a) administering a solution to the subject by subretinal injection in an amount effective to at least partially detach the retina to form a subretinal bleb, wherein the solution does not comprise the polynucleotide or viral vector; and

(b) administering a medicament composition by subretinal injection into the bleb formed by step (a), wherein the medicament comprises the polynucleotide or viral vector.

In one example, the AAV vector is administered to a subject in a single dose.

- 5 The AAV vector may, for example, be in a suspension at a concentration of about $1-2 \times 10^9$, $1-2 \times 10^{10}$, $1-2 \times 10^{11}$, $1-2 \times 10^{12}$ or $1-2 \times 10^{13}$ genome particles (gp) per mL. Thus a dose of AAV vector of about 2×10^{10} gp may, for example, be administered by injecting about a 10 μ L dose of AAV vector at a concentration of about 2×10^{12} gp per mL. The skilled person is readily able to adjust the dose, volume and concentration of the AAV vector as necessary.
- 10 The volume of the AAV vector administered may be, for example, about 1-500 μ L, for example about 10-500, 50-500, 100-500, 200-500, 300-500, 400-500, 50-250, 100-250, 200-250, 50-150, 1-100 or 1-10 μ L. The volume may be, for example, about 1, 2, 5, 10, 50, 100, 150, 200, 250, 300, 350, 400, 450 or 500 μ L. Preferably, the volume of the AAV vector composition injected is about 100 μ L.
- 15 In one example, the AAV vector is administered at a dosage of at least 2×10^7 , 2×10^8 , 2×10^9 , 2×10^{10} , 2×10^{11} or 2×10^{12} gp per eye. In another example, the AAV vector is administered at a dosage of about $1-2 \times 10^7$, $1-2 \times 10^8$, $1-2 \times 10^9$, $1-2 \times 10^{10}$, $1-2 \times 10^{11}$ or $1-2 \times 10^{12}$ gp per eye. Preferably, the AAV vector is administered at a dosage of about 2×10^{11} gp per eye, preferably by subretinal injection.
- 20 In one example, photoreceptor cell degeneration due to retinitis pigmentosa is substantially prevented for the lifetime of the subject. The photoreceptor cells may comprise cone cells and/or rod cells, preferably cone and rod cells. In another example, less than about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the number of photoreceptor cells (e.g. cone cells and/or rod cells) present in the
- 25 treated eye at the time of administration of the polynucleotide or viral (e.g. AAV) vector subsequently degenerate due to retinitis pigmentosa over the lifetime of the subject. Preferably, the surviving cells remain functional.

- 30 In one example, visual function is substantially restored or maintained in the treated eye. Visual function (e.g. as determined by a test of visual function described herein) may, for example, be restored to about the same level in an affected eye as existed before the onset of retinitis pigmentosa. Alternatively, visual function may, for example, be maintained at about the same level in a healthy subject at risk of developing retinitis pigmentosa, or in a subject already suffering from retinitis pigmentosa (e.g. substantially no deterioration or

further deterioration of visual function occurs as a result of retinitis pigmentosa following the administration of the polynucleotide or viral (e.g. AAV) vector of the disclosure).

If left untreated, most or all rod cells may degenerate (e.g. die) over time as a result of retinitis pigmentosa. Cone cells may also degenerate during progression of the disease.

- 5 In another example, the disclosure provides a method of treating or preventing retinitis pigmentosa comprising administering the polynucleotide or viral vector of the disclosure to a subject in need thereof. The disclosure also provides a method of reducing photoreceptor cell death in a subject suffering from or at risk of developing retinitis pigmentosa comprising administering the polynucleotide or viral vector of the disclosure to the subject.
- 10 The mode (e.g. method and dosage) and effect of administration, and the subject to be treated may be as described herein.

The disclosure further provides the use of the polynucleotide or viral vector of the disclosure for reducing or avoiding the generation of alternatively spliced variants and/or truncated RPGR^{ORF15} proteins relative to a vector or polynucleotide comprising the wild type

- 15 RPGR^{ORF15} gene.

The disclosure further provides the use of the polynucleotide or viral vector of the disclosure for increasing the stability and/or fidelity of replication of a nucleotide sequence comprising the RPGR^{ORF15} gene relative to a nucleotide sequence comprising the wild type RPGR^{ORF15} gene.

- 20 The disclosure further provides the use of the polynucleotide or viral vector of the disclosure for effecting higher rates of translation and/or protein expression of RPGR^{ORF15} protein relative a vector or polynucleotide comprising the wild type RPGR^{ORF15} gene.

The disclosure further provides the use of the polynucleotide or viral vector of the disclosure for increasing the yield of an RPGR^{ORF15}-encoding nucleotide sequence relative to a nucleotide sequence comprising the wild type RPGR^{ORF15} gene.

- 25

DESCRIPTION OF THE DRAWINGS

Figure 1

Comparison of the human, mouse and dog genome sequences of RPGR.

Figure 2

CLAIMS

1. A composition comprising a nucleic acid comprising
(a) a sequence encoding a rhodopsin kinase promoter, and
5 (b) a sequence encoding a retinitis pigmentosa GTPase regulator ORF15 isoform (RPGR^{ORF15}) and comprising a nucleotide sequence that has at least 80% identity to the nucleic acid sequence of SEQ ID NO: 3.
2. The composition of claim 1, wherein the sequence encoding the promoter has at least 90% identity to the nucleic acid sequence of SEQ ID NO: 7.
- 10 3. The composition of claim 1, wherein the sequence encoding the promoter comprises the nucleic acid sequence of SEQ ID NO: 7.
4. The composition of claim 1, wherein the sequence encoding the promoter consists of the nucleic acid sequence of SEQ ID NO: 7.
- 15 5. The composition of claim 1, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence encoding an amino acid sequence that has at least 80% identity to the amino acid sequence of SEQ ID NO: 1.
6. The composition of claim 2, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence encoding an amino acid sequence that has at least 80% identity to the amino acid sequence of SEQ ID NO: 1.
- 20 7. The composition of claim 3, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence encoding an amino acid sequence that has at least 80% identity to the amino acid sequence of SEQ ID NO: 1.
8. The composition of claim 4, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence encoding an amino acid sequence that has at
25 least 80% identity to the amino acid sequence of SEQ ID NO: 1.
9. The composition of claim 1, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence that has at least 97% identity to the nucleic acid sequence of SEQ ID NO: 3.

10. The composition of claim 2, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence that has at least 97% identity to the nucleic acid sequence of SEQ ID NO: 3.

5 11. The composition of claim 3, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence that has at least 97% identity to the nucleic acid sequence of SEQ ID NO: 3.

12. The composition of claim 4, wherein the sequence encoding the RPGR^{ORF15} comprises a nucleotide sequence that has at least 97% identity to the nucleic acid sequence of SEQ ID NO: 3.