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(54) **GENE THERAPY FOR THE TREATMENT OF CNGB1-LINKED RETINITIS PIGMENTOSA**

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(60) Provisional application No. 62/474,409, filed on Mar. 21, 2017.

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(57) **ABSTRACT**

The present invention relates to a polynucleotide comprising a promoter comprising a human photoreceptor-specific promoter element, a core promoter and at least one transgene. Further, the invention provides a plasmid comprising the polynucleotide, a viral vector comprising the polynucleotide and a pharmaceutical composition comprising the polynucleotide. The invention also relates to the plasmid, the viral vector or the pharmaceutical composition for use as a medicament, in particular for use in the therapy of diseases of the retina.

Specification includes a Sequence Listing.





Fig. 1

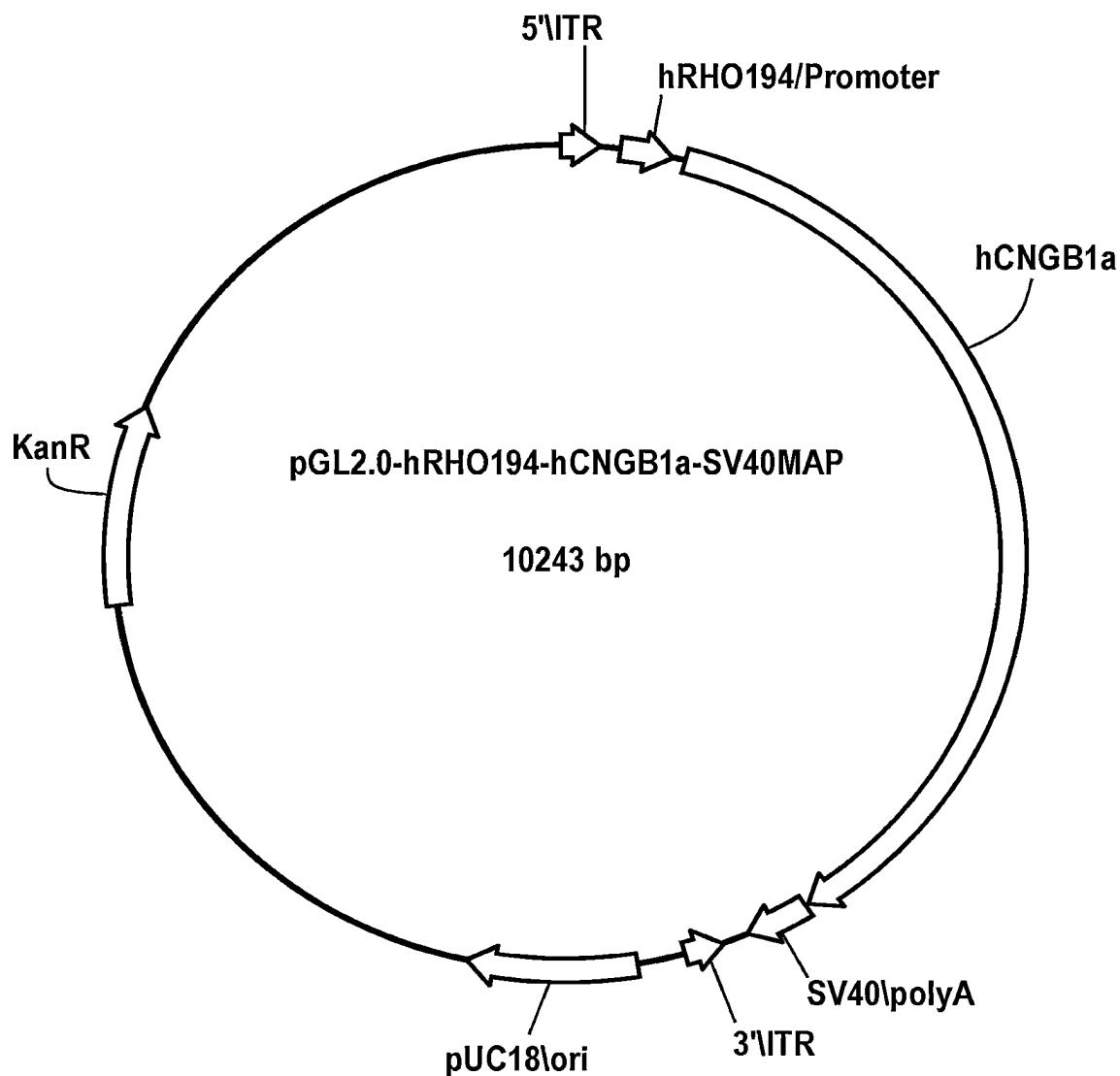


Fig. 2

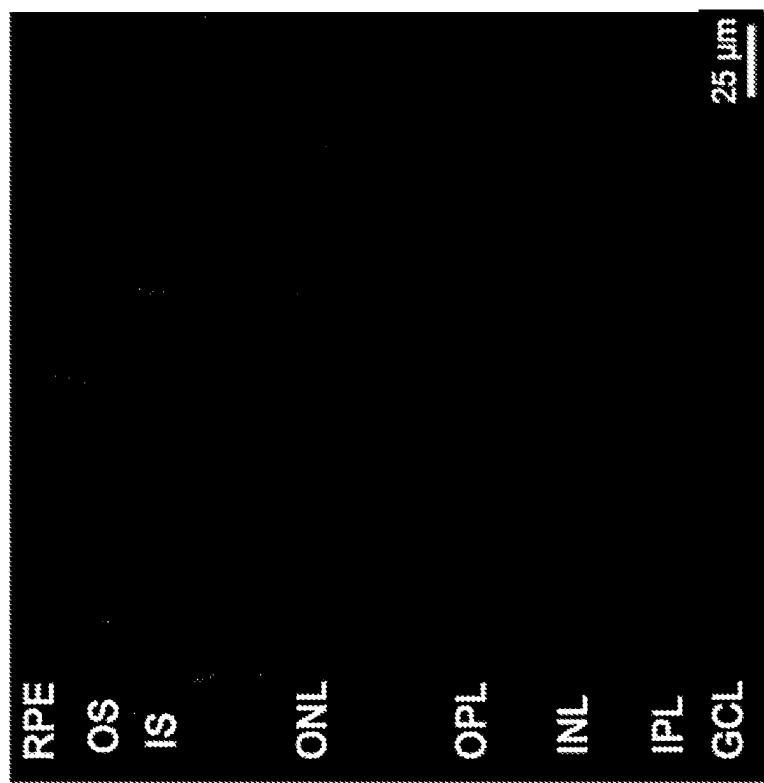


Fig. 3B

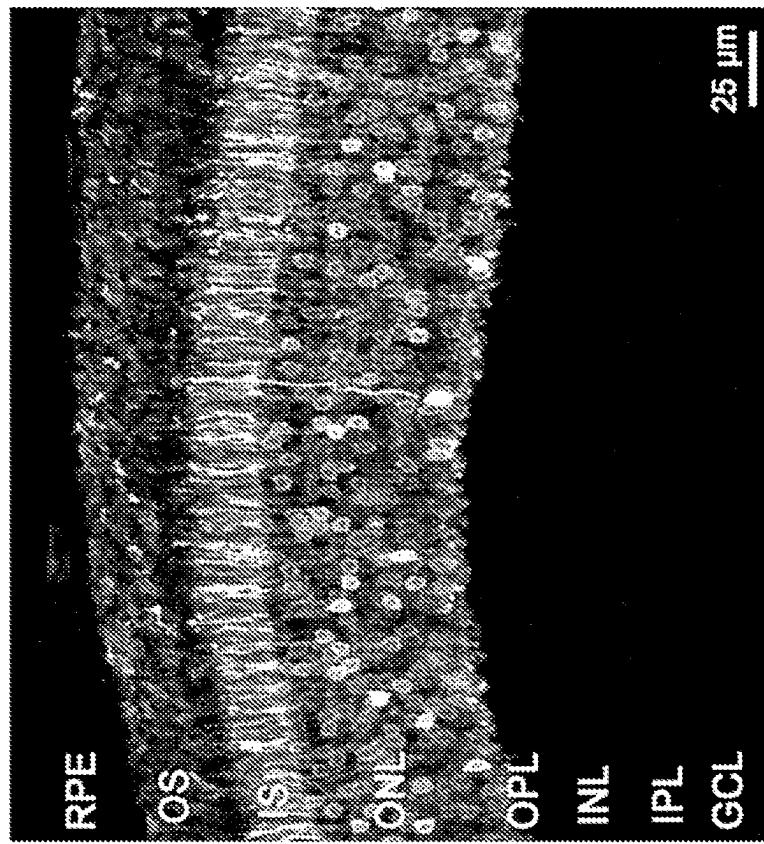


Fig. 3A

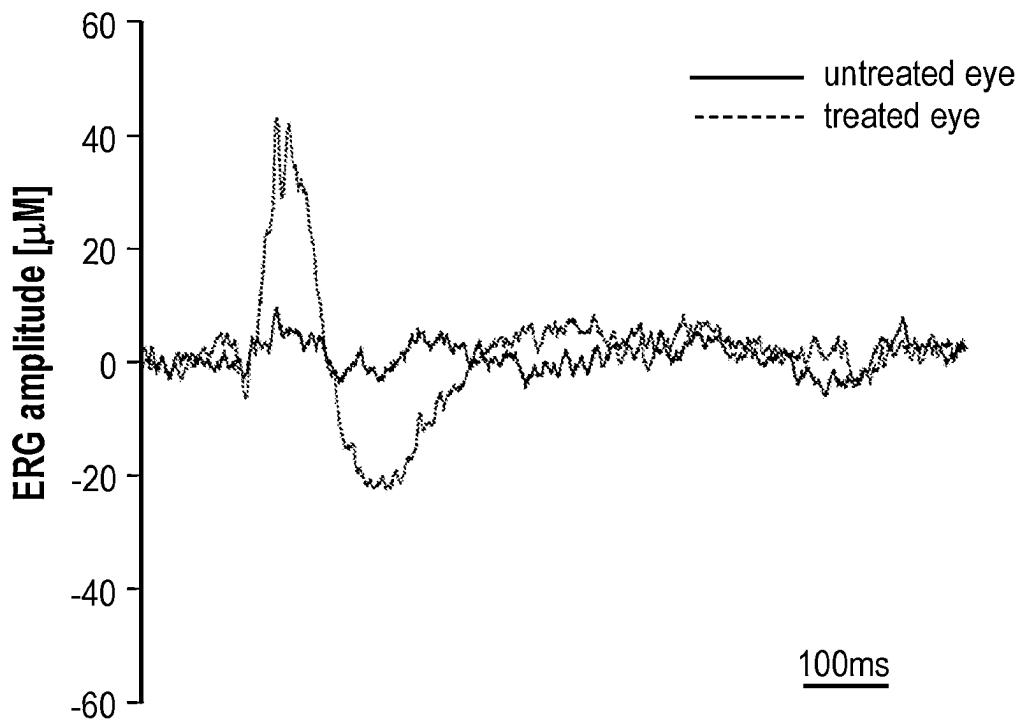


Fig. 4A

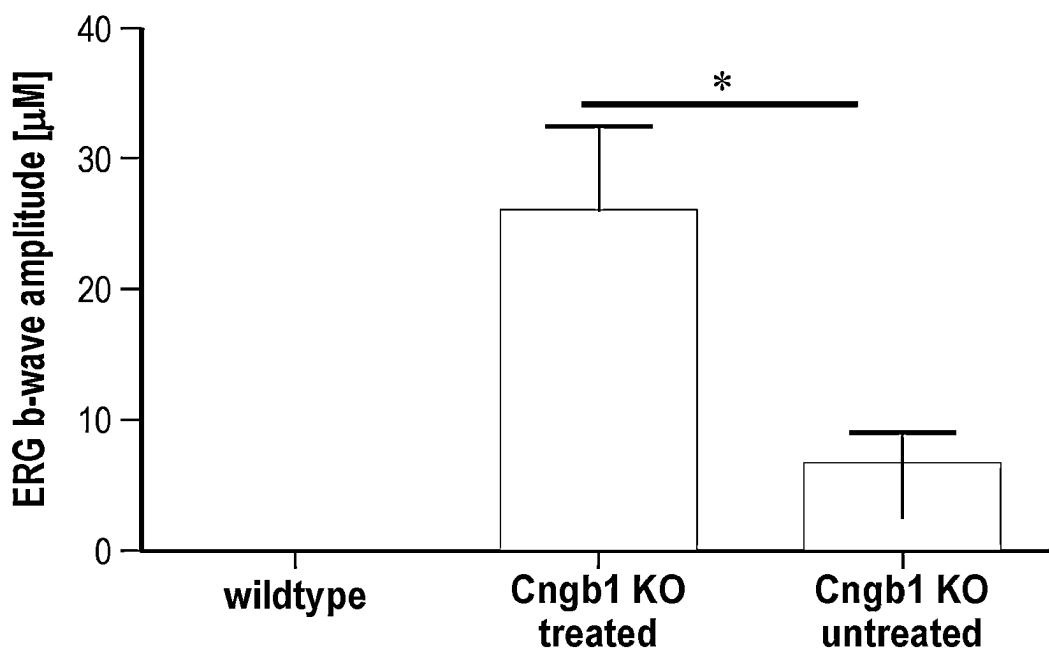


Fig. 4B

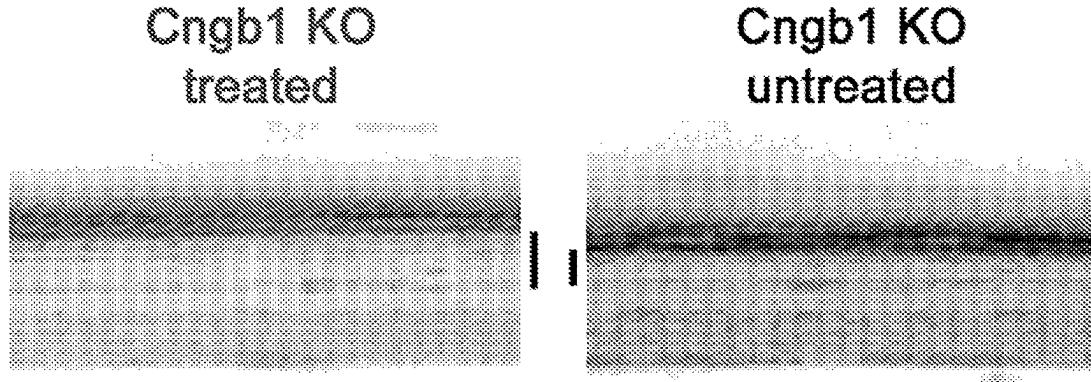


Fig. 5A

Fig. 5B

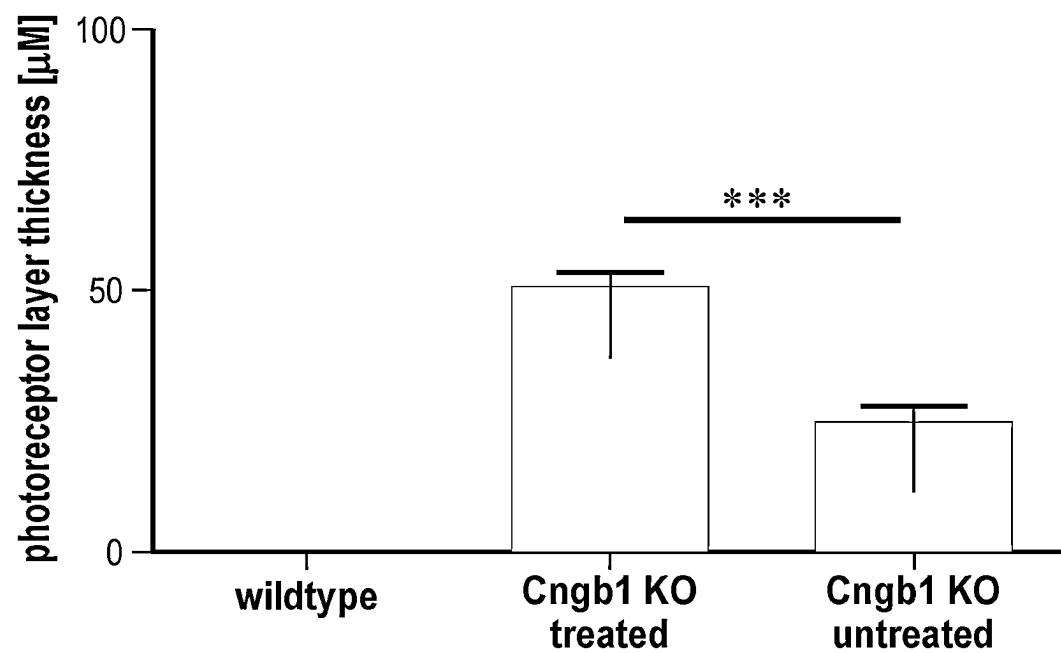


Fig. 5C

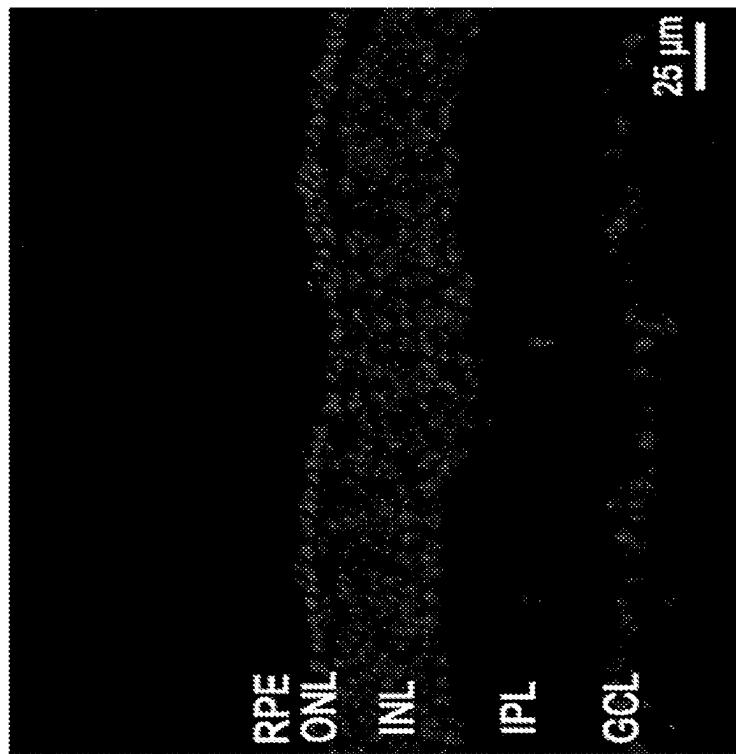


Fig. 6B

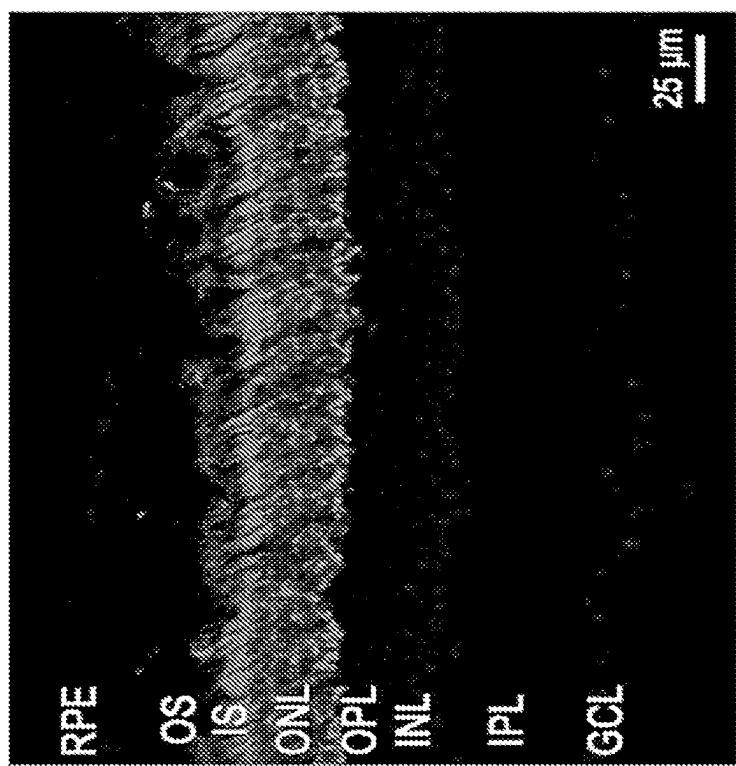


Fig. 6A

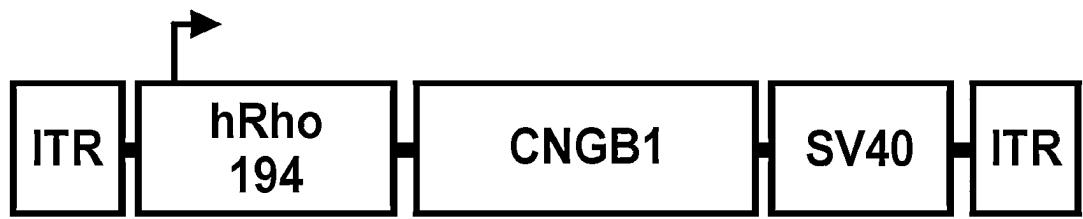


Fig. 7

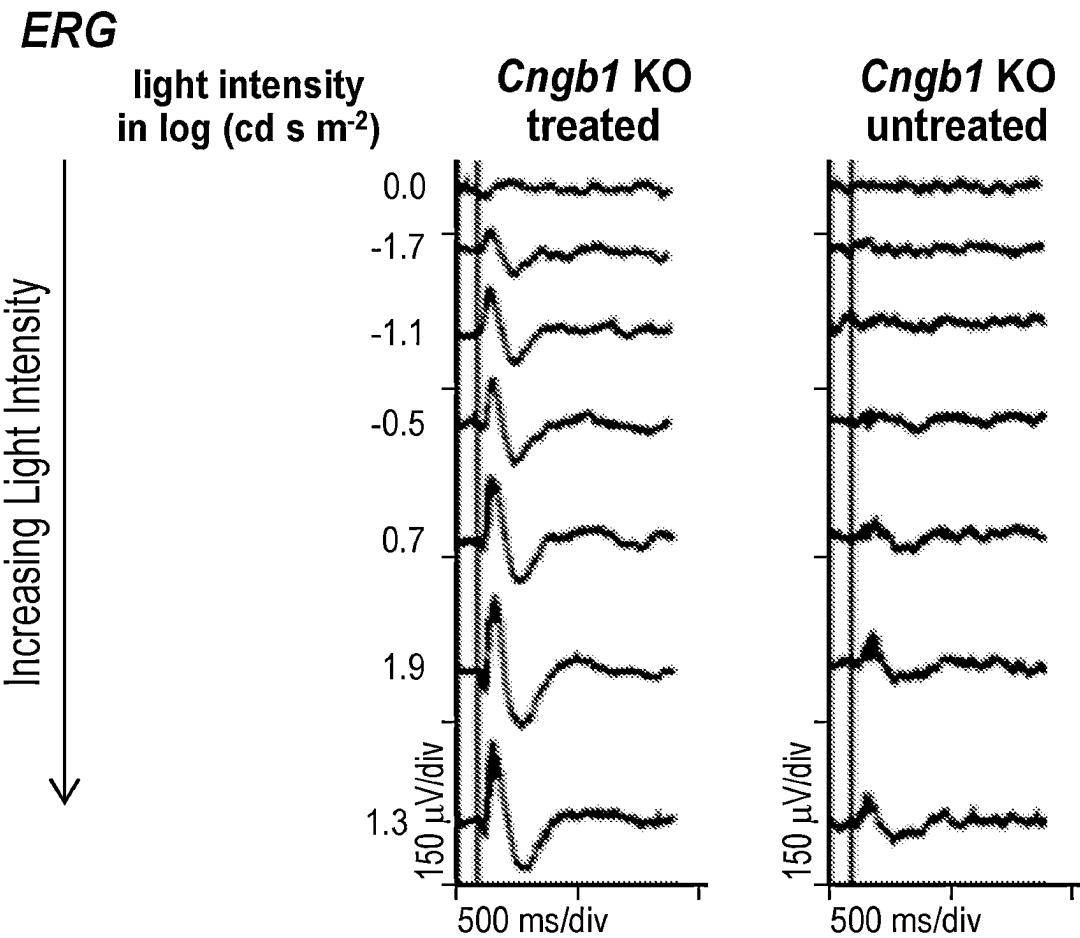


Fig. 8A

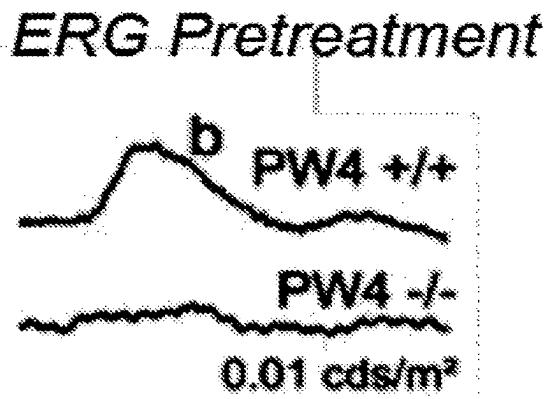


Fig. 8B

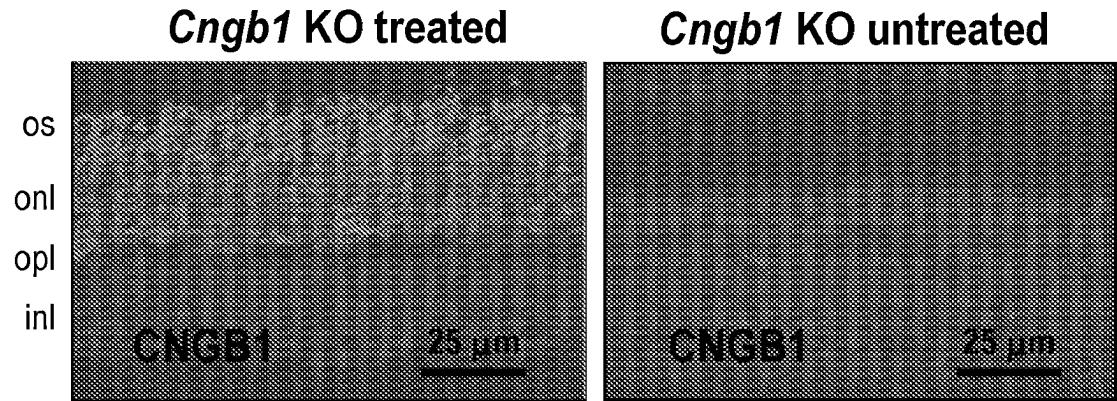


Fig. 9A

Fig. 9B

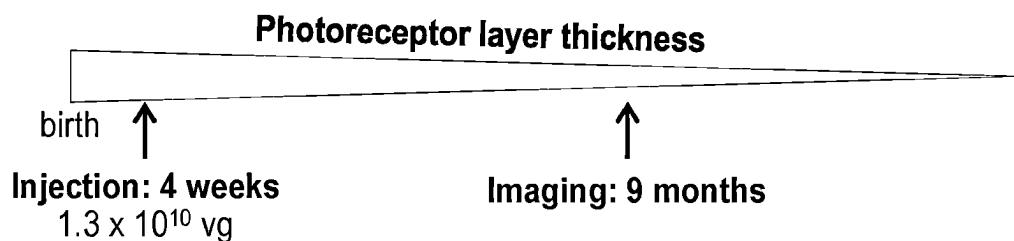


Fig. 10A

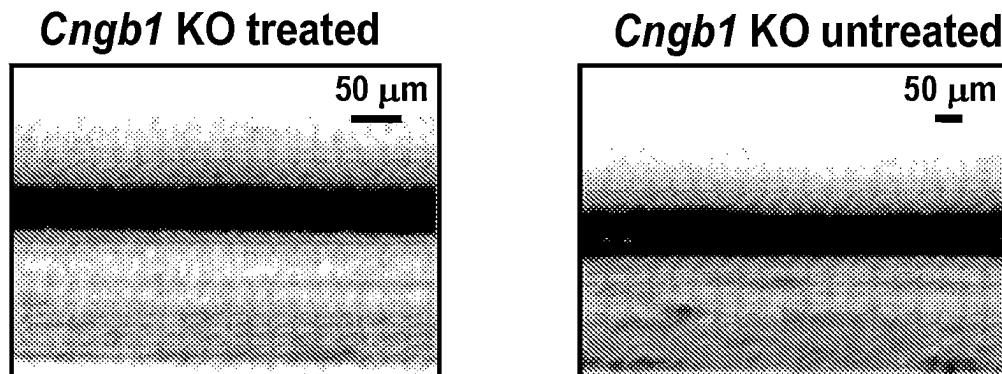


Fig. 10B

Fig. 10C

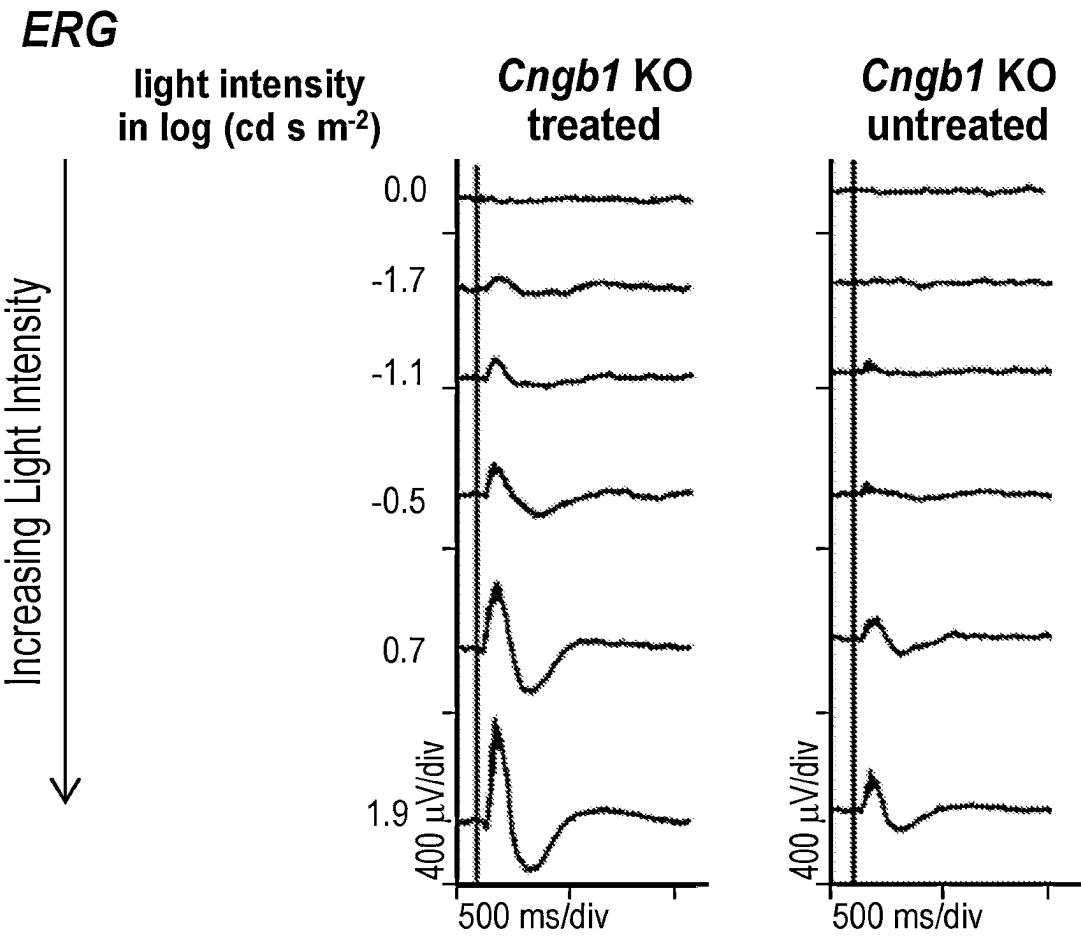


Fig. 11A

b-wave amplitude in response to a light stimulus of -0.5 log (cd s/m²)

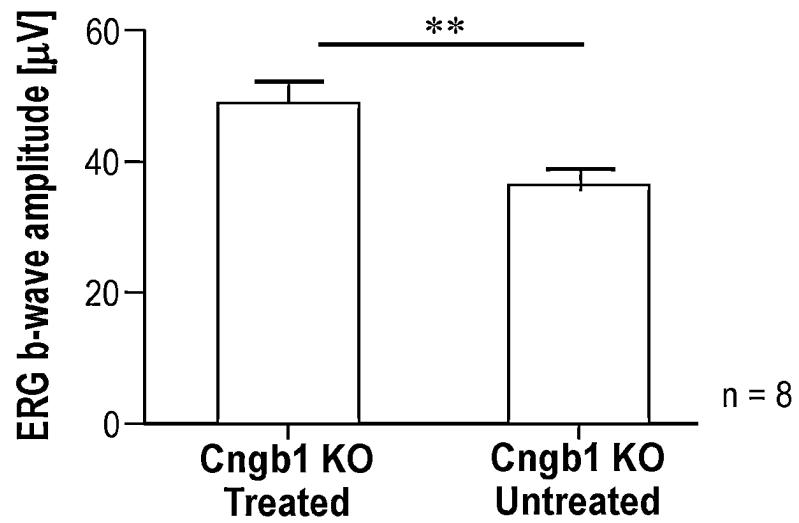


Fig. 11B

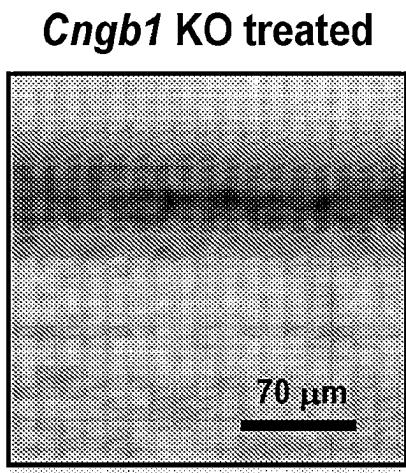


Fig. 11C

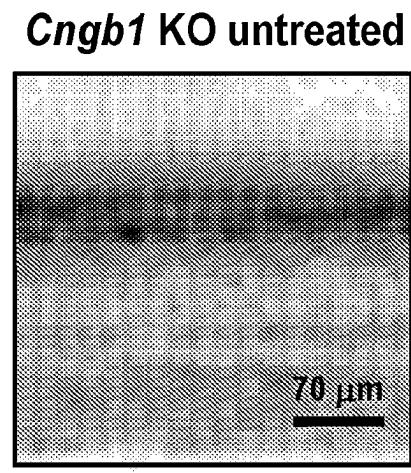


Fig. 11D

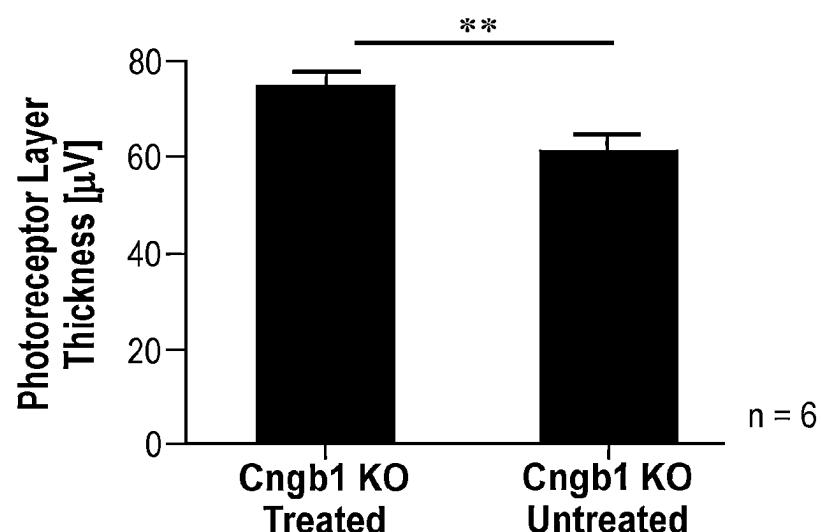


Fig. 11E

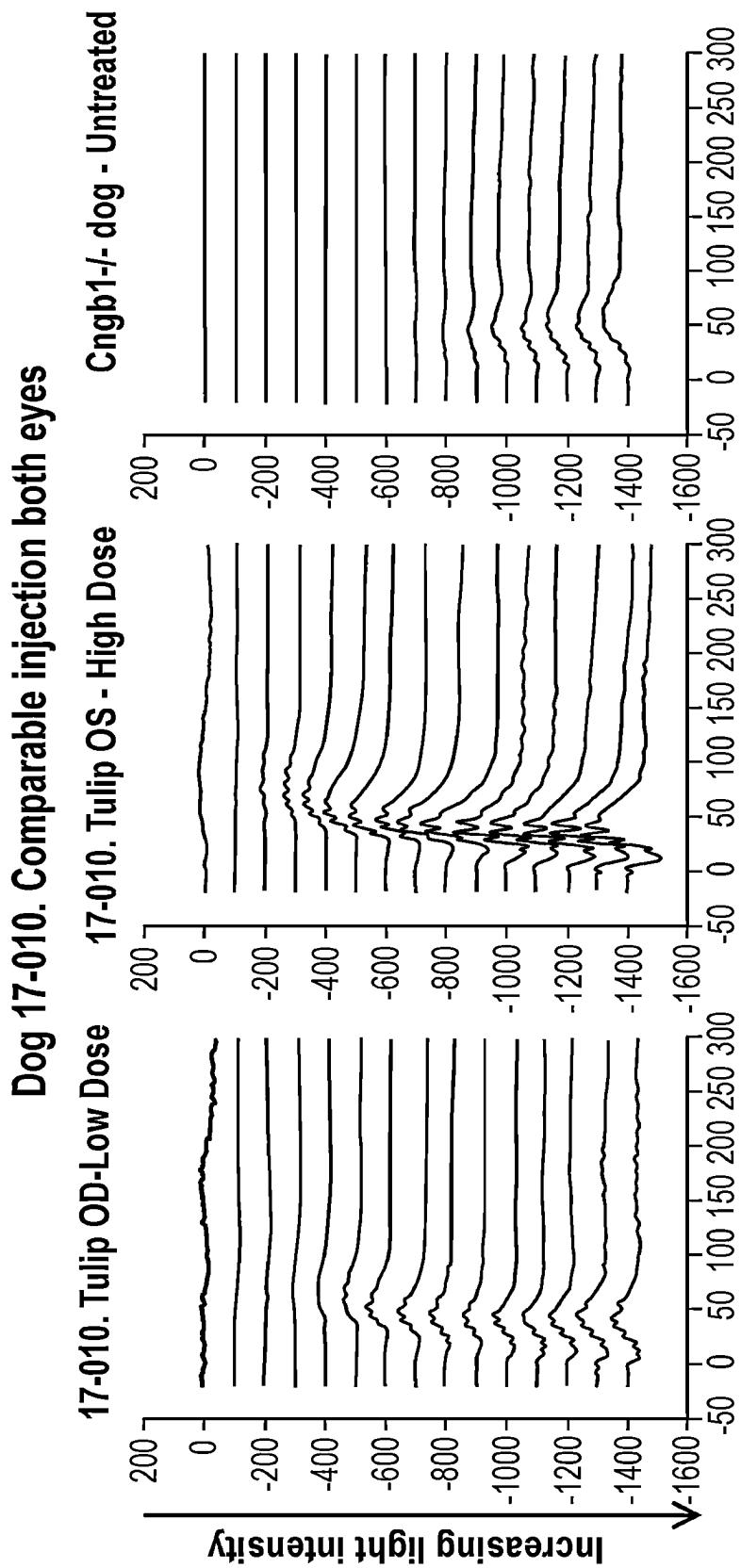


Fig. 12A

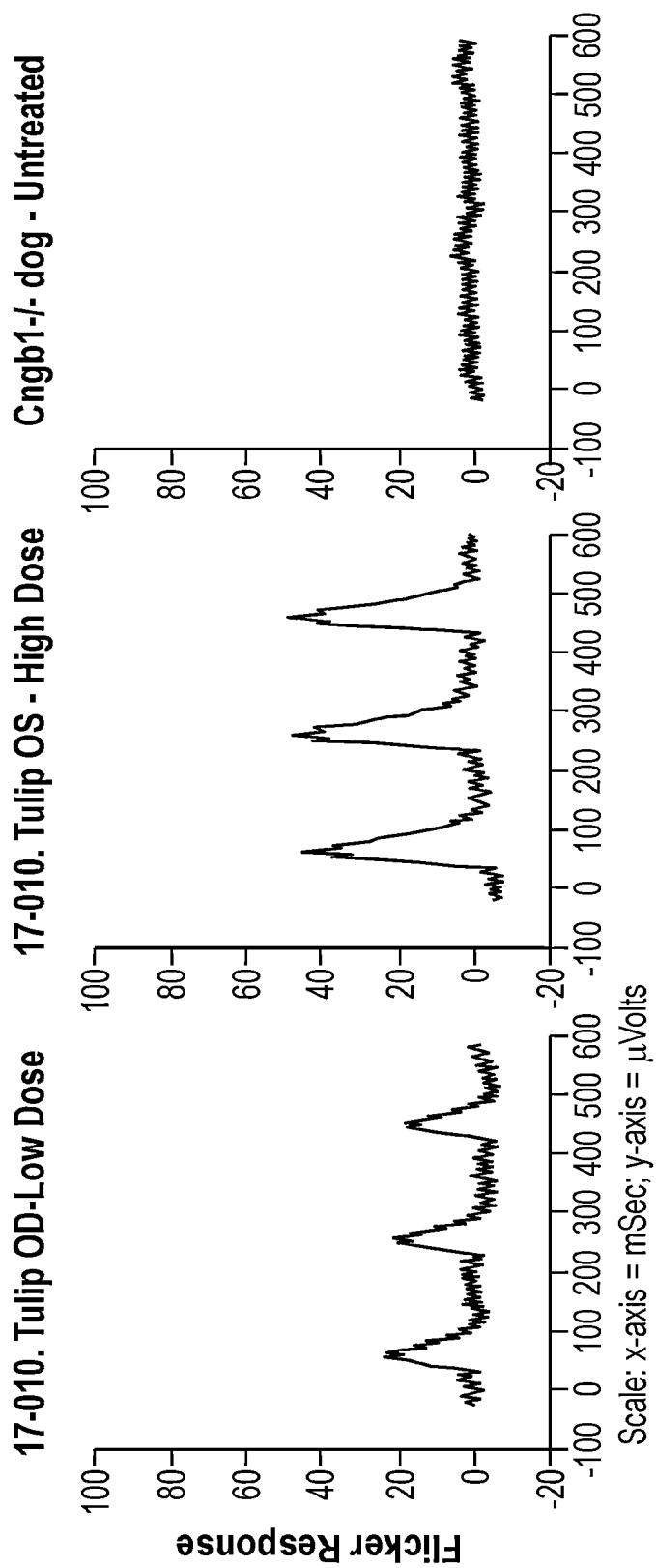


Fig. 12B

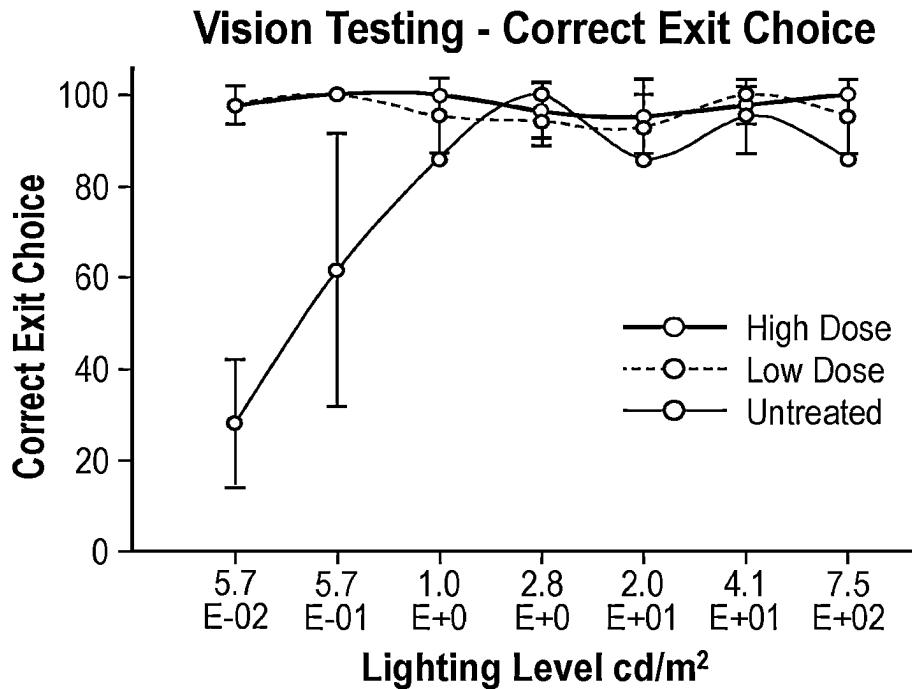


Fig. 13A

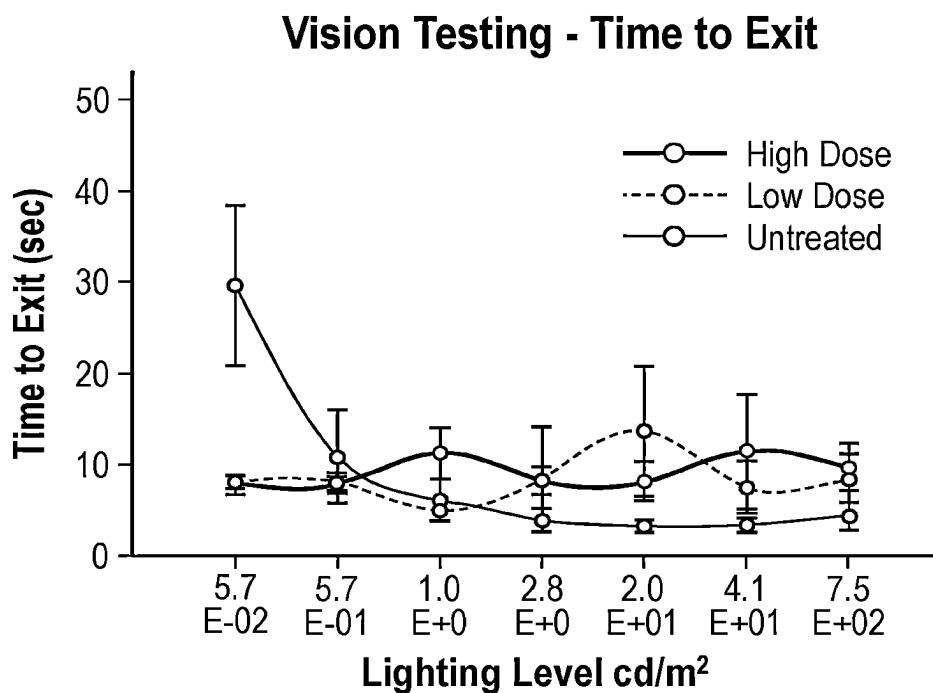


Fig. 13B

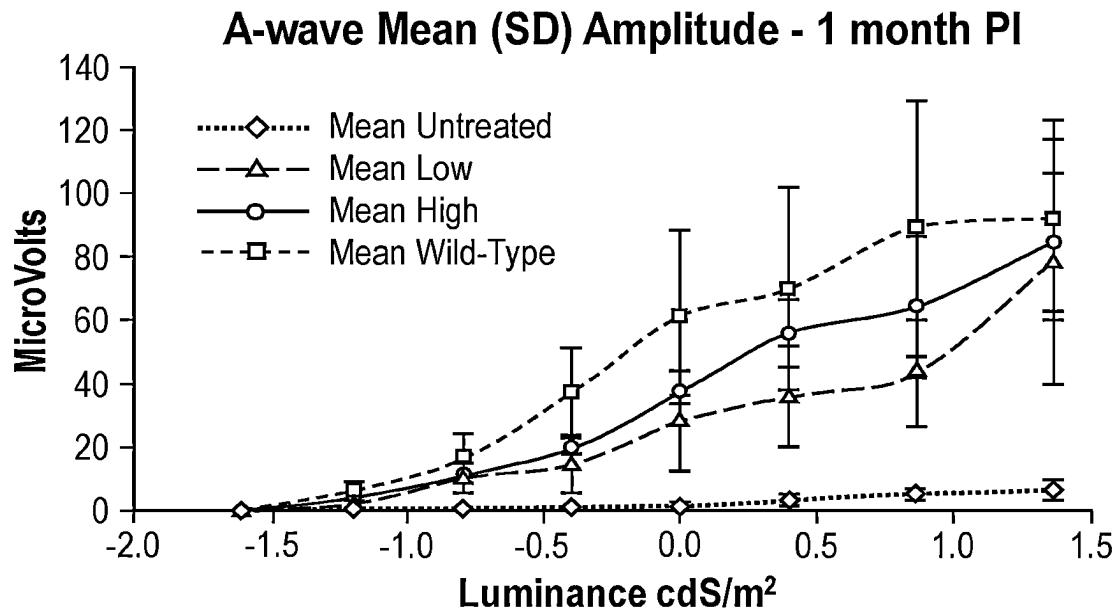


Fig. 14A

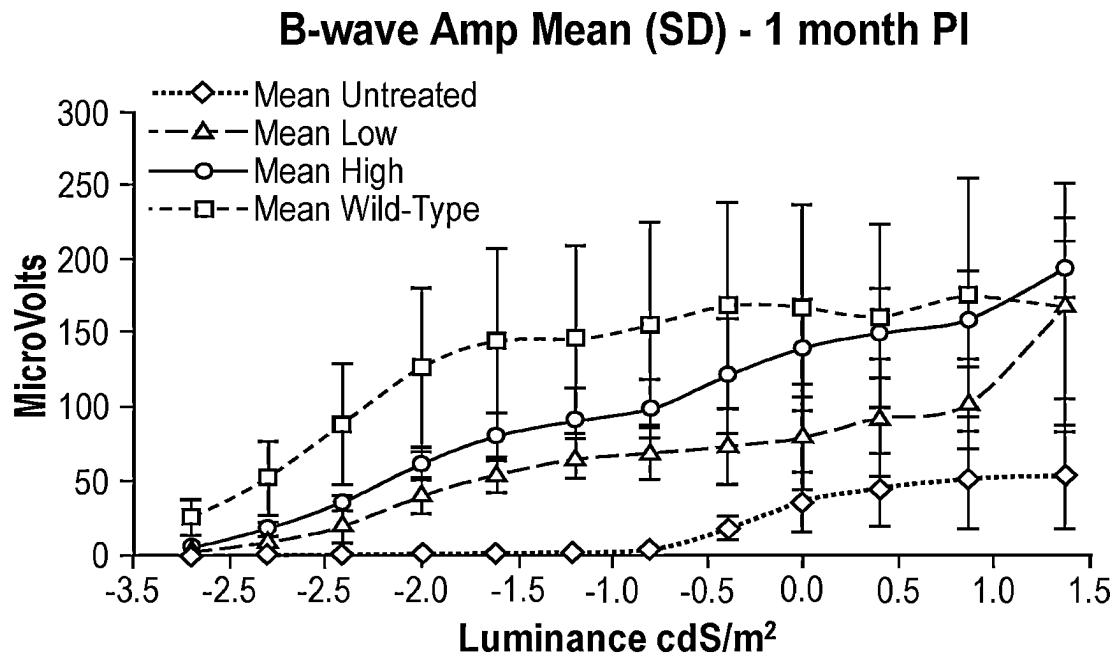


Fig. 14B

**GENE THERAPY FOR THE TREATMENT OF
CNGB1-LINKED RETINITIS PIGMENTOSA****CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a continuation of U.S. application Ser. No. 16/495,826, filed on Sep. 19, 2019, which is a US National Phase filing of PCT/IB2018/051905, filed on Mar. 21, 2018, which claims the benefit of U.S. Provisional Application No. 62/474,409, filed on Mar. 21, 2017. The disclosures therein are expressly incorporated entirely by reference.

SEQUENCE LISTING STATEMENT

[0002] A computer readable form of the Sequence Listing is filed with this application by electronic submission and is incorporated into this application by reference in its entirety. The Sequence Listing is contained in the file created on Feb. 3, 2025 having the file name "19-2343-WO-US-CON.xml" and is 125,488 bytes in size.

BACKGROUND OF THE INVENTION

[0003] Retinitis pigmentosa (RP) is a term that is used to refer to a genetically diverse group of inherited degenerative diseases of the retina affecting the photoreceptors. The genetic mutation concerns genes that are either exclusively or primarily expressed in rod photoreceptors. Accordingly, the disease is characterized by a primary impairment or loss of rod function and structure. Deterioration of rods is followed by a secondary degeneration of the cones. Onset and time course of retinal degeneration varies from early-onset and fast progressing forms to late-onset and slow progressing forms, respectively. The most common symptoms of RP are night blindness, progressive constriction of the visual field, and abnormal accumulation of pigmentation in the retina. Clinical features include characteristically shaped pigmentary deposits and a progressive attenuation of retinal vessels. In many cases RP finally leads to legal blindness. The overall prevalence of RP is estimated to 1:4,000. RP is genetically very heterogeneous and the number of identified RP genes approximates 50 (Daiger S P, et al. (1998) Investigative Ophthalmology and Visual Science (Supplement) 39:S295). Many disease genes encode proteins required for light detection and processing (e.g. rhodopsin) or for maintenance of rod cellular morphology (e.g. peripherin-2). 10-25% of RP cases show an autosomal dominant pattern of inheritance (adRP), 6-18% are X-linked (xRP) and 20-30% are autosomal recessively inherited (arRP). Another 40-50% are sporadic arRP and is genetically the most diverse RP subgroup and none of the known disease genes has a relative frequency of more than 15%. The most prevalent arRP genes are EYS (5-12%), USH2A (5-15%), CRB1 (approx. 5%), and PDE6B (4-10%). However, most likely due to founder effects these values vary between different subpopulations and across regions.

[0004] CNGB1 encodes the beta subunit of the rod cyclic nucleotide-gated (CNG) channel (RP45 locus). Mutations in the RP45 locus causing so-called CNGB1-linked RP or RP type 45, respectively, are found in 2-4% of arRP cases (Hartong D T, et al. (2006) Lancet 368 (9549): 1795-1809). Therefore, the estimated number of patients with CNGB1-linked arRP is approximately 900 in Germany and 5,000 in the EU. Vision impairment is considered one of the most

important non-mortal handicaps with high clinical and socioeconomic importance. RP Patients suffer from severe loss of quality of life throughout an extensive period of their lifetime. Unfortunately, no curative or symptomatic treatments of RP exist. Clinical experts and health organizations list RP as one of the top candidates for gene therapy. Previously, it could be demonstrated that gene supplementation therapy restores vision and delays degeneration in the CNGB1 (-/-) mouse model of retinitis pigmentosa (Koch S, et al. (2012) Hum Mol. Genet. 21 (20): 4486-96) by using recombinant AAV2/8 vector comprising the mouse Cngb1 gene under the control of the mouse rhodopsin (Rho) promoter: AAV2/8 (Y733F)-Rho-Cngb1. The vector was injected into the eye of mice with a genetic deletion in exon 26 of the gene encoding Cngb1 (Cngb1 KO). The injection enhanced survival of photoreceptors and improved retinal function. However, several issues render this approach less promising for the treatment of humans suffering from retinal degenerations due to CNGB1-linked RP:

[0005] (a) the rAAV cis vector genome size (5.0 kb) was above the size of the wildtype AAV genome (<4.7 kb);

[0006] (b) a murine rhodopsin (Rho) gene promoter was used; and

[0007] (c) a murine Cngb1 gene sequence was used.

[0008] Petersen-Jones et al. (2016) Invest. Ophthalmol. 57:1842, describe an rAAV2/5 vector comprising the coding sequence of the canine Cngb1 gene (cCngb1) under control of a human rhodopsin kinase 1 (hGRK1) promoter: AAV5-hGRK1-cCngb1. The vector was injected into the eye of dogs with a mutation in exon 26 of the Cngb1 gene. The injection improved retinal function. However, the following issues render this approach less promising for the treatment of humans suffering from retinal degenerations due to CNGB1-linked RP:

[0009] (a) the hGRK1 promoter used in this approach drives expression in rods, but also off-target expression in cone photoreceptors. This off-target expression could have a negative impact on retinal function and morphology; and

[0010] (b) a canine Cngb1 gene sequence was used.

[0011] Thus, there is a need in the art to identify transgenic elements that have a small size without negatively affecting or losing their activity in the in vivo situation.

SUMMARY OF THE INVENTION

[0012] The present invention is based on the surprising discovery that a short part of the human rod promoter transfers rod photoreceptor-specific expression to transgenes operably linked to this promoter element in vivo. When the promoter element defined herein was used in an in vivo setting, stable expression of a transgene was observed. The expression level was suitable to improve the visual capabilities of the test animals infected with an adeno-associated virus vector comprising the transgene. This surprising finding provides inter alia the following advantages over the prior art: (i) reduction of the size of the construct that is introduced into a cell, (ii) an increase of the packaging efficiency of the transgene into viral vectors, (iii) a decrease of the chance that recombination events occur in vivo, (iv) an increase the efficiency of introduction of the transgene into the target cells, in particular into the nucleus of the target cell; (v) a suitable expression level in a human patient

to treat rod associated diseases, (vi) preservation and/or improvement of retinal function and (vii) preservation and/or improvement of vision.

[0013] In a first aspect the invention relates to a polynucleotide comprising in this order:

[0014] a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising, consisting essentially of or consisting of the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0015] b) a transgene (TG) operably linked to the promoter of a);

[0016] wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1 and wherein the length of the promoter is in particular 350 bases or less.

[0017] In certain exemplary embodiments, the 5' end of the hRPSPE is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 290 to 310 of SEQ ID NO: 2 or variants thereof.

[0018] In certain exemplary embodiments, the CP comprises a TATA-box and/or an initiator (Inr).

[0019] In certain exemplary embodiments, the 5' end of the promoter is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 340 to 350 of SEQ ID NO: 2 or variants thereof.

[0020] In certain exemplary embodiments, the transgene comprises a nucleic acid encoding a protein that maintains or improves the physiological function of rods.

[0021] In certain exemplary embodiments, the transgene: (i) comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, API1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MY07A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USHIC, USHIG, USH2A or functional fragments or variants thereof; a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof; and/or a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof; or (ii) comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, preferably a toxin; a prodrug converting enzyme, e.g. thymidine kinase; cell cycle inhibitors, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2; comprises a mRNA encoding a dominant negative mutant of the cell cycle inhibitor thereof; and/or comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor thereof.

[0022] In certain exemplary embodiments, the hCNGB1 comprises an amino acid sequence according to SEQ ID NOs: 3, 40, or 41, or variants thereof.

[0023] In certain exemplary embodiments, the polynucleotide comprises one or more further nucleotide sequence elements selected from the group consisting of: (i) a polyadenylation signal (PAS); and/or (ii) one or two inverted terminal repeat (ITR) sequences; and/or (iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

[0024] In certain exemplary embodiments, the polyadenylation signal comprises, essentially consists or consists of a Simian-Virus 40 PAS.

[0025] In certain exemplary embodiments, the polyadenylation signal comprises, essentially consists or consists of a nucleic acid according to SEQ ID NO: 4 or functional variants thereof.

[0026] In certain exemplary embodiments, the ITR sequence is an adeno-associated virus (AAV) ITR.

[0027] In certain exemplary embodiments, the AAV is AAV serotype 2, 5, 8 or 9.

[0028] In certain exemplary embodiments, the promoter and the transgene are flanked at their 5' with a L-ITR and at their 3' end with a R-ITR.

[0029] In certain exemplary embodiments, the L-ITR comprises, essentially consists or consists of a sequence according to SEQ ID NO: 5 or variants thereof and/or the R-ITR comprises, essentially consists or consists of a sequence according to SEQ ID NO: 6 or variants thereof.

[0030] In certain exemplary embodiments, the total length of the polynucleotide is 5200 bases or less, preferably 5100 bases or less, more preferably 5000 bases or less.

[0031] In a second aspect the invention further relates to a plasmid comprising the polynucleotide of the first aspect.

[0032] In certain exemplary embodiments, the plasmid comprises a nucleic acid sequence according to SEQ ID NOs: 7, 42-44, or variants thereof.

[0033] A third aspect of the invention relates to a viral vector comprising the polynucleotide of the first aspect of the invention.

[0034] In certain exemplary embodiments, the virus is selected from the group consisting of AAV2, AAV5, AAV8, AAV9 or variants thereof.

[0035] A fourth aspect of the invention relates to the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention for use as a medicament.

[0036] A fifth aspect of the invention relates to a pharmaceutical composition comprising the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention, and a pharmaceutically acceptable carrier.

[0037] A sixth aspect of the invention relates to the polynucleotide according to the first aspect of the invention, the plasmid according to the second aspect of the invention and/or the viral vector according to the third aspect of the invention for use in the therapy of a disease of the retina, in particular retinal degeneration.

[0038] In certain exemplary embodiments, the route of administration is selected from intraocular, intrabulbar, intravitreal or subretinal.

[0039] In certain exemplary embodiments, the retinal degeneration is associated with a genetic mutation, substitution, and/or deletion.

[0040] In certain exemplary embodiments, the retinal degeneration is selected from the group consisting of night blindness, blindness, retinal degeneration, retinal dystrophy and retinitis pigmentosa.

[0041] In certain exemplary embodiments, the retinitis pigmentosa is CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45).

[0042] A seventh aspect of the invention relates to a polynucleotide comprising in this order:

[0043] a) a human rhodopsin promoter comprising the nucleic acid sequence according to SEQ ID NO: 9 or variants thereof; and

[0044] b) at least one transgene (TG) operably linked to the promoter of a).

[0045] In certain exemplary embodiments, the transgene comprises a nucleic acid encoding a protein that maintains or improves a physiological function of rods.

[0046] In certain exemplary embodiments, the transgene: (i) comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, AIPL1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MYO7A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USH1C, USH1G, USH2A or functional fragments or variants thereof; a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof; and/or a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof; or (ii) comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, preferably a toxin; a prodrug converting enzyme, e.g. thymidine kinase; cell cycle inhibitors, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2; comprises a mRNA encoding a dominant negative mutant of the cell cycle inhibitor thereof; and/or comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor thereof.

[0047] In certain exemplary embodiments, the polynucleotide comprises one or more further nucleotide sequence elements selected from the group consisting of:

[0048] (i) a polyadenylation signal (PAS);

[0049] (ii) one or two inverted terminal repeat (ITR) sequences; and

[0050] (iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

[0051] In certain exemplary embodiments, the polyadenylation signal comprises a Simian-Virus 40 PAS.

[0052] In certain exemplary embodiments, the ITR sequence is an adeno-associated virus (AAV) ITR.

[0053] In certain exemplary embodiments, the AAV is AAV serotype 2, 5, 8 or 9.

[0054] An eighth aspect of the invention relates to a viral vector comprising the polynucleotide according to the seventh aspect of the invention.

[0055] In certain exemplary embodiments, the virus is selected from the group consisting of AAV2, AAV5, AAV8, AAV9 or variants thereof.

[0056] A ninth aspect of the invention relates to a method for treating retinal degeneration in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polynucleotide according to the seventh aspect of the invention, or the viral vector according to the eighth aspect of the invention.

[0057] In certain exemplary embodiments, the polynucleotide or viral vector comprises the nucleic acid sequence set forth in SEQ ID NO: 43.

[0058] A tenth aspect of the invention relates to a method for treating retinitis pigmentosa in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polynucleotide according to the seventh aspect of the invention, or the viral vector according to the eighth aspect of the invention.

[0059] In certain exemplary embodiments, the polynucleotide or viral vector comprises the nucleic acid sequence set forth in SEQ ID NO: 43.

[0060] An eleventh aspect of the invention relates to a method for treating retinal degeneration in a subject in need thereof, wherein the retinal degeneration is characterized by a defect or absence of CNGB1 in the retinal cells of the subject, the method comprising administering to the subject a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43.

[0061] In certain exemplary embodiments, the retinal degeneration is CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45).

[0062] A twelfth aspect of the invention relates to a method for treating CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45) in a subject in need thereof, comprising subretinal administration to the subject a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43.

[0063] A thirteenth aspect of the invention relates to a polynucleotide comprising in this order:

[0064] a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0065] b) a transgene encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1) operably linked to the promoter of a), wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1.

[0066] A fourteenth aspect of the invention relates to a pharmaceutical composition comprising a polynucleotide comprising in this order:

[0067] a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0068] b) a transgene encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1) operably linked to the promoter of a);

[0069] wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1, and

[0070] a pharmaceutically acceptable carrier.

[0071] A fifteenth aspect of the invention relates to a pharmaceutical composition comprising a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43 and a pharmaceutically acceptable carrier.

LIST OF FIGURES

[0072] In the following, the content of the figures comprised in this specification is described. In this context please also refer to the detailed description of the invention above and/or below.

[0073] FIG. 1 shows the structure of the rAAV hRHO194. hCNGB1 vector genome.

[0074] FIG. 2 shows the pGL2.0-hRHO194-hCNGB1a-SV40 cis vector plasmid map.

[0075] FIGS. 3A-3B depict representative confocal images showing native eGFP fluorescence in wild type mice treated with a version of the vector expressing eGFP instead of hCNGB1. These representative confocal images show native eGFP fluorescence in retinal cross-sections from 8-week-old wildtype mice treated subretinally at 4 weeks with rAAV.hRHO194.eGFP vector. Intense and rod-specific eGFP signal was observed in treated animals (FIG. 3A), but was absent in non-injected controls (FIG. 3B).

[0076] FIGS. 4A-4B show representative ERG measurements from CNGB1 (-/-) mice treated with the vector according to the invention; Electroretinography (ERG) measurement data from CNGB1 (-/-) mice treated in one eye with the vector according to the invention. (FIG. 4A) Representative ERG traces obtained upon 4.4 cd/m² single flash stimulation. The hatched trace is from the treated eye and the black trace from the untreated eye of a CNGB1 (-/-) mouse at 4 months after treatment. (FIG. 4B) Summary graph showing the ERG b-wave amplitudes measured under the same conditions from wild type mice (grey), treated CNGB1 (-/-) mice (dark grey) and untreated CNGB1 (-/-) mice (black). * p<0.05, Student's t-test, N=4.

[0077] FIGS. 5A-5C show optical coherence tomography (OCT) measurements of photoreceptor layer thickness from CNGB1 (-/-) mice treated in one eye with the vector according to the invention. (FIGS. 5A-5B) Representative OCT scans from treated (FIG. 5A) and untreated eye (FIG. 5B). The thickness of the photoreceptor layer is marked with a vertical black bar. Quantification of photoreceptor layer thickness using OCT (FIG. 5C). ***p<0.001, 1 way ANOVA, N=9.

[0078] FIGS. 6A-6B depict representative confocal images from immunohistological stainings of hcNGB1 in CNGB1 (-/-) mice treated with the vector according to the invention (FIG. 6A) or untreated (FIG. 6B).

[0079] FIG. 7 depicts a schematic showing the general vector design according to the invention.

[0080] FIGS. 8A-8B show representative ERG measurements from CNGB1 (-/-) mice treated with the vector according to the invention (FIG. 8A). Representative ERG measurements in wild-type and CNGB1 (-/-) mice before treatment (FIG. 8B).

[0081] FIGS. 9A-9B depict representative confocal images from immunohistological stainings of hCNGB1 in CNGB1 (-/-) mice treated with the vector according to the invention (FIG. 9A), and untreated mice (FIG. 9B).

[0082] FIGS. 10A-10C depict OCT analysis revealing a significant delay in retinal degeneration. General injection schedule of the vector according to the invention (FIG. 10A). OCT images collected at 9 months in CNGB1 (-/-) mice treated with the vector according to the invention (FIG. 10B), and untreated mice (FIG. 10C).

[0083] FIGS. 11A-11E depict restoration of rod function by two months in CNGB1 (-/-) mice treated with the vector according to the invention. Representative ERG B-wave measurements in CNGB1 (-/-) mice treated with the vector according to the invention, and untreated mice (FIG. 11A). Summary graph showing the ERG b-wave amplitudes measured in response to a light stimulus of -0.5 log (cd s/m²) in CNGB1 (-/-) mice treated with the vector according to the invention, and untreated mice (FIG. 11B). OCT measurements of photoreceptor layer thickness from CNGB1 (-/-) mice treated with the vector according to the invention (FIG. 11C), and untreated mice (FIG. 11D). Quantification of photoreceptor layer thickness using OCT (FIG. 11E). N=6.

[0084] FIGS. 12A-12B depict obvious ERG rescue observed in eyes of CNGB1 (-/-) dogs treated with the vector according to the invention, and untreated dogs, using a rod-specific stimulus (FIG. 12A), and a flicker response (FIG. 12B).

[0085] FIGS. 13A-13B depict vision testing data showing that CNGB1 (-/-) dogs treated with the vector according to the invention have rod-mediated vision and improved vision testing performance. Restored rod vision indicated by improved performance in correct exit choice (FIG. 13A), and time to exit (FIG. 13B).

[0086] FIG. 14A-14B depict ERG measurements showing improvement in A- and B-wave amplitude in CNGB1 (-/-) dogs treated with the vector according to the invention. A-wave amplitude indicated-improvement in response threshold in treated eyes was found to be greater than 1.5 log units (FIG. 14A). B-wave amplitude-indicated improvement in response threshold in treated eyes was found to be greater than 2 log units (FIG. 14B).

List of Sequences

SEQ ID NO: 1	Sequence of a 99 nucleotides long fragment of the human rhodopsin promoter comprising the core tissue specific elements;
SEQ ID NO: 2	Sequence of a 350 nucleotides long fragment of the human rhodopsin promoter comprising the tissue specific elements and the transcriptional start site;
SEQ ID NO: 3	Sequence of the human CNGB1 protein;
SEQ ID NO: 4	Sequence of a polyadenylation signal SV40;
SEQ ID NO: 5	Sequence of the left inverted terminal repeat (L-ITR);
SEQ ID NO: 6	Sequence of the right inverted terminal repeat (R-ITR);
SEQ ID NO: 7	Sequence of vector construct: pGL2.0-hRho194-hCNGB1a-SV40;
SEQ ID NO: 8	Sequence of the human CNGB1 gene;
SEQ ID NO: 9	Sequence of a fragment of the human rhodopsin promoter 194 bp;
SEQ ID NO: 10	Sequence of the human Abca4 protein;
SEQ ID NO: 11	Sequence of the human AIPL1 protein;
SEQ ID NO: 12	Sequence of the human BEST1 protein;
SEQ ID NO: 13	Sequence of the human CACNA1F protein;
SEQ ID NO: 14	Sequence of the human CLN3 protein;
SEQ ID NO: 15	Sequence of the human CLRNI protein;
SEQ ID NO: 16	Sequence of the human CNGA1 protein;
SEQ ID NO: 17	Sequence of the human CEP290 protein;

-continued

List of Sequences

SEQ ID NO: 18	Sequence of the human CRB1 protein;
SEQ ID NO: 19	Sequence of the human CRB2 protein;
SEQ ID NO: 20	Sequence of the human CRX protein;
SEQ ID NO: 21	Sequence of the human GPR98 protein;
SEQ ID NO: 22	Sequence of the human GUCA1A protein;
SEQ ID NO: 23	Sequence of the human GUCA1B protein;
SEQ ID NO: 24	Sequence of the human MYO7A protein;
SEQ ID NO: 25	Sequence of the human NRL protein;
SEQ ID NO: 26	Sequence of the human PDE6A protein;
SEQ ID NO: 27	Sequence of the human PDE6B protein;
SEQ ID NO: 28	Sequence of the human PRPH2 protein;
SEQ ID NO: 29	Sequence of the human PROM1 protein;
SEQ ID NO: 30	Sequence of the human RHO protein;
SEQ ID NO: 31	Sequence of the human ROM1 protein;
SEQ ID NO: 32	Sequence of the human RP1 protein;
SEQ ID NO: 33	Sequence of the human RP2 protein;
SEQ ID NO: 34	Sequence of the human RPGR protein;
SEQ ID NO: 35	Sequence of the human SAG protein;
SEQ ID NO: 36	Sequence of the human USH1C protein;
SEQ ID NO: 37	Sequence of the human USH1G protein;
SEQ ID NO: 38	Sequence of the human USH2A protein;
SEQ ID NO: 39	Sequence of the human NR2E3 protein;
SEQ ID NO: 40	Sequence of the human CNGB1 protein (next generation sequencing; NGS);
SEQ ID NO: 41	Sequence of the human CNGB1 protein (GenBank NG_016351);
SEQ ID NO: 42	Sequence of 5'ITR-hRHO promoter-CNGB1a-SV40poly A-3'ITR;
SEQ ID NO: 43	Sequence of 5'ITR-hRHO promoter-CNGB1a-SV40poly A-3'ITR (NGS);
SEQ ID NO: 44	Sequence of 5'ITR-hRHO promoter-CNGB1a-SV40poly A-3'ITR (GenBank); and
SEQ ID NO: 45	Sequence of the human RPE65 protein.

DETAILED DESCRIPTION OF THE INVENTION

[0087] Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0088] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions etc.), whether supra or infra, is hereby incorporated by reference in its entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. Some of the documents cited herein are characterized as being "incorporated by reference". In the event of a conflict between the definitions or teachings of such incorporated references and definitions or teachings recited in the present specification, the text of the present specification takes precedence.

[0089] In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be under-

stood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

Definitions

[0090] To practice the present invention, unless otherwise indicated, conventional methods of chemistry, biochemistry, and recombinant DNA techniques are employed which are explained in the literature in the field (cf., e.g., *Molecular Cloning: A Laboratory Manual*, 2nd Edition, J. Sambrook et al. eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor 1989).

[0091] In the following, some definitions of terms frequently used in this specification are provided. These terms will, in each instance of its use, in the remainder of the specification have the respectively defined meaning and preferred meanings.

[0092] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents, unless the content clearly dictates otherwise.

[0093] The term "nucleic acid" as used in this specification comprises polymeric or oligomeric macromolecules, or large biological molecules, essential for all known forms of life. Nucleic acids, which include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are made from monomers known as nucleotides. Most naturally occurring DNA molecules consist of two complementary biopolymer strands coiled around each other to form a double helix. The DNA strand is also known as polynucleotides consisting of nucleotides. Each nucleotide is composed of a nitrogen-

containing nucleobase as well as a monosaccharide sugar called deoxyribose or ribose and a phosphate group. Naturally occurring nucleobases comprise guanine (G), adenine (A), thymine (T), uracil (U) or cytosine (C). The nucleotides are joined to one another in a chain by covalent bonds between the sugar of one nucleotide and the phosphate of the next, resulting in an alternating sugar-phosphate backbone. If the sugar is deoxyribose, the polymer is DNA. If the sugar is ribose, the polymer is RNA. Typically, a polynucleotide is formed through phosphodiester bonds between the individual nucleotide monomers. In the context of the present invention the term "nucleic acid" includes but is not limited to ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and mixtures thereof such as e.g. RNA-DNA hybrids (within one strand), as well as cDNA, genomic DNA, recombinant DNA, CRNA and mRNA. A nucleic acid may consist of an entire gene, or a portion thereof, the nucleic acid may also be a miRNA, siRNA, piRNA or shRNA. miRNAs are short ribonucleic acid (RNA) molecules, which are on average 22 nucleotides long but may be longer and which are found in all eukaryotic cells, i.e. in plants, animals, and some viruses, which functions in transcriptional and post-transcriptional regulation of gene expression. miRNAs are post-transcriptional regulators that bind to complementary sequences on target messenger RNA transcripts (mRNAs), usually resulting in translational repression and gene silencing. Small interfering RNAs (siRNAs), sometimes known as short interfering RNA or silencing RNA, are short ribonucleic acid (RNA molecules), between 20-25 nucleotides in length. They are involved in the RNA interference (RNAi) pathway, where they interfere with the expression of specific genes. A short hairpin RNA (shRNA) also referred to as small hairpin RNA is an artificial RNA molecule with a tight hairpin turn that can be used to silence target gene expression via RNA interference (RNAi). Expression of shRNA in cells is typically accomplished by delivery of plasmids or through viral vectors.

[0094] The term "polynucleotide" when used in the context of the present invention, refers to a nucleic acid not restricted to a specific number of nucleotides in length.

[0095] The term "human rod photoreceptor" used in the context of the present invention refers to a special type of cells, i.e. photoreceptor cells. The retina of the human eye contains two type of photoreceptor: rods and cones. On average, there are approximately 90 million rod cells in the human retina. Rods are more sensitive than cones. However, they are not sensitive to color. They are responsible for dark-adapted, or scotopic, vision. Rods are usually found concentrated at the outer edges of the retina and are used in peripheral vision. Thus, the peripheral vision is more light-sensitive, enabling one to see dimmer objects in your peripheral vision. Rod cells are more sensitive than cone cells and are almost entirely responsible for night vision. Rods employ a sensitive photopigment called rhodopsin. Photoreceptors are highly specialized, light-sensitive neurons and designed for capturing light quanta triggering a change in the cell's membrane potential. Rod photoreceptors enable dim light vision, whereas cone photoreceptors mediate color vision and high visual acuity under brighter light conditions. Only one type of rod photoreceptor, carrying the rhodopsin visual pigment, is present in the vertebrate retina, including in mouse and human. When in its 'ready to be activated' state, each opsin molecule is covalently bound to a light-sensitive chromophore, 11-cis retinal. Upon photon

capture, the chromophore isomerizes to all-trans retinal, causing a conformational change in rhodopsin and activation to meta-rhodopsin II. This initiates the process of phototransduction, a cascade of biochemical events that culminate in closure of ionic channels in the cell membrane hyperpolarization of the photoreceptor and transmission of the signal(s) to second-order neurons in the inner retina via modulation of neurotransmitter release at the synaptic terminals. The integrity and function of photoreceptors are absolutely crucial for vision, and mutations that affect photoreceptor function or survival disrupt the phototransduction process, leading to vision loss.

[0096] The term "promoter" in the context of the present invention refers to a nucleotide sequence that comprises both elements required for transcription control including binding sites for transcriptional activator and repressor proteins and elements that initiate transcription. The binding sites for transcriptional activator and/or repressor proteins are typically located directly upstream or at the 5' end of the transcription initiation site comprised within the core promoter. Thus, RNA polymerase and the necessary transcription factors bind to the promoter sequence and initiate transcription. Promoter sequences define the direction of transcription and indicate which DNA strand will be transcribed; this strand is known as the sense strand. The promoter of the present invention transfers rod-photoreceptor specificity on a transgene that is positioned downstream, i.e. at the 3' end of the promoter.

[0097] The term "core promoter" (CP) is used herein in its ordinary sense to refer to a nucleotide region including a DNA regulatory sequence, wherein the regulatory sequence is derived from a gene which is capable of binding RNA polymerase and initiating transcription of a downstream (3'-direction) coding sequence. Thus, the core promoter is the minimal portion of the promoter required to properly initiate gene transcription and contains a binding site for RNA polymerase (RNA polymerase I, RNA polymerase II, or RNA polymerase III). The RNA polymerase binding site of the CP is approximately 25 to 35 bases upstream (5') from the transcriptional TSS. The core promoter may comprise a so-called TATA box (also called the Goldberg-Hogness box) which is a DNA sequence (*cis*-regulatory element) often found in the promoter region of genes in archaea and eukaryotes. The TATA box has the core DNA sequence 5'-TATAAA-3' or variants thereof, which is usually followed by three or more adenine bases. The TATA box is usually located 25-35 base pairs upstream of the transcription start site. The core promoter may also be TATA box-less. Genes lacking a TATA box use an initiator element or downstream core promoter instead. The core promoter also may comprise an initiator (Inr). An Inr consists of an initiator motif and is similar in function to the TATA box. The Inr element facilitates binding to transcription factor II D (TFIID).

[0098] The term "human rod photoreceptor specific promoter element" (hrPSPE) as used in the context of the present invention means a promoter element which mediates transcription of the downstream transgene only in rod cells, in particular in human rod cells. Use of the tissue-specific promoter allows a protein or a functional RNA to be expressed tissue-specifically in retina cells of the human eye. The hrPSPE only comprises parts or fragments of the naturally occurring human rod photoreceptor promoter sequence.

[0099] The term “gene” or “coding sequence” or a sequence which “encodes” a particular protein or peptide is used in the context of the invention to refer to a nucleic acid molecule that is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide in vitro or in vivo when placed under the control of appropriate regulatory sequences. The boundaries of the gene are determined by a start codon at the 5' (i.e., amino) terminus and a translation stop codon at the 3' (i.e., carboxy) terminus. The term gene includes, but is not limited to prokaryotic or eukaryotic mRNA, cDNA, genomic DNA sequences from prokaryotic or eukaryotic DNA, and even synthetic DNA sequences. A transcription termination sequence will usually be located 3' to the gene sequence.

[0100] The term “transgene” is used in the context of the present invention to refer to a gene that is removed from its natural context and placed under the expression control of a heterologous promoter. An example of a transgene of the present invention is the “rod cyclic nucleotide-gated channel beta” (CNGB1) gene which encodes the rod cyclic nucleotide-gated channel beta subunit. In further embodiments transgenes may comprise the human proteins: ATP Binding Cassette Subfamily A Member 4 (ABCA4), Aryl Hydrocarbon Receptor Interacting Protein Like 1 (AIPL1), Bestrophin 1 (BEST1), Calcium Voltage-Gated Channel Subunit Alpha 1 F (CACNA1F), Ceroid-Lipofuscinosis Neuronal 3 (CLN3), Clarin 1 (CLRN1), Cyclic Nucleotide Gated Channel Alpha 1 (CNGA1), Centrosomal Protein 290 (CEP290), Crumbs 1 (CRB1), Crumbs 2 (CRB2), Cone-Rod Homeobox (CRX), G-Protein Coupled Receptor 98 (GPR98), Guanylate Cyclase Activator 1A (GUCA1A), Guanylate Cyclase Activator 1B (GUCA1B), Myosin VIIA (MYO7A), Nuclear Receptor Subfamily 2 Group E Member 3 (NR2E3), Neural Retina Leucine Zipper (NRL), Phosphodiesterase 6A (PDE6A), Phosphodiesterase 6B (PDE6B), Peripherin 2 (PRPH2), Prominin 1 (PROM1), Rhodopsin (RHO), Retinal Outer Segment Membrane Protein 1 (ROM1), Retinitis Pigmentosa 1 Protein (RP1), Retinitis Pigmentosa 2 Protein (RP2), Retinal Pigment Epithelium Specific Protein 65 (RPE65), Retinitis Pigmentosa GTPase Regulator (RPGR), S-Antigen Visual Arrestin (SAG), Usher Syndrome Type-1C Protein (USHIC), Usher Syndrome Type-1G Protein (USH1G), Usher Syndrome Type-2A Protein (USH2A) or functional fragments or variants thereof. The amino acid sequences of particular embodiments of above proteins are indicated in SEQ ID NO: 10 to 41, and 45. Functional fragments are those fragments that maintain the function of the respective protein in normal function of the rod photoreceptor. Similarly, variants also maintain the function of the respective protein in the rod photoreceptor. Proteins with long amino acid sequences, for example human CACNA1F, CEP290, GPR98, MYO7A, RP1 and USH2A protein, which are too long to be encoded by a transgene deliverable by the respectively chosen vector system, in particular AAV vector. To fit the size limitation of AAV vectors “split vector” technologies using the development of an intein-mediated split system for gene therapy can be used. By the use of split-inteins the packaging limit of the AAV can be bypassed. Therefore, each half transgene of interest can be fused to the corresponding split-intein moiety and, only upon co-expression, the intein-mediated trans-splicing occurs and the full transgenic protein is reconstituted. Thus, it would be possible to construct two vectors encoding

fragments of the transgenic protein that would upon cotransduction assemble in the target cell into the full-length functional protein.

[0101] The term “CNGB1” as used in the context of the present application refers to either the gene or the protein encoded by the CNGB1 gene, i.e. the rod photoreceptor cGMP-gated cation channel which helps regulate ion flow into the rod photoreceptor outer segment in response to light-induced alteration of the levels of intracellular cGMP. This channel consists of two subunits, alpha and beta, with the protein encoded by this gene representing the beta subunit. Diseases associated with CNGB1 and defects in this gene include Retinitis Pigmentosa 45 and CNGB1-related Retinitis Pigmentosa. The CNGB1 subunit of cyclic nucleotide-gated channels plays an important role in both visual and olfactory signal transduction. When associated with CNGA1, it is involved in the regulation of ion flow into the rod photoreceptor outer segment (ROS), in response to light-induced alteration of the levels of intracellular cGMP.

[0102] The term “proliferation” as used herein refers to an increase in the number of cells as a result of cell growth and cell division which may lead to either increased or decreased cell proliferation. Extensive cell proliferation occurs with hyperproliferative disorders, wherein the cell division of the cells is increased in relation to normal tissue. Such disorders are characterized by an abnormal proliferation (production) i.e. overproduction of cells. Hyperproliferative disorders comprise tumor diseases. Tumor diseases may comprise benign or malignant tumors wherein malignant tumor diseases are referred to as cancer. The term hyperproliferative disorder comprises cancers as well as pre-cancerous disorders. In particular embodiments the hyperproliferative disorders are hyperproliferative disorders of rod cells, in particular retinoblastoma.

[0103] The term “amino acid” generally refers to any monomer unit that comprises a substituted or unsubstituted amino group, a substituted or unsubstituted carboxy group, and one or more side chains or groups, or analogs of any of these groups. As used herein, the term “amino acid” includes the following twenty natural or genetically encoded alpha-amino acids: alanine (Ala or A), arginine (Arg or R), asparagine (Asn or N), aspartic acid (Asp or D), cysteine (Cys or C), glutamine (Gln or Q), glutamic acid (Glu or E), glycine (Gly or G), histidine (His or H), isoleucine (Ile or I), leucine (Leu or L), lysine (Lys or K), methionine (Met or M), phenylalanine (Phe or F), proline (Pro or P), serine (Ser or S), threonine (Thr or T), tryptophan (Trp or W), tyrosine (Tyr or Y), and valine (Val or V). In cases where “X” residues are undefined, these should be defined as “any amino acid.” The structures of these twenty natural amino acids are shown in, e.g., Stryer et al., Biochemistry, 5th ed., Freeman and Company (2002). Additional amino acids, such as selenocysteine and pyrrolysine, can also be genetically coded for (Stadtman (1996) “Selenocysteine,” Annu Rev Biochem. 65:83-100 and Ibba et al. (2002) “Genetic code: introducing pyrrolysine,” Curr Biol. 12 (13): R464-R466). Amino acids can be linked by peptide bonds to form peptides or polypeptides.

[0104] In the context of the present invention, the term “peptide” refers to a short polymer of amino acids linked by peptide bonds. It has the same chemical (peptide) bonds as proteins, but is commonly shorter in length. The shortest peptide is a dipeptide, consisting of two amino acids joined by a single peptide bond. There can also be a tripeptide,

tetrapeptide, pentapeptide, etc. Typically, a peptide has a length of up to 8, 10, 12, 15, 18 or 20 amino acids. A peptide has an amino end and a carboxyl end, unless it is a cyclic peptide.

[0105] In the context of the present invention, the term “polypeptide” refers to a single linear chain of amino acids bonded together by peptide bonds and typically comprises at least about 21 amino acids. A polypeptide can be one chain of a protein that is composed of more than one chain or it can be the protein itself if the protein is composed of one chain.

[0106] The term “fragment” used herein refers to naturally occurring fragments (e.g. splice variants) as well as artificially constructed fragments, in particular to those obtained by gene-technological means. Typically, a fragment has a deletion of up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, or 300 amino acids at its N-terminus and/or at its C-terminus and/or internally as compared to the parent polypeptide, preferably at its N-terminus, at its N- and C-terminus, or at its C-terminus.

[0107] As used herein, the term “variant” is to be understood as a polypeptide or polynucleotide which differs in comparison to the polypeptide or polynucleotide from which it is derived by one or more changes in its length or sequence. The polypeptide or polynucleotide from which a polypeptide or polynucleotide variant is derived is also known as the parent polypeptide or polynucleotide. The term “variant” comprises “fragments” or “derivatives” of the parent molecule. Typically, “fragments” are smaller in length or size than the parent molecule, whilst “derivatives” exhibit one or more differences in their sequence in comparison to the parent molecule. Also encompassed are modified molecules such as but not limited to post-translationally modified proteins (e.g. glycosylated, biotinylated, phosphorylated, ubiquitinated, palmitoylated, or proteolytically cleaved proteins) and modified nucleic acids such as methylated DNA. Also mixtures of different molecules such as but not limited to RNA-DNA hybrids, are encompassed by the term “variant”. Typically, a variant is constructed artificially, preferably by gene-technological means, whilst the parent protein or polynucleotide is a wild-type protein or polynucleotide, or a consensus sequence thereof. However, also naturally occurring variants are to be understood to be encompassed by the term “variant” as used herein. Further, the variants usable in the present invention may also be derived from homologs, orthologs, or paralogs of the parent molecule or from artificially constructed variant, provided that the variant exhibits at least one biological activity of the parent molecule, i.e. is functionally active.

[0108] In particular, the term “peptide variant”, or “polypeptide variant” is to be understood as a peptide, polypeptide, or protein which differs in comparison to the peptide, polypeptide, or protein from which it is derived by one or more changes in the amino acid sequence. The peptide, polypeptide, or protein, from which a peptide, polypeptide, or protein variant is derived, is also known as the parent peptide, polypeptide, or protein. Further, the variants usable in the present invention may also be derived from homologs, orthologs, or paralogs of the parent peptide, polypeptide, or protein or from artificially constructed variant, provided that the variant exhibits at least one biological activity of the parent peptide, polypeptide, or protein. The changes in the amino acid sequence may be amino acid exchanges, inser-

tions, deletions, N-terminal truncations, or C-terminal truncations, or any combination of these changes, which may occur at one or several sites. A peptide, polypeptide, or protein variant may exhibit a total number of up to 200 (up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200) changes in the amino acid sequence (i.e. exchanges, insertions, deletions, N-terminal truncations, and/or C-terminal truncations). The amino acid exchanges may be conservative and/or non-conservative. Alternatively or additionally, a “variant” as used herein, can be characterized by a certain degree of sequence identity to the parent peptide, polypeptide, or protein from which it is derived. More precisely, a peptide, polypeptide, or protein variant in the context of the present invention exhibits at least 80% sequence identity to its parent peptide, polypeptide, or protein. The sequence identity of peptide, polypeptide, or protein variants is over a continuous stretch of 20, 30, 40, 45, 50, 60, 70, 80, 90, 100 or more amino acids.

[0109] The “percentage of sequences identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the sequence in the comparison window can comprise additions or deletions (i.e. gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0110] The term “identical” in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences or subsequences that are the same, i.e. comprise the same sequence of nucleotides or amino acids. Sequences are “substantially identical” to each other if they have a specified percentage of nucleotides or amino acid residues that are the same (e.g., at least 70%, at least 75%, at least 80, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity over the aligned region), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. These definitions also refer to the complement of a test sequence. Accordingly, the term “at least 80% sequence identity” is used throughout the specification with regard to polypeptide and polynucleotide sequence comparisons. This expression preferably refers to a sequence identity of at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the respective reference polypeptide or to the respective reference polynucleotide.

[0111] The term “sequence comparison” refers to the process wherein one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference

sequences are entered into a computer, if necessary subsequence coordinates are designated, and sequence algorithm program parameters are designated. Default program parameters are commonly used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities or similarities for the test sequences relative to the reference sequence, based on the program parameters. In case where two sequences are compared and the reference sequence is not specified in comparison to which the sequence identity percentage is to be calculated, the sequence identity is to be calculated with reference to the longer of the two sequences to be compared, if not specifically indicated otherwise. If the reference sequence is indicated, the sequence identity is determined on the basis of the full length of the reference sequence indicated by SEQ ID, if not specifically indicated otherwise.

[0112] “Operably linked” as used in the context of the present invention refers to an arrangement of elements, wherein the components so described are configured so as to perform their usual function. A nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For example, a promoter is operably linked to one or more transgenes, if it affects the transcription of the one or more transgenes. Further, control elements operably linked to a coding sequence are capable of effecting the expression of the coding sequence. The control elements need not be contiguous with the coding sequence, so long as they function to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between a promoter sequence and the coding sequence and the promoter sequence can still be considered “operably linked” to the coding sequence.

[0113] The term “polyadenylation signal” (PAS) as used herein refers to a sequence involved in the process of mature messenger RNA (mRNA) production for translation. It, therefore, forms part of the larger process of gene expression. The process of polyadenylation begins as the transcription of a gene terminates. The 3'-most segment of the newly made pre-mRNA is first cleaved off by a set of proteins; these proteins then synthesize the poly (A) tail at the RNA's 3' end. In some genes these proteins add a poly(A) tail at one of several possible sites. Therefore, polyadenylation can produce more than one transcript from a single gene (alternative polyadenylation), similar to alternative splicing. The poly(A) tail is important for the nuclear export, translation, and stability of mRNA. The tail is shortened over time, and, when it is short enough, the mRNA is enzymatically degraded. However, in a few cell types, mRNAs with short poly(A) tails are stored for later activation by re-polyadenylation in the cytosol. The PAS of the present invention may comprise a nucleic acid encoding a short Simian-Virus 40 (SV40) poly adenylation signal (SV 40 PAS). This modification of the polynucleotide has the advantage that expression of the gene of interest, for example the hCNGB1 in photoreceptor cells is significantly enhanced. The long-term expression that is achieved by the inclusion of SV40 PAS qualifies the polynucleotide for its use as an active gene therapy agent. In particular, the PAS can comprise the nucleic acid sequence according to SEQ ID NO: 4.

[0114] As used in this specification the term “vector”, also referred to as an expression construct, is usually a virus designed for protein expression in cells. The term “vector” refers to a protein or a polynucleotide or a mixture thereof

which is capable of being introduced or of introducing proteins and/or nucleic acids comprised therein into a cell. Examples of vectors include but are not limited to plasmids, cosmids, phages, viruses or artificial chromosomes. In particular, a vector is used to transport the promoter and transgene of the invention into a suitable host cell. Vectors may contain “replicon” polynucleotide sequences that facilitate the autonomous replication of the vector in a host cell. Foreign DNA is defined as heterologous DNA, which is DNA not naturally found in the host cell, which, for example, replicates the vector molecule, encodes a selectable or screenable marker, or encodes a transgene. Once in the host cell, the vector can replicate independently of or coincidental with the host chromosomal DNA, and several copies of the vector and its inserted DNA can be generated. In addition, the vector can also contain the necessary elements that permit transcription of the inserted DNA into an mRNA molecule or otherwise cause replication of the inserted DNA into multiple copies of RNA. Vectors may further encompass “expression control sequences” that regulate the expression of the gene of interest. Typically, expression control sequences are polypeptides or polynucleotides such as but not limited to promoters, enhancers, silencers, insulators, or repressors. In a vector comprising more than one polynucleotide encoding for one or more gene products of interest, the expression may be controlled together or separately by one or more expression control sequences. More specifically, each polynucleotide comprised on the vector may be controlled by a separate expression control sequence or all polynucleotides comprised on the vector may be controlled by a single expression control sequence. Polynucleotides comprised on a single vector controlled by a single expression control sequence may form an open reading frame. Some expression vectors additionally contain sequence elements adjacent to the inserted DNA that increase the half-life of the expressed mRNA and/or allow translation of the mRNA into a protein molecule. Many molecules of mRNA and polypeptide encoded by the inserted DNA can thus be rapidly synthesized.

[0115] The term “AAV vector” as used in the context of the present invention refers to a complete virus particle, i.e., including a linear, single-stranded AAV nucleic acid genome associated with an AAV capsid protein coat. In this regard, single-stranded AAV nucleic acid molecules of either complementary sense (i.e., “sense” or “antisense” strands) can be packaged into any one AAV virion; both strands are equally infectious. The AAV vector of the present invention may also be an infectious and replication-defective virus composed of an AAV protein shell, encapsidating a heterologous DNA molecule of interest (e.g., hCNGB1) which may be flanked on both sides by an AAV ITR. An exemplary AAV 5' ITR has the nucleic acid sequence according to SEQ ID NO: 5 and an exemplary AAV 3' ITR has the nucleic acid sequence of the complement of SEQ ID NO: 6. An AAV vector of the present invention may be produced in a suitable host cell which has had an AAV vector, AAV helper functions and accessory functions introduced therein. In this manner, the host cell is rendered capable of encoding AAV polypeptides that are required for packaging the AAV genome (i.e., containing a recombinant nucleotide sequence of interest) into recombinant virion particles for subsequent gene delivery.

[0116] Various naturally occurring serotypes of adeno-associated virus (AAV), including 12 human serotypes

(AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12) and several serotypes from nonhuman primates have been identified. The different AAV serotypes also differ in their genome sequence, e.g. in the sequence of the inverted terminal repeats (ITRs) or the sequence encoding the capsid. The term “AAV genome” as used in the context of the present invention refers to any nucleic acid sequence derived from an adeno-associated virus serotype, including, without limitation, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-9, AAV-7, etc. AAV genome can have one or more of the AAV wild-type genes deleted in whole or in part, preferably the Rep and/or Cap genes, but retain functional flanking inverted terminal repeat (“ITR”) sequences. Functional ITR sequences are generally necessary for the rescue, replication and packaging of the AAV genome. Thus, an AAV genome is defined herein to include at least those sequences required in cis for replication and packaging (e.g., functional ITRs) of the virus. The ITRs need not be the wild-type nucleotide sequences, and may be altered (e.g., by the insertion, deletion or substitution of nucleotides) so long as the sequences provide for functional rescue, replication and packaging. The ITRs may comprise sequences according to SEQ ID NO: 5 and/or SEQ ID NO: 6.

[0117] “Antibodies” as used in the context of the present invention are glycoproteins belonging to the immunoglobulin superfamily; the terms antibody and immunoglobulin are often used interchangeably. An antibody refers to a protein molecule produced by plasma cells and is used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. The antibody recognizes a unique part of the foreign target, its antigen.

[0118] The term “antibody binding fragment” as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. Examples of binding fragments encompassed within the term “antibody binding fragment” include a fragment antigen binding (Fab) fragment, a Fab' fragment, a F(ab')₂ fragment, a heavy chain antibody, a single-domain antibody (sdAb), a single-chain fragment variable (scFv), a fragment variable (Fv), a V_H domain, a V_L domain, a single domain antibody, a nanobody, an IgNAR (immunoglobulin new antigen receptor), a di-scFv, a bispecific T-cell engager (BiTEs), a dual affinity re-targeting (DART) molecule, a triple body, a diabody, a single-chain diabody, an alternative scaffold protein, and a fusion protein thereof.

[0119] The term “pharmaceutical composition” as used in the present application include the formulation of the active compound or ingredient, i.e. the polynucleotide, the plasmid and/or the vector of the present invention and refers to a substance and/or a combination of substances being used for the identification, prevention, maintenance or treatment of a tissue status or disease. The pharmaceutical composition is formulated to be suitable for administration to a patient in order to prevent and/or treat disease and/or maintain the physiological state. Further a pharmaceutical composition refers to the combination of an active agent with a carrier, inert or active, making the composition suitable for therapeutic use. Pharmaceutical compositions can be formulated for oral, parenteral, topical, inhalative, rectal, sublingual, transdermal, subcutaneous or vaginal application routes according to their chemical and physical properties. Pharmaceutical compositions comprise solid, semisolid, liquid, transdermal therapeutic systems (TTS). Solid compositions

are selected from the group consisting of tablets, coated tablets, powder, granulate, pellets, capsules, effervescent tablets or transdermal therapeutic systems. Also comprised are liquid compositions, selected from the group consisting of solutions, syrups, infusions, extracts, solutions for intravenous application, solutions for infusion or solutions of the carrier systems of the present invention. Semisolid compositions that can be used in the context of the invention comprise emulsion, suspension, creams, lotions, gels, globules, buccal tablets and suppositories.

[0120] “Pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0121] A “carrier” as referred to within this specification comprises a composition capable of delivering a reagent to a desired compartment, e.g. a certain cell type, of the human body and is useful for providing and controlling release of drugs after being administered by the chosen administration route and scheme.

[0122] As used in herein the route of administration describes the uptake of a xenobiotic in the human body and is classified by the location at which the xenobiotic is applied. The pharmaceutical composition comprising the polynucleotide and/or the viral vector, in particular in the method of treatment, is selected from intraocular, intrabulbar, intravitreal or subretinal

[0123] The term “disease” refers to an abnormal condition, especially an abnormal medical condition such as an illness or injury, wherein a cell, a tissue, an organ, or an individual is not able to efficiently fulfil its function anymore. Typically, but not necessarily, a disease is associated with specific symptoms or signs indicating the presence of such disease. The presence of such symptoms or signs may thus, be indicative for a cell, a tissue, an organ, or an individual suffering from a disease. An alteration of these symptoms or signs may be indicative for the progression of such a disease. A progression of a disease is typically characterised by an increase or decrease of such symptoms or signs which may indicate a “worsening” or “bettering” of the disease. The “worsening” of a disease is characterised by a decreasing ability of a cell, tissue, organ or individual/patient to fulfil its function efficiently, whereas the “bettering” of a disease is typically characterised by an increase in the ability of a cell, tissue, an organ or an individual/patient to fulfil its function efficiently. A cell, a tissue, an organ or an individual being “susceptible” to a disease is in a healthy state but especially vulnerable to the emergence of a disease, e.g. due to genetic predisposition, lacking vaccination, poorly developed or immature immunity, poor nutritional status, or the like.

[0124] A “disease of the retina” in the context of the present invention refers but is not limited to any kind of retinal degeneration. Retinal dystrophies, belonging to the group of retinal degenerations, are a broad group of genetic retinal disorders of varying severity and with differing inheritance patterns. A retinal dystrophy belongs to the group of pigmentary retinopathies. Retinitis Pigmentosa is the most common retinal dystrophy and 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

the condition of the disease progresses, patients suffering the disease lose their far peripheral visual field and eventually central vision as well. The retinal degeneration may be associated with a genetic mutation, substitution, and/or deletion. The retinal degeneration is selected from the group consisting of night blindness, blindness, retinal degeneration, retinal dystrophy and Retinitis Pigmentosa. The Retinitis Pigmentosa can be CNGB1-linked Retinitis Pigmentosa or Retinitis Pigmentosa type 45 (RP45).

[0125] Other examples of retinal disorders include, without limitation, RPE65-mediated retinal disorders, macular degeneration (e.g., age-related macular degeneration), inherited juvenile macular degeneration (e.g., Stargardt disease), Rod-cone dystrophy, Cone-rod dystrophy, Oguchi disease, Malattia Leventinese, and others.

[0126] As used herein, "CNGB1-linked Retinitis Pigmentosa" refers to a class of diseases involving progressive degeneration of the retina, typically starting in the mid-periphery and advancing toward the macula and fovea (Ferrani et al. (2011) *Curr. Genomics* 12 (4): 238). Typical phenotypic symptoms include night blindness followed by decreasing visual fields, leading to tunnel vision and eventually legal blindness or, in many cases, complete blindness. On the cellular level, this correlates with a predominantly affected rod photoreceptor system. In later stages, the disease may further affect the cone photoreceptor eventually causing complete blindness. The diseased photoreceptors undergo apoptosis, which is reflected in reduced outer nuclear layer thickness within the retina, as well as in lesions and/or retinal pigment deposits in the fundus. Patients may lose a significant portion of their photoreceptors before experiencing loss of visual acuity. Clinical phenotypical hallmarks include, but are not limited to: (i) an abnormal fundus with bone-spicule deposits and attenuated retinal vessels; (ii) abnormal, diminished or absent a- and b-waves in the electroretinogram (ERG); and (iii) reduced visual field. Symptoms typically start in the early teenage years and severe visual impairment occurs by ages 40 to 50 years.

[0127] An example of a genetic variation that is known to be pathogenic for Retinitis Pigmentosa is a homozygous splice site mutation at the donor site of exon 32 of the CNGB1 gene (3444+1G-A) that results in a frameshift and truncation of the last 28 amino acids. Another example of a genetic variation that is known to be pathogenic for Retinitis Pigmentosa is a homozygous 2978G-T transversion in exon 30 of the CNGB1 gene that is predicted to result in a Glycine to Valine substitution at position 993 of the protein (G993V). Glycine 993 of CNGB1 is a conserved residue. Another example of a genetic variation that is known to be pathogenic for Retinitis Pigmentosa is a homozygous c. 1589C-G transversion in the CNGB1 gene, resulting in a proline to arginine substitution at position 530 of the CNGB1 protein (P530R). Another known genetic variation that is pathogenic for Retinitis Pigmentosa includes a c.2128C-T change in the CNGB1 gene, resulting in a Glutamine to Termination substitution at position 710 of the CNGB1 protein (Q710Stop). Other genetic variations that are pathogenic for Retinitis Pigmentosa can be found in the Online Mendelian Inheritance in Man (OMIM) database, and the ClinVar database maintained by the National Center for Biotechnology Information, incorporated herein by reference in their entirety for all purposes.

[0128] CNGB1-linked Retinitis Pigmentosa can be identified with methods known in the art to detect one or more

phenotypic signs described herein, and/or one or more genetic variations in the CNGB1 gene. Any genetic variation that results in a change in a conserved residue of CNGB1 may be pathogenic for Retinitis Pigmentosa.

[0129] As used herein, "treat," "treating," "treatment," or "therapy" of a disease or disorder means accomplishing one or more of the following: (a) reducing the severity of the disorder; (b) limiting or preventing development of symptoms characteristic of the disorder(s) being treated; (c) inhibiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting or preventing recurrence of the disorder(s) in an individual that has previously had the disorder(s); and (e) limiting or preventing recurrence of symptoms in individuals that were previously symptomatic for the disorder(s).

EMBODIMENTS

[0130] In the following different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

[0131] In gene therapeutic and/or gene corrective therapy approaches in which nucleic acids are introduced into cells, e.g., to augment expression, replace a defective gene, and/or inhibit expression of a defective gene, it is generally desirable that all transgenic elements are small. Nevertheless, it is often difficult to identify transgenic elements that can be reduced in size without negatively effecting or losing their activity in the in vivo situation. Generally, in vitro experiments are not suitable to indicate the in vivo behaviour of the elements making the determination of possible size reductions difficult and unpredictable. In the work leading to the present invention, it was surprisingly shown that a short part of the human rod promoter, i.e. an element smaller than 200 bases, could transfer rod-photoreceptor specific expression on transgenes operably linked to this promoter element in vivo. When the promoter element defined herein was used in an in vivo setting, stable integration and expression of a transgene was observed. The expression level was suitable to improve the visual capabilities of the test animals transfected with an adeno-associated virus vector comprising the transgene.

[0132] This surprising finding provides inter alia the following advantages over the art: (i) reduction of the size of the construct that is introduced into a cell, (ii) an increase of the packaging efficiency of the transgene into viral vectors, (iii) a decrease of the chance that recombination events occur in vivo, (iv) increase the efficiency of introduction of the transgene into the target cells, in particular into the nucleus of the target cell; (v) a suitable expression level in a human patient to treat rod associated diseases, (vi) preservation and/or improvement of retinal function in vivo and/or (vii) preservation and/or improvement of vision in vivo.

[0133] In a first aspect the present invention relates to a polynucleotide comprising in this order:

[0134] a) promoter comprising a human rod photoreceptor-specific promoter element (hRSPPE) comprising, consisting essentially of or consisting of the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0135] b) at least one transgene (TG) operably linked to the promoter of a);

[0136] wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1 and wherein the length of the promoter is in particular 350 bases or less. The promoter that provides one or more of above advantages may also be longer than 350 bases, e.g. 600 bp or less, 500 bp or less, or 400 bp or less. In particular embodiments the promoter has a length of 300 bases or less, in other embodiments it has a length of 300 bases or less, in other embodiments it has a length of 250 bases or less, in other embodiments it has a length of 200 bases or less, in other embodiments it has a length of 194 bases or less.

[0137] In an attempt to minimize the overall length of heterologous bases introduced into a patient, the polynucleotide comprises no other human rod promoter and/or gene nucleotide sequence other than expressly defined in a) above.

[0138] The indicated nucleotides are to be preserved in variants of SEQ ID NO: 1 since the present inventors believe that these nucleotide sequences are instrumental in conferring rod photoreceptor-specific expression to the hRPSPE. Outside the putative transcription factor binding sequences (TFBs) 1 or more nucleotides can be mutated or inserted. If nucleotides are inserted, the insertion of 1 to 70 nucleotides is an advantageous number with multiples of seven being particularly advantageous since this number maintains the relative rotational positions of the TFBs. It is, however advantageous, if the distance between the TFBs is not altered to avoid rotational displacement of the transcription factors binding to the promoter element. Thus, within the 99 bp long sequence according to SEQ ID NO: 1 it is permissible to mutate one or more nucleotides at positions 1 to 5, 14 to 31, 41 to 69, 84 to 86 and 95 to 99. Thus, maximally 50 nucleotides may be mutated within SEQ ID NO: 1. Accordingly, particular variants comprise between 1 to 50 mutations, i.e. 1, 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, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50. Other particular variants comprise between 5 to 40, between 10 to 30 or between 20 to 25 mutations. The promoter comprising a variant of the hRPSPE shows a rod photoreceptor-specific expression level as a promoter comprising the hRPSPE comprising the nucleic acid sequence according to SEQ ID NO: 1, preferably a promoter consisting of nucleotides 155 to 350 or 155 to 348 of SEQ ID NO: 2. It is advantageous, if the variant shows at least 10% of the expression level of a promoter consisting of nucleotides 155 to 350 or 155 to 348 of SEQ ID NO: 2. Other advantageous expression levels are at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 100%. Different expression levels may be advantageous depending on the respective therapeutic approach, in particular lower expression levels than those obtained with a promoter consisting of nucleotides 155 to 350 of SEQ ID NO: 2 may be advantageous, if a higher expression level of the transgene overcompensates the deficiency or leads to deleterious effect.

[0139] It is also envisioned that the polynucleotide of the invention comprises two or more transgenes operably linked to the promoter of a). In such a situation separate expression

of the two or more transgenes can be obtained by inserting a nucleotide sequence allowing separate translation of the two transgenes, e.g. encoding an Internal Ribosomal Entry Site (IRES), between the two transgenes.

[0140] In an embodiment of the first aspect of the invention the 5' end of the hRPSPE comprised in the promoter of a) is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 290 to 310 of SEQ ID NO: 2 or variants thereof. In a particular embodiment the 5' end of the hRPSPE is at one of the following nucleic acid positions: 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 145, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159 or 160 of SEQ ID NO: 2. In a particular embodiment the 3' end of the hRPSPE is at one of the following nucleic acid positions: 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, or 310 of SEQ ID NO: 2. Thus, according to particular embodiments the hRPSPE comprised in the promoter of a) spans nucleic acid positions 1 to 310, 10 to 309, 20 to 308, 30 to 307, 40 to 306, 50 to 305, 60 to 304, 70 to 303, 80 to 302, 90 to 301, 100 to 300, 110 to 299, 120 to 298, 130 to 297, 140 to 296, 150 to 295, 151 to 294, 152 to 293, 153 to 292, 154 to 291 or 155 to 290 of SEQ ID NO: 2. The term "variants of hRPSPE" has the meaning outlined above. Thus, variants of the fragments indicated in this paragraph have the respectively indicated 5' and 3' end and may additionally comprise mutations outside the sequences indicated above with reference to SEQ ID NO: 1.

[0141] In an embodiment of the first aspect of the invention the CP comprises a TATA-box and/or an initiator (Inr). In a particular embodiment the TATA-box and Inr of the human rho promoter. In a particular embodiment the 5' end of the CP comprised in the promoter of a) is at nucleotide position 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314 of SEQ ID NO: 2 and the 3' end is at nucleic acid position from 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 342, 343, 344, 345, 346, 347, 348, 349 or 350 of SEQ ID NO: 2. Thus, according to particular embodiments the CP comprised in the promoter of a) spans nucleic acid positions 300 to 350, 301 to 350, 302 to 350, 303 to 350, 304 to 349, 305 to 349, 306 to 349, 307 to 349, 308 to 348, 309 to 348, 310 to 348, 311 to 348, 312 to 348, 313 to 348, or 314 to 348 of SEQ ID NO: 2. In an embodiment of the first aspect of the invention the 5' end of the promoter is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 340 to 350 of SEQ ID NO: 2 or variants thereof. In a particular embodiment the 5' end of the promoter is at one of the following nucleic acid positions: 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 342, 343, 344, 345, 346, 347, 348, 349 or 350 of SEQ ID NO: 2. Thus, according to particular embodiments the promoter of a) spans nucleic acid positions 1 to 350, 10 to 350, 20 to 350, 30 to 350, 40 to 350, 50 to 350, 60 to 350, 70 to 350, 80 to 350, 90 to 349, 100 to 349, 110 to 349, 120 to 349, 130 to 349, 140 to 348, 150 to 348, 151 to 348, 152 to 348, 153 to 348, 154 to 348 or 155 to 348 of SEQ ID NO: 2. In a particular embodiment the promoter comprises, essentially consists or consists of SEQ ID NO: 9.

[0142] In an embodiment of the first aspect of the invention the transgene comprises, essentially consists or consists

of a nucleic acid encoding a protein that maintains or improves the physiological function of rod cells and/or inhibits proliferation of rod cells. Typically, such genes are naturally expressed in healthy rod cells. The skilled person is aware of a large number of genes expressed in rod cells that are involved in the physiological function of rod cells. This function comprises inter alia, the detection of photons and the generation of nerve pulses in response to the detection of one or more photons.

[0143] In an embodiment of the first aspect of the invention the transgene:

[0144] (i) comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, AIPL1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MYO7A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USH1C, USH1G, USH2A or functional fragments or variants thereof; a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof; and/or a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof; or

[0145] (ii) comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, preferably a toxin; a prodrug converting enzyme, e.g. thymidine kinase; cell cycle inhibitors, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2; comprises a mRNA encoding a dominant negative mutant of the cell cycle inhibitor thereof; and/or comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor thereof.

[0146] Some diseases of rod cells are characterized by recessive mutations in one or more of the genes that maintain or improve the function of rod cells or that prevent hyperproliferation, in particular genes encoding the proteins indicated in (i) or (ii). In such cases it is often sufficient in order to cure or at least to ameliorate the disease, if a transgene encoding the functional protein is introduced into the rod cell, in particular using a vector. If the disease is however, caused by a dominant negative mutation the provision of a transgene encoding the functional protein or functional fragment thereof, is often not sufficient to cure or ameliorate the disease. In such cases it is preferred that the expression or function of the dominant negative mutant protein is reduced in the cell, i.e. is knocked-down. Such knock-down may be affected by expressing a transgene encoding an inhibitory RNA that specifically reduces expression of the dominant negative mutant protein or by one or more transgenes encoding an antibody or fragment thereof that specifically binds to and inactivates the dominant negative mutant protein and does not significantly bind to the corresponding functional protein. The skilled person is well aware how to design such inhibitory RNA specific to the mRNA encoding the respective dominant negative mutant protein. Similarly, the skilled person knows how to generate antibodies that specifically bind only to the dominant negative mutant protein and not to the wild-type protein. In its natural form antibodies comprise two different protein chains. Thus, if both protein chains of an antibody are expressed to knock-down a protein, then one transgene may comprise nucleotides encoding the light chain linked through an Internal Ribosomal Entry Site (IRES) to another

transgene encoding the heavy chain. In this way both antibody chains can be expressed from a single mRNA. It is apparent to the skilled person that the order of light and heavy chain can be reversed without affecting expression of the antibody within the rod cell. Alternatively, a single chain antibody may be encoded by the transgene.

[0147] In a particular embodiment the diseases to be treated are characterized by dominant negative mutations in one or more of the genes that maintain or improve the function of rod cells or that promote hyperproliferation, in particular in one or more of AIPL1, BEST1, NR2E3, NRL, PRPH2, RHO, ROM1, and/or RP1. In this case it is preferred that expression and/or function of the proteins encoded by the dominant negative mutant gene is knocked down and that a transgene encoding the functional protein or a functional fragment thereof. If size limitations of the respective vector allows, it is preferred that the polynucleotide comprises both a transgene encoding the functional protein or a functional fragment thereof and a transgene encoding an inhibitory RNA or an inhibitory antibody or fragment thereof. If both transgenes encode proteins they can be under the control of the same promoter and use, e.g. an IRES sequence between the two transgenes or if one transgene encodes a protein and the other an inhibitory RNA each transgene may be operably linked to a separate promoter according to i) of the first aspect of the invention.

[0148] The term "functional fragments" refers to N- and/or C-terminal deletions of the respective protein that does not lead to a loss of the rod cell specific function of the respective proteins. The term "variants thereof" refers to proteins that have at least 70% sequence identity to the respectively indicated human wild-type protein, in particular the proteins according to SEQ ID NO: 3, 10 to 41, and 45. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 3. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 10. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 11. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 12. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 13. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 14. In a particular embodiment the variant has at least 70%

and more particularly 95% sequence identity to SEQ ID NO: 40. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 41. In a particular embodiment the variant has at least 70% sequence identity, particularly 75% sequence identity, more particularly 80% sequence identity, more particularly 85% sequence identity, more particularly 90% sequence identity, and more particularly 95% sequence identity to SEQ ID NO: 45.

[0149] Functional fragments of the above indicated proteins are those fragments that maintain the function of the respective protein in normally functioning rod photoreceptor, in particular in detecting photons and/or transmitting the information on the detection of photons. Similarly, variants also maintain the function of the respective protein in normally functioning rod photoreceptors.

[0150] In an embodiment of the first aspect of the invention the hCNGB1 encoded by the transgene comprises an amino acid sequence according to SEQ ID NO: 3 or variants thereof. In an embodiment of the first aspect of the invention the hCNGB1 encoded by the transgene comprises an amino acid sequence according to SEQ ID NO: 40 or variants thereof. In an embodiment of the first aspect of the invention the hCNGB1 encoded by the transgene comprises an amino acid sequence according to SEQ ID NO: 41 or variants thereof.

[0151] In an embodiment of the first aspect of the invention the polynucleotide comprises one or more further nucleotide sequence elements selected from the group consisting of:

[0152] (i) a polyadenylation signal (pA); and/or

[0153] (ii) one or two inverted terminal repeat (ITR) sequences; and/or

[0154] (iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adeno-associated virus, an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

[0155] Viral nucleotide sequences that are essential to forming an infectious viral vector of the respective type are well known in the art. Any of these elements may be comprised in the polynucleotide of the first aspect of the invention.

[0156] In an embodiment of the first aspect of the invention the polyadenylation signal comprises, essentially consists or consists of a Simian-Virus 40 PAS.

[0157] In an embodiment of the first aspect of the invention the polyadenylation signal comprises, essentially consists or consists of a nucleic acid according to SEQ ID NO: 4 or functional variants thereof.

[0158] In an embodiment of the first aspect of the invention the ITR sequence is an adeno-associated virus (AAV) ITR.

[0159] In an embodiment of the first aspect of the invention the AAV ITR is of an AVV serotype 2, 5, 8 or 9.

[0160] In an embodiment of the first aspect of the invention the promoter and the transgene are flanked at their 5' with a L-ITR and at their 3' end with a R-ITR. In one particular embodiment the elements are arranged in 5' to 3' direction in the following order: L-ITR-promoter-transgene-R-ITR, L-ITR-transgene-promoter-R-ITR, R-ITR-pro-

moter-transgene-L-ITR, or R-ITR-transgene-promoter-L-ITR. In another particular embodiment the elements are arranged in 5' to 3' direction in the following order: L-ITR-promoter-transgene-PAS-R-ITR, L-ITR-PAS-transgene-promoter-R-ITR, R-ITR-promoter-transgene-PAS-L-ITR, or R-ITR-PAS-transgene-promoter-L-ITR.

[0161] In an embodiment of the first aspect of the invention the L-ITR comprises, essentially consists or consists of a sequence according to SEQ ID NO: 5 or variants thereof and/or the R-ITR comprises, essentially consists or consists of a sequence according to SEQ ID NO: 6 or variants thereof.

[0162] Depending on the viral vector used the length of the nucleic acid that can be efficiently packaged in the viral vector greatly varies. Some vectors like adenoviral vectors can accommodate large nucleic acid inserts while others, like adeno-virus associated vectors efficiently package polynucleotides that have a length of 4700 bases or less. Irrespective of the nucleic acid packaging ability of a vector it is generally desirable to minimize the length of any heterologous nucleic acid introduced into a patient, in particular if the heterologous nucleic acid is stably introduced into the genome. Accordingly, in an embodiment of the first aspect of the invention the total length of the polynucleotide is 5200 bases or less, in particular 5100 bases or less, in particular 5000 bases or less, in particular 4900 bases or less, in particular 4800 bases or less, and more particular 4700 bases or less.

[0163] In a particular embodiment of the first aspect of the invention the polynucleotide comprises, essentially consists in 5' to 3' direction of the following nucleic acids elements: L-ITR-promoter-transgene-SV40 PAS-R-ITR, L-ITR-SV40 PAS-transgene-promoter-R-ITR, R-ITR-promoter-transgene-SV40 PAS-L-ITR, or R-ITR-SV40 PAS-transgene-promoter-L-ITR, wherein the transgene comprises, essentially comprises or consists of a nucleotide sequence encoding the hCNGB1 protein of SEQ 'ID NO: 3, the PAS comprises, essentially comprises or consists of the nucleotide sequence of SEQ ID NO: 4, the L-ITR comprises, essentially comprises or consists of the nucleotide sequence SEQ ID NO: 5, the R-ITR comprises, essentially comprises or consists of the nucleotide sequence SEQ ID NO: 6, and the promoter comprises, essentially comprises or consists of the nucleotide sequence that spans nucleotides 155 to 348 of SEQ ID NO: 1. Also in this embodiment the total length of the polynucleotide is 5200 bases or less, in particular 5100 bases or less, in particular 5000 bases or less, in particular 4900 bases or less, in particular 4800 bases or less, and more particular 4700 bases or less.

[0164] A second aspect of the invention relates to a plasmid comprising the polynucleotide of the first aspect of the invention. A plasmid is a circular DNA that can be replicated in bacteria.

[0165] In an embodiment of the second aspect of the invention the plasmid comprises, essentially consists or consists of a nucleic acid sequence according to SEQ ID NO: 7 or variants thereof. In an embodiment of the second aspect of the invention the plasmid comprises, essentially consists or consists of a nucleic acid sequence according to SEQ ID NO: 42 or variants thereof. In an embodiment of the second aspect of the invention the plasmid comprises, essentially consists or consists of a nucleic acid sequence according to SEQ ID NO: 43 or variants thereof. In an embodiment of the second aspect of the invention the plasmid comprises,

essentially consists or consists of a nucleic acid sequence according to SEQ ID NO: 44 or variants thereof.

[0166] A third aspect of the invention relates to a viral vector comprising the polynucleotide of the first aspect of the invention. In a particular embodiment the viral vector is an AAV, an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector. In a particular embodiment the viral vector is an AAV.

[0167] In an embodiment of the third aspect of the invention the virus is selected from the group consisting of AAV2, AAV5, AAV8, AVV9 or variants thereof.

[0168] A fourth aspect of the invention relates to the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention for use as a medicament.

[0169] A fifth aspect of the invention relates to a pharmaceutical composition comprising the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention, and a pharmaceutically acceptable carrier.

[0170] A sixth aspect of the invention relates to the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention for use in the therapy of a disease of the retina.

[0171] Advantageously the polynucleotide according to the first aspect of the invention, the plasmid of the second aspect of the invention and/or the viral vector according to the third aspect of the invention can be used in diseases that are associated with a loss of or aberrant rod receptor function, in particular retinal degeneration or hyperproliferation of rod cells, in particular retinoblastoma. While tissue specific expression of the transgene is obtained through the promoter of the polynucleotide of the first aspect of the invention and, thus systemic administration of the therapeutic polynucleotide, plasmid or viral vector can be systemic without and will still be limited to rod receptors it is more efficient, if the therapeutic polynucleotide, plasmid or viral vector of the invention is directly administered to the eye of the patient. Accordingly, particular routes of administration are selected from intraocular, intrabulbar, intravitreal or subretinal administration.

[0172] In an embodiment of the sixth aspect of the invention the retinal degeneration is associated with a genetic mutation, substitution, and/or deletion.

[0173] In an embodiment of the sixth aspect of the invention the retinal degeneration is associated with a genetic mutation, substitution, and/or deletion.

[0174] In an embodiment of the sixth aspect of the invention the degeneration is selected from the group consisting of night blindness, blindness, retinal degeneration, retinal dystrophy and retinitis pigmentosa.

[0175] In an embodiment of the sixth aspect of the invention the retinitis pigmentosa is CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45).

[0176] A seventh aspect of the invention relates to a polynucleotide comprising in this order:

[0177] a) a human rhodopsin promoter comprising the nucleic acid sequence according to SEQ ID NO: 9 or variants thereof; and

[0178] b) at least one transgene (TG) operably linked to the promoter of a).

[0179] In an embodiment of the seventh aspect of the invention, the transgene comprises a nucleic acid encoding a protein that maintains or improves a physiological function of rods.

[0180] In an embodiment of the seventh aspect of the invention the transgene:

[0181] (i) comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, APL1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MYO7A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USH1C, USH1G, USH2A or functional fragments or variants thereof; a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof; and/or a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof, or

[0182] (ii) comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, preferably a toxin; a prodrug converting enzyme, e.g. thymidine kinase; cell cycle inhibitors, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2; comprises a mRNA encoding a dominant negative mutant of the cell cycle inhibitor thereof; and/or comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor thereof.

[0183] In an embodiment of the seventh aspect of the invention, the polynucleotide further comprises one or more nucleotide sequence elements selected from the group consisting of:

[0184] (i) a polyadenylation signal (PAS);

[0185] (ii) one or two inverted terminal repeat (ITR) sequences; and

[0186] (iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

[0187] In an embodiment of the seventh aspect of the invention, the polyadenylation signal comprises a Simian-Virus 40 PAS.

[0188] In an embodiment of the seventh aspect of the invention, the ITR sequence is an adeno-associated virus (AAV) ITR.

[0189] In an embodiment of the seventh aspect of the invention, the AAV is AVV serotype 2, 5, 8 or 9.

[0190] An eighth aspect of the invention relates to a viral vector comprising the polynucleotide of the seventh aspect of the invention.

[0191] In an embodiment of the eighth aspect of the invention, the virus is selected from the group consisting of AAV2, AAV5, AAV8, AVV9 or variants thereof.

[0192] The polynucleotides of the invention comprising a human rod photoreceptor-specific promoter element (hRPSPE) or variants thereof and a core promoter (CP) operably linked to a transgene (e.g., CNGB1), or polynucleotides comprising a human rhodopsin promoter operably linked to a transgene (e.g., CNGB1) can be used in gene therapeutic and/or gene corrective therapies. In such therapies, the polynucleotides are introduced into cells to aug-

ment expression, replace a defective gene, and/or inhibit expression of a defective gene.

[0193] Accordingly, a ninth aspect of the invention relates to a method for treating retinal degeneration in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polynucleotide according to a seventh aspect of the invention, or the viral vector according to an eighth aspect of the invention.

[0194] In an embodiment of the ninth aspect of the invention, the polynucleotide or viral vector comprises the nucleic acid sequence set forth in SEQ ID NO: 43.

[0195] A tenth aspect of the invention relates to a method for treating retinitis pigmentosa in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polynucleotide according to a seventh aspect of the invention, or the viral vector according to an eighth aspect of the invention.

[0196] In an embodiment of the tenth aspect of the invention, the polynucleotide or viral vector comprises the nucleic acid sequence set forth in SEQ ID NO: 43.

[0197] An eleventh aspect of the invention relates to a method for treating retinal degeneration in a subject in need thereof, wherein the retinal degeneration is characterized by a defect or absence of CNGB1 in the retinal cells of the subject, the method comprising administering to the subject a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43.

[0198] In an embodiment of the eleventh aspect of the invention, the retinal degeneration is CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45).

[0199] A twelfth aspect of the invention relates to a method for treating CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45) in a subject in need thereof, comprising subretinal administration to the subject

a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43.

[0200] A thirteenth aspect of the invention relates to a polynucleotide comprising in this order:

[0201] a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0202] b) a transgene encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1) operably linked to the promoter of a),

[0203] wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1.

[0204] A fourteenth aspect of the invention relates to a pharmaceutical composition comprising a polynucleotide comprising in this order:

[0205] a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and

[0206] b) a transgene encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1) operably linked to the promoter of a);

[0207] wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1, and

[0208] a pharmaceutically acceptable carrier.

[0209] A fifteenth aspect of the invention relates to a pharmaceutical composition comprising a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43 and a pharmaceutically acceptable carrier.

TABLE 1

Table of select sequences of the invention			
SEQ ID NO:	Description	Sequence	
1	99 nucleotide long human RHO promoter fragment	AGAAGCCAATTAGGCCCTCAGTTCTGCAGCGGGGATAATAT GATTATGAAACCCCCAATCTCCCAGATGCTGATTAGCCAGG AGCTTAGGAGGG	
2	350 nucleotide long human RHO promoter fragment	AAACCAGAAAAGTCTCTAGCTGTCCAGAGGACATAGCACAGAGG CCCATGGTCCCTATTCAAACCCAGGCCACCAACTGAGCTGG GACCTTGGGACAGACAAGTCATGCAGAACTTAGGGGACCTTCT CCTCCCTTTCTGGATCTGAGTACCTCTCTCCCTGACCTCAG GCTTCTCTCTAGTGTACCTTGGCCCTCTTAGAACGCAATTAG GCCCTCAGTTCTGCAGCGGGGATAATATGATTAGAACACCC CCAATCTCCAGATGCTGATTAGCCAGGAGCTTAGGAGGG AGGTCACTTTATAAGGGTCTGGGGGGTCAGAACCCAGAGTC TC	
3	Sequence of the human CNGB1 protein	MLGWVQRVLQPQPGTPRKTQMEEEEVEPEPEMEAEEVEPEPNPEE AETESESMPPPEESFKEEEVAVADPSPQETKEAALTSTISLRAQGAEI SEMNSPSPHRVLTWLMKGVEKVIQPQVHSITEDPAQILGHGSTGDT GCTDEPNEALEAQDTRPGLRLLLWLEQNLERVLQPQPKSSEVWRD EPAVATAPPGRPQEMGFKLQARETPSLPTPIPLQPKEPKEAPAPEP QPGSQAQTSLLPPTDRDPARLVAWLHRLLEMALPQPVLHGKIGEQE PDSPGICDVQTISILPGGGVEPDLVLEEVPEPWEDAHQDVTSPGDT EVVPAYEEENKAVEKMPRELSRIEEEEEDEEEEEEEEEEVEV EVLLDSCVVSQVGVGQSSEDGTRPQSTDQLWEEVGEEAKKEA EEKAKEEAEVAEEAEKEPDWAETKEEPAEAEAAASSGVPATK QHPEVQVEDTDADSCPLMAEENPPSTVLPPPSPAKSDTLIVPSSASG	

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
		THRKKLPSEDDEAEELKALSPAESPVVAWSDPPTPKDTDGQDRAA STASTNSAIINDRLQELVKLFKERTEKVKEKLIDPDVTSDEESPKPS PAKKAPEPAPDTKPAEAEPVVEEHYCDMLCKFKHRPWKKYQFP QSIDPLTNLMLYVWLFFVVMAWNWNWCWLIPVRWFAPYQTPDNIH HWLLMDYLCDLIYFLDITVFOTRLQFVRGGDIITDKDDMRNNYLK SRRFKMDLSSLLPDLDFLYLKVGVNPLLRLPRCLKYMAFFEFNSRLE SILSKAYVYRVIRTTAXLLYSLHLSNCLYYWASAYQGLGSTHWVY DGVGNSYIRCYYFAVKTLLTIGGLPDPKTLEIIVFQLLNFTGVFAF SVMIGQMRDVVAATAGQTYYRSCMDSTVKYMFYKIPKSVON RVKTYWEYTWHSQGMLDESELMVQLPDKMRDLAIDVNVNIVS KVALFQGCDRQMI FDMKLRLRSVYVLNDYVCKKGIEGREMYIIQ AGQVQVLGGPDGKSVLVTLKAGSVFGEISLLAVGGGNRRTANVV AHGFTNLFI LDKDLNEI LVHYPESQKLRLRKARRMLRSNNKPKE EKSVLILPPRAGTPKLFNAALAMTGMGGKGAKGGKLAHLRARL KELAALEAAAKQOEVLVEQAKSSQDVKGEEEGSAAPDQHTHPKEAA TDPAPRPTPPEPPGSPPSPPPASLGRPEGEEEGPAAPEEHSVRCMS PGPEPGEQILSVKMPEEREKAE
4	SV40 polyadenyl- ation signal	GGCCGGCAGACATGATAAGATACTATTGATGAGTTTGGACAAACC ACAACATAGAATGCGAAAAAAATGCTTATTGTGAAATT GTGATGCTATTGTTTATTGTAACCATTTAAAGCTGCAATAAA CAAGTTAACACAACAATTGCATTCACTTTATGTTTCAGGTCA GGGGGAGGGTGGGAGGTTTTAAAGCAAGTAAAACCTCTAC AAATGTGTTA
5	Left inverted terminal repeat (L- ITR)	CTGCGCGCTCGCTCGTCACTGAGGCCGCCGGGCAAAGCCCG GGCGTCGGGCACCTTGGTCGCCCGCCCTCAGTGAGCGAGCG AGCGCGCAGAGAGGGACTGGCCAACTCCATCACTAGGGTTCC T
6	Right inverted terminal repeat (R- ITR)	AGGAACCCCTAGTGATGGAGTTGGCACTCCCTCTGCGCGCT CGCTCGCTACTGAGGCCGGCGACCAAGGTGCCCCGACGCC CGGGCTTGCCTGGCGCCCTCAGTGAGCGAGCGAGCGCAG C
7	Sequence of vector construct: pGL2.0- hRho194- hCNGBl-a- SV40	CAGCTGCGCGCTCGCTCGTCACTGAGGCCGCCGGGCAAAGC CCGGCGTGGCGACCTTGGTCGCCCGCCCTCAGTGAGCGA GCGAGCGCCAGAGGGAGTGCCAACTCCATCACTAGGGT TCCTTGATGTTAATGATTAACCGCCATGCTACTTATCTACGTA GCCATGCTCTAGGAAGATCGGAATTGCCCTTAAGCTCTCC CCTGACCTCAGGCTTCCCTCTAGTGTACCTGGCCCTCTTAG AAAGCCAATTAGGCCCTCAGTTCTGAGCAGGGGATTAATATGA TTATGAAACACCCCCAATCTCCAGATGCTGATTAGCCAGGAG CTTAGGAGGGGGAGGTCACTTTATAAGGGTCTGGGGGGTCA AACCCAGAGTCATCACTAGTAACGGCCGCCAGTGTGCTGGA ATTCGGCCCTTCTCCACCGGCCATGTTGGGCTGGGCTCAGAGGGTCT GCCCTAGGCCCTCAGGGACCCCTCGGAAGACAGATGCGAGGAG GAAGAGGAAGTGGAAACAGAGCCAGAGATGGAGGCGAGGTG GAACCAGAACCGAATCTGAGGGCCGAGACAGAGTCCGAG TCCATGCCCTCCAGGAGACTTCAAGGGAGGAAGTGGCT TGGCAGAGCCCCAAGCCCCTAGGGAGACCAAGGGCTGCCCTTAC TTCCACCATATCCCTCCGGGCCAGGGCTGAGATTCTGAAA TGAATAGTCCCAAGGCCACAGGGTACTGACCTGGCTCATGAAGGG TGTAGAGAAAGGTGATCCCGCAGGCTGTCAACAGCATTACGGAG GACCCGGCTCAGATCCTGGGAGATGGCAGCAGTGGGACACAG GGTCACAGATGAACCCAATGAGGCCCTTGAGGGCCAAGAAC TAGGCCCTGGGCTGGGCTGCTCTGTGGCTGGAGCAGAATCTG GAAAGAGTGCTTCTCAGCCCCCAAATCCTCTGAGGCTCTGGA GAGATGAGCCCTGAGTTGCTACAGGGCCTCAGGACGCC GGAAATGGGGCCAAGCTGCAAGGCCGGAGACCCCTCC CCCCACACCCATCCCCCTGCAAGGCCAAGGGAGAACCAAGGAGG CACCAAGCTCAGAGCCCCAGGCCGGCTCCAGGCCAGACCTC CTCCCTGCCACCAACCCAGGGGACCCCTGCCAGGCTGGGCT GTCTGCAAGGCTGGAGATGGCCTTGGCGAGCCAGTGTCTAC ATGGGAAAATAGGGGAAACAGGGAGGCTGACTCCCTGGGATATG TGATGTGAGACCATCAGCATCTTCTGGAGGGACAAGTGGAG CCTGACCTTGTCTAGAGGGAGGTGAACCGCCCTGGGAGGATG CCCACCCAGATGTCAGTACCGCCACAGGGTACAGAGGTGG TCCAGCTTATGAAGAGAGAACAAAGCTGTGGAGAACAGTGC

TABLE 1-continued

Table of select sequences of the invention

SEQ ID	NO: Description	Sequence
		AGAGAGCTGCCGGATTGAAGAGGAGAAAGAAGATGAGGAG GAGGAAGAGGAAGAGGAGGAGGAGGAGGAAGAGGAGGAGGT GACTGAGGTGCTGCTGGATACTGTGTGGTGCAGGTGGC GTGGGCCAGAGTGAAAGAACGGGACCCGGGCCCCAGAGCACT TCAGATCAGAAGCTGTGGGAGGAAGTTGGGAGGAGGCCAAG AAGGAGGCTGAAGAGAAGGCCAAGGAGGAGGCCAGGGAGGTG GCTGAAGAGGAGGCTGAAAAGAGGCCAGGGACTGGCGGAG ACCAAGGGAGGAGGCCAGGCTGAGGCTGAGGCCAGGCTTCAG GAGTGCCCTGCCACGAAACAGCACCCAGAAAGTGAGGGAAG ATACTGATGCTGATAGCTGCCCTCATGGCAGAAGAGAAATCC ACCTCTAACCGTGTGCCACCATCTCCGCCAATCAAGACA CCCTTATAGTCCCAGCTCAGCCTGGGGACACACAGGAAGAA GCTGCCCTGAGGATGATGAGGCTGAAGAGCTCAAGGGTTG TCACCAGCAGAGTCCCAGTGGTGTGCTGGTCTGCCACAC CCCGAAGGACACTGATGCCAGGACCTGCGGCCCTCACGCC AGCACAAATAGGCCATCATCAACGACCGGCTCCAGGAGCTGG TGAAAGCTCTCAAGGAGGGACAGAGAAAGTGAGGAGAAC TCATTGACCTGACGTACCTCTGATGAGGAGAGGCCCAAGCC CTCCCCAGCCAAGAAAGCCCAGAGCAGCTCCAGACACAAG CCCGCTGAAGGGCAGGTGAAGAGGGAGCATTGCGACA TGCCTCTGCAAGTTAACACCGCCCTGGAAAGAAGTACCA GTTTCCCAGAGCATTGACCCGTGACCAACCTGATGATGTC TATGGCTGTTCTCGTGTGGTGTGGCTGGAAATTGAAACTGTG CTGATTCCCGTGCCTGGGCTTCCCCTACAGACCCCCGGACAA CATCCACCACTGGCTGATGGATTACCTATGCGACCTCATCT ACTCTCTGGACATCACGTGTCCAGACAGCCTGCACTGTC AGAGGCGGGGACATCATTACGGACAAAAGGACATGCGAAAT AACTACCTGAAGTCTCGCGCTCAAGATGGACCTGCTCAGCCT CCTGCCCTGGATTTCTCTATTGAAAGTCGGTGTGAACCCCC TCTCCGCTGCCCCGCTGTTAAAGTACATGCCCTCTCGAG TTAACAGCCGCTGGAAATCCATCCTCAGCAAAGCCTACGTGA CAGGGTCATCAGGACCAACGGCTACCTCTACAGCCTGCACT TGAATTCCCTGTTTATTACTGGGCATCGGCCATCAGGGCTC GGCTCCACTCACTGGGTTACGATGGCGTGGAAACAGTTATA TTCGCTGTTACTACTTGTGTGAAGACCTCATCACCCTGGG GGCTGCTGACCCAGAACAGACTCTTGAATTTGCTTCCAGCT GCTGAATTATTCAGGCCGCTTTGTTCTCTGTGATGATCG GACAGATGAGAGATGTGGTAGGGGCCACCGCGGAGAGA CCTACTACCGCAGCTGCATGGACAGCACGGTGAAGTACATGAA TTTCTACAAGATCCCCAAGTCCGTGAGAACCCGCTAACGAC TGGTACGAGTACACCTGGCAGTCGAAGGGCATGCTGGATGAGT CAGAGCTGATGGTGCAGCTTCCAGACAAAGATGCCGCTGGACCT CGCCATCGACGTGAACACACATCGTTAGCAAAGTCGCACTC TTTCAGGGCTGTGACCGGGAGATGATCTTGACATGCTGAAAGA GGCTTCGCTCTGTTGTCACCTGCCAACGACTATGTTGCAAG AAAGGGGAGATCGGCCGTGAGATGTCATCATCCAGGCAGGG AAAGTGCAGGCTTGGCGCCCTGTGGGAAATCTGTGCTGGT GACGCTGAAAGCTGGATCTGTTGGAGAAATAAGCTTGCTG GCTGTTGGGGGGGGGAACCGGGCAGCAGGCAACGACTGGTGGCG ACGGGTTACCAACCTCTCATCTGGATAAGAAGGACCTGAA TGAGATTTGGTCATTACCTGAGTCTCAGAAGTTACTCCGG AGAAAGGCCAGGGCAGTGTGAGAAGAACAAATAAGCCCAAGG AGGAGAAGAGGCCATGCTGAGAACAGAACAACTGGCG AAAGCTCTCAACGCTGCCCTCGCTATGACAGGAAAGATGGT GGCAAGGGGGCAAAGGGCGCAAACCTGCTCACCTCGGGGCC GGCTCAAAGAAGTGGCCGCGCTGGAGGGGGGCTGCAAAGCAGC AAAGAGTGGTGGAAACAGGCCAGAGACTCGCAAGACGTCAGG GAGAGGAGGCTCGCCGCCAGACAGCACGCAACGCCAA AGGAGGCCGCCACCGACCCACCGCGCCCCGGACGCCCG GCCCGCGGGCTCCACCGAGCTCTCACCGCCTGCCCTCTG GGAGGGCGGGAGGGAGAGGAGGGGGCGGGCGAGGCCGAAG AGCACTCGGTGAGGATCTGCATGAGCCGGCCGGAGGCCGG AGAGCAGATCTGTGGTGAAGATGCCGGAGGAAGGGAGGA GAAGGCGGAGTAAGGTGGGTGAGGCCGATCCATGGCCGAG ACATGATAAGATACTTGTGAGTTGGACAAACCAACACTAG AATGCACTGAAAAAAATGCTTTATTGTGAAATTGATGCTA TTGCTTTATTGTAACCATTATAAGCTGCAATAAACAGTTAAC AACAAACATTGCAATTCTGTTGAGGTTCAAGGGGGAGGT GTGGGAGGTTTTAAAGCAAGTAAAACCTCTACAAATGTG ACTCGAGTTAAGGGCGAATTCCGATAAGGATCTCCTAGAGC ATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAAC

TABLE 1-continued

Table of select sequences of the invention

SEQ ID	NO: Description	Sequence
		CAAGGAACCCCTAGTGTGAGTTGGCACTCCCTCTCGGC GCTCGCTCGCTACTGAGGCCGGCGACCAAAGGTGCGCCGAC GCGCGGGCTTGGCCGGCGCTCAGTGAGCGAGCGAGCGG CAGCTGGGCCCTAGTGTGAGCGAGGCCGAGCTGCATTAA GAATCGGCAACCGCGGGAGAGCGGTTGGTATTGGGG CTCTTCGCTCTCGCTACTGACTCGCTCGCTCGTCTCG GCTCGGCCAGCGGTATCAGCTACTCAAAGGCCGTAATAACCG TTATCCACAGAATCAGGGATAACGCAGGAAGAACATGTCGC GTTGCTGGCGTTTCCATAGGCTCCGCCCCCTGACGAGCATC ACAAAAATGACGCTCAAGTCAGAGGTGGCAAACCGACAG GACTATAAAGATAACCAGCGTTTCCCCCTGGAAGGCTCCCTCG CGCTCTCTGTTCCGACCCCTGCCGTTACCGGATACCTGTC CTTCTCCCTCGGAAGCGTGGCGTTCTCATAGCTCACGCT GTAGGTATCTCAGTTCGGTGTAGGTGTTGCTCCAAGCTGG TGTGTGACGAACCCCCGTTAGCCGACCGCTGCCCTTATC CGGTAACATATCGTCTGAGTCCAACCCGTAAGACACGACTAT CGCCTACTGGCAGCAGCACTGGTAACAGGATTAGCAGAGCAG GTATGTTAGGCGGTCTACAGAGTTCTGAAAGTGGCTAAC TACCGCTACACTAGAAGAACAGTATTGGTATCTGGCTCTGCT GAAGCCAGTTACCTTGGAAAGAGTTGGTAGCTCTTGATCC GGCAAAACAAACACCGCTGGTACCGGTTGGTTTGATC GCAGCAGATTACGCGCAGAAAAAAAGGATCTAAGAAGATCCT TTGATCTTCTACGGGGTCTGACGCTCAGTGGAAACGAAAAC ACGTTAAGGGATTGGTCTAGACTGTGGAATGTGTGTCAGTTA GGCAGACATGGTATCTGAGTGAAGCCTAGTGGAAACAGGTTA GTTTGAGTAGCTTGTAGAATGTAATTCTGGATCATAGTGTAGT AATCTCTAATTAAACGGTGACGGTTGTAAAGACAGGTCTCG AAATCAGCGCAGGGTATTCAACAGATTCTGCTGATGGTTTA GGCGTACAATGCCCTGAAAGATAAGAGAAATAGCAGCTCCT CGTGCCTAGAAATTACCTACCGCGTCCACCATACCTCG TCGCGCCACTCTCCATTAGTCGGCACAGGTGGATGTTGCG ATAGCCCCTAAGATATTCTAAGCGTAACCGAGATGAATT CTACAGAGTTGCCATTAGCGCTGAGTCATCGAAGTGGTGT AATGTTGCGTATAGAGCGTGTAGTCATCGAAGTGGTGT TCGTAACATCGCCCGCTCTACAGTACACAGCTGCCT TGAATGACATACTCATCATTAAACTTTCTAACAGTC CAACTGCAATTCAAGGAGTCCGAAGGAGATTCAATTCTCG CAGCACTGTAAGACGGTGTGAAACAAGCGCTTACGGTCA TCTGATTTCCTGTCGAGTCCCGTCAAGTGGCTACTCC AGTGTACTAGCAAGCCGAGAAGGCTGTGCTGGAGTC ATGTTAGGATGGTCTCAGACACCGGGCACCACTCTCACCG AGAAGCATAGAACGTCGAGCAGACATCAAAGCTTACCG ACGTGCCCTTCACTCGGAATTACCTGTAAGCTGTACCGTT TGCGAGCAAGGTGACAGTGTGCTCTTACATATTGTT CGACAGCCCTTCGCGGTTCTCAGACTAGATCGAATACA GGCTTATTGAGGAGCAGGCCCTGTTAGTGGCTGGC AAATCTCCGATCCCTGCTAACCAGTAACTCTCA TTGAAGACCCCTAATATGTCATATTAGTGTGTT AAATACCGCTAGAAATGCTATGATGTGTC GATTCAAAACGACTGCTAGAATCGCGTGTAGGGCAT ATGTTAGGATGGTCTCAGACACCGGGCACCACTCTCACCG CGAAGTGGTACGGATGCAATTCAAGGCCGTGAGAGCGGT AGAGCGTTACCGTACGCTACGGCGATTCTGATAAGA ATGCACATTGCGTGTGATTCTAAGATGTC ACTGTGAAAGTGTCTACATCCCTAAGCGCAT AACCGAATATGTCGGCAT AGCTCACCGAATTAGTGTAGAGATTGTAAGAGCTG TTAGTTAGCTCGCTCAGCTAATAGTGGCCACACA TAGAGAACGGTGTAAACATTATGGTGTCTCTA AGTACCCACGACTCGACTCTGCCGAGCTAGG AGCCAGTCAGCGTTAAGGAGTGTCTGAC TAGTGAGAGTTACTTGTGCTGCTTCC TTGCCCAACGACCCACTTGAGGTCTGAGCC AAGCATCTCGTTGCGAGCTTGGCCAGCA CTATTGTTATTCTAAATACATTCA TGAGACAATAACCGTGTAAATGCT AGAGAGTGGCGCTCGGCT TTGCA GCTATGACTGGCACA ACAGACA ATCGGCTGCTG ATGCGC

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
CGTGTTCGGCTGTCAGCGCAGGGCGCCGGTTCTTTGTCA AGACCGACCTGTCGGTGCCTGAATGAAGTCAAGACGAGGC AGCGCGGCTATCGTGGTGGCACGACGGGCTTCCTGGCCA GCTGTGCTGAGCTGACTGAAGCGGGAAAGGGACTGGCTGC TATTGGCGAAGTGGCGGGGAGGATCTCCCTGTCATCTCACCTT GCTCCTGCCGAGAAAGTATCCATCATGGCTGATGCAATGCGGC GGCTGCAACCGCTTGATCGGCTACCTGCCATTGACCAACCAA GCGAAACATCGCATCGAGCGAGCACGTAACCTGGGATGGAAGCCG GTCTTGTGCGATCAGGATGATCTGGACGAAGGACATCAGGGGT CGGCCAGCCAACTGTTGCCAGGCTCAAGGCAGCATGCC GACGGCGAGGATCTCGTGAACCATGGCGATGCGCTGCTTGC CGAATATCATGGTGGAAAATGGCGCTTTCTGGGATTATCGAC TGTTGCGGCGTGGGTGCGGACCGCTATCAGGACATAGCGT TGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGAATGGC TGACCGCTTCTCGTGTACCGTATCGCCGCTCCGATTGCG AGCGCATCGCCCTCTCATCGCCTTGTGAGGTTCTCGAGGT ACCATGATCGCTGATGGTAGAATGACTTTGATAACGGACTT CGACTAGGCAATATCCCTGTCAACTTGTGAGGAGAAAAGTA TTGACTGAAGCGCTCCCGCAACCGCCAAAGAAGTCTCAGC AATGTTCTTATTCCGAAATGACATCGCTCTTGCAGGTTAAAT CGCCGACCCAAAATCTAGGAGCCAGGATAAGATAAGGCTAA CTTAGGTTAAGGGAGTAATCTGGGATCGTTAGTTGTAACC ATATACTTACGCTGGGCTTCTCGGCGGATGTTACTGTACCA ACACAGGAGATTGAACTAACCGCATGATTGAGCACATAGCC GCTATCCGACAATCTCCAAATTGATAACATAACCGTTCATGAA GCCAGAAATTACTTACCGGCCCTTCCATCGCTGCGCCATACCGC ACTCTGCGCTATCGCTGAGGGAGAGTGTGCGATCCTCCGT TAAGATAATTCACTGAGCTATGACGTTAGCTATGTCAGAGGT AGCGAAGGGCTTGAACACTCACAGATGGGGGATTGGGCA AAGGGCGTGTAACTTGGGACTAACATAGGCTAAACTACCGA TGGCACCAACTCAATCGCAGCTGCGCCCTGAACTAACGTA CTCATCTCAACTGATTCTCGGAATCTACGGAGCGACTTGTGATTA TCAACACCTGTCTAGCAGTTCTAATCTCTGCCAACATCGTACA TAGCCTCAAGAGATTATCATACCTATCGGACACAGAAGTGTACA CGACGCCGAGGGTAGCGGACTTCTGGTCAACCACAATTCCC AGGGGACAGGTCTCGGCTGCGCATCACTTGTAAAGTGTGCA AACCCAACTGAGCCCAAGCTGGACTGAGCTGGTTCTGTGTC GGTCAGGGCTGCAAGGCTGAGAAACTCATAGTACCTCGGGTAG CAACTTACTCAGGTTATTGCTGAAGCTGTACTATTTCAGGAGC GCTGAAGGTCTCTCTGTAGACTGAACTCGCAAGGGTCTG AAAGTCGGTTCTCAATGCTAAACAAGAACAAAGGTTACTGT GCAGACTGGAACGCCCATCTAGCGCTCGCTTGAATGTC GGTCCCTTTGTCATTGGGATACAATCCATTCCCTCATTCA CAGCTTGCGAAGTCTACATTGAGTAGACGAAATGCGACCTAGAA GAGGTGGCTTCAAGACTTGTGAGGAGTGGTGTGATGCTATA CTCCATTGGTGTTCGTCATACCGCGATAGGCTGACAAGAG GTCCTGACATTGAATAGCAAGGCACTTCCGGTCTCATAGAAG AGAGCACGGGATAAGGATACGGCGCTGGTACGGGAGGATCAAG GGGCTACACGATGAAAGCTTCTCCCTCACTCGCTAGGAGGC AAATGCAGAACGCTGGTTACTACTACGATACTGAAACTTGTG CAACGGTTGCCAAAGTGTAAAGTGTCTATCACCCTAGTGGCGT TTCCCGAGAAAAGCCAGGTTGATCCGCAATTGAAAGCTACG ATGGTGAAGTCTGGGTGAGCGGCCGATGTTGATGGTGTGA GTAGGCTGACAGACCGCTGAGTTAGAAAATGGTAGCAGCATGG TTCTGACAGACCGCTGAGTTAGAAAATGGTAGCAGCATGG TTCGCACTCAATCAAGTGTGATGAACTACGCTGTCAGGCA GCGCTACCCATGCCCTGAATCCAGCTGTCAGGCAAGGACACAATCCA CTCTCCGGGACGCCGATGAAGTAACATACATACCTTGCGAC GGTGACTGCGGTCGTTCAAGACTCGACCAAGGACACAATCCA GCGATCGGTGGGGCCCTTCGCTATTACGC	8 Sequence of the human CNGB1 gene	ATGTTGGGCTGGGTCAGAGGGTGTGCTCAGCCCCAGGGA CCCCCTCGGAAGACCAAGATGCAGGAGGAAGAGGAAGTGGAAAC CAGAGCCAGAGATGGAGGCGAGGTGGAACCGAGAACCGAAC CTGAGGAGGCCAGACAGACTGGCTGAGTCCAGTCCCCCGAAGA GTCATTCAAGGAGGAGGAAGTGGCTGAGCAGACCCAAAGCCT CAGGAGACCAAGGAGGAGCTGCCCTTACTTCCACCATATCCCTC GGGCCCCAGGGCGCTGAGATTCTGAAATGAATAGTCCCAGCCA CAGGGTACTGACCTGGCTCATGAAGGGTAGAGAAGGTGATC CCCGCAGCCTGTTACAGCATCACGGAGGACCCGGCTCAGATCC

TABLE 1-continued

Table of select sequences of the invention

SEQ ID	NO: Description	Sequence
TGGGGCATGGCAGCACTGGGACACAGGGCACAGATGAAC CCAATGAGGCCCTGAGGCCAAGACACTAGGCCTGGCTGCG GCTGCTTCTGGCTGGAGCAGAATCTGGAAGAGTGCTTCCTC AGCCCCCAAATCTCTGAGGCTGGAGAGATGAGCTGCGAGT TGCTACAGGCCCTCAGGACGCCAGGAATGGGCCAAG CTGCAGGGCCGGAGACCCCTCCCTGCCACACCCATCCCC GCAGCCAAAGGAGGAACCCAAGGAGGCCAGCTCCAGAGCC CCAGCCGGCTCCAGGCCAGACCTCCCTGCCACCAACC AGGGACCCCTGCCAGGCTGGCATGGGTCTGACAGGCTGG AGATGGCCTGCCAGCCAGTGCTACATGGAAAATAGGGGA ACAGGAGCCTGACTCCCTGGGATATGTGATGTGACACCATC AGCATCCTTCTGGAGGACAATGTGAGGCTGACCTTGTCTTAG AGGAGTTGAACGCCCTGGGAGGATGCCACCCAGGATGTAG TACAGCCCACAGGGTACAGAGGTGGTTCAGCTTATGAAGAA GAGAACAAAGCTGGAGAAGATGCCAGAGAGCTGTCCCC AT'GAAGAGGAGAAAAGAGATGAGGAGGAGGAAGAGGAAGA GGAGGAGGGAGGAAGGAGGAGGAGTGACTGAGGTCTGCT GGATAGCTGTGTTGTCGAGGTGGCGTGGCCAGAGTGA GAAGACGGGACCCGGCCAGGACACTTCAGATCAGAGCTGT GGGAGGAAGTTGGGAGGAGGCCAAGAAGGAGGCTGAAGAGA AGGCCAACGGAGGCCAGGAGGTGGCTGAAGAGGAGGCTG AAAAGGAGCCCAAGGACTGGCGAGACCAAGGAGGAGCCTG AGGCTGAGGCCAGGCTGCCAGTCAGGAGTGCCTGCCACGAA ACAGCACCCAGAAGTGCAGGTGAAGATACTGATGCTGATAGC TGCCCCCTCATGCCAGAAAGAATCCACCCCAACCTGTTG CGCACCACATCTCTGCCAACATCAGACACCCCTTATAGTCCC TCAGCCTCGGGACACACAGGAAGAGCTGCCCTCTGAGGATG ATGAGGCTGAAGAGCTAAGGGCTTGTACACAGCAGAGTCCC AGTGGTTGCTGCTGACCCCACCCCGAAGGACACTGAT GGCAGGACCGCTGCCAGCAGCACAAAGCCGCTGAAGGCC TCATCAACGACCGCTCCAGGAGCTGGTAAGCTCTCAAGGA GCCAGACAGAAAAGTGAAGGAGAAACTCATTGACCTGACCTC ACCTCTGATGAGGAGGCCAAGCCCTCCCAGCCAAGAAAG CCCCAGAGCCAGCTCCAGACACAAAGCCGCTGAAGGCC AGTGAAGAGGAGCACTATTGCGACATGCTGCTGCAAGTTC AAACACCCGCCCTGGAGAAGTACCACTTCCCGAGAGCATG ACCCGCTGACCAACCTGATGTCATGCTCATGGCTGTTCTG GTGATGGCTGGAAATTGGAACTGTTGGCTGATTCCCTGCGCT GGCCTTCCCTACAGACCCCGACAACATCCCACACTGGCTG CTGATGGATTACCTATGCCACCTCATCTACTTCTGGACATAC CGTGTCCAGACACGCCAGCTGCAAGTTGTCAAGAGGGGG ATTACGGCAAAAAGGACATGCCAAATAACTACCTGAAGTCTC GCCGCTCAAGATGGACCTGCTCAGCCTCTGCCCTGGATTT CTCTATTGAAAGCTGGTGTGAACCCCTCTCCGCTGCC CTGTTAAAGTACATGCCATCTTCGAGTTAACAGCCGCTGG AAATCCATCTCAGCAAAGCTAGTGACAGGGTCACTCAGGAC CACAGCCTACCTCTACAGCCTGATTGAAATTCTGTT TTACTGGGCATCGGCCATCACGGGCTCGGCTTCACTCACTGG TTACGATGGCTGGAAACAGTTATATTGCTGTTACTACTTT GCTGTAAGACCCCTCATCACCATGGGGGCTGCCATGACCC AGACACTCTTGAAATTGCTTCCAGCTGCTGAATTATTCA GGCTCTTGCTTCTCTGTGATGATGGACAGATGAGAGATGT GGTAGGGGCCGCCACGCCGGAGACACTAACCGCAGCTG ATGGACACCGCTGAACTACATGAATTCTACAAAGATCCCC AGTCCTGCGAGAACCGCGTCAAGACCTGGTACAGAGTACACTG GCACTCGCAAGGCATGCTGGATGAGTCAGAGCTGATGTTG CTTCCAGACAGAACAGTGCCTGGGACCTCGCCATCGACGTGA ACACACATCGTAAAGTCGCACTCTTCAGGGCTGTGACCG GCAGATGATCTTGACATGCTGAAGAGGCTCGCTGTT ACCTGGCCAACGACTATGTGCAAGAAGGGGGAGATGCC TGAGATGTAACATCAGGCCAGGGCAAGTGCAAGGTCTGG GGCCTGATGGAAATCTGCTGGTACGCTGAAAGCTGGAT CTGTGTTGGAGAATAAGCTGCTGGCTGTTGGGGGG CCGGCGCACGCCAACGTTGGCTGGCGACGGGTTACCAACCTC TTCATCTGGATAAGAAGGACCTGAAATGAGATTGCTG TCTGAGTCTCAGAAGTTACTCGGAAGAAAGCCAGGGCATG CTGAGAAGCAAAATAAGCCAAAGGAGGAGAGAGCTG ATCTTCCACCCGGGGGGCACCCAAAGCTTCAACGCTG CCTCGCTATGACAGGAAAGATGGGTGCAAGGGGG CGGAAACTTGTCAACCTCCGGGGCGCTAAAGAACTGGC GGCTGGAGGGCGCTGCAAAGCAGCAAGAGTTGGTGG ACAG		

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
		GCCAAGAGCTCGAAGACGTCAAGGGAGAGGAAGGCTCCGCC GCCCCAGCACAGCACGCACCAAAGGAGGCCGCCACCGACC CACCGCGCCCCCGAGCAGCCCCGGGGCTCCACC GAGCTCTCCACCGCTGCCTCCCTTGGGAGCCGGAGGGAGAG GAGGAGGGCCCGCCGAGCCCGAAGGAGCACTCGGTAGGGATC TGCATGAGCCGGCCGGAGCCGGAGAGCAGATCCTGTCGG TGAAGATGCCGGAGGAAAGGGAGGAGAAGGCCGAGTAA
9	194 nucleotide long fragment of human RHO promoter	TCTCCTCCCTGACCTCAGGCTTCTCTTAGTGTACCTTGCCCC TCTTAGAACGCAATTAGGCCCTCAGTTCTGCAGCGGGGATTA TATGATTATGAACACCCCCAATCTCCAGATGCTGATTCAAGCA GGAGCTTAGGAGGGGGAGGTCACTTATAAGGGTCTGGGGGG TCAGAACCCAGACTCATC
40	Sequence of the human CNGB1 protein translated from next generation sequencing (NGS) results	MLGWVQRVLPQPPGTPRKTMQEEEEVEPEPEMEAEVEPEPNPEE AETESESMMPPEESPKKEEEVAVADPSPQETKEALTSTISLRAQGAEI SEMNSPSHRLVTLMKGVEKVIQPVHSITEDPAQILGHGSTGDT GCTDEPNEALEAQDTRPGLRLLLWLEQNLERVLPQPPKSSEWRD EPAVATGAASDPAPPGRPQEMGPKLQARETPSLPTPIPLQPKEEP EAAPAEPPQGSQAQTSSLPPTRDPARLVAVLHRLEMALPQPVHL GKIGEQEPDSPGICDVQTISILPGGVQEPDLVLEEVEPWPEDAHQD VSTSPQGTTEVVPAYEEENKAVEKMPRELRSRIEEKEDEEEEEEEE EEEEEVTEVLLDSCVVSQVGQSEEDGTRPQSTS DQLWEEVGE EAKKEAEEKAKEEAEVAAAEEKEPQDWAEKKEEPAEAEAASS GVPATKQHPEVQVEDTDADSCPMLMAEENPPSTVLPPPSPAKSDTLI VPSSASGTHRKKLPSDEDAEELKALSPAESPVVAWSDPTTPKD GDRAASTASTNSAIINDRQLVELKLFKERTBEVKKEKLIDPDT EESPCKPSPAKKAPEPAPDTKPAEAEVPVEEEHYCDMLCCKFKHRPW KKYQFPQSIDPLTNLMVWLWFFVVMAWNWNWCWLIPVRWAFPY QTPDNIIHHWLLMDYLCDLIYFLDITVQTRLQFVRGGDIITDKDM RNNYLKSRRFKMDLSSLLPLDFLYLKVGVPNPLLRLPRCLKYM EFNSRLESILSKAYVYRVIRTTAYLLYSLHLSCLYYWASAYQGL GSTHWVYDGVGNSYIRCYYFAVKTLTIGGLPDPKTLFEIVFQLLN YFTGVFAFSVMIQMRDVVGAAATAGQTYRSCMDSTVKYMFY KIPKSVQNRVKTWEYTWHSQGMLDES ELMVQLPDKMRLDIA VNINIVSKVALFQGCDRQMI FDMLKRLRSVYLPNDYVCKKGEI GREMYIIQAGQVQVLGGPDGKSVLVTLKAGSVFGEISLLAVGGGN RRTANVAHGFNLFILDKKDNEILVHYPESQKLLRKARRMLR SNNKPKEEKSVLILPPRAGTPKLFNAALAMTGMGGKA AHLRRLKELAALEAAAKQQELVEQAKSSQDVKGEEGSA THPKEAATDPAPRTPPEPPGSPPSSPPASLGRPEGE SVRICMSPGPEPGEQILSVKMP EEEREKAE
41	Sequence of the CNGB1 protein (GenBank NG_016351)	MLGWVQRVLPQPPGTPRKTMQEEEEVEPEPEMEAEVEPEPNPEE AETESESMMPPEESPKKEEEVAVADPSPQETKEALTSTISLRAQGAEI SEMNSPSRRLVTLMKGVEKVIQPVHSITEDPAQILGHGSTGDT CTDEPNEALEAQDTRPGLRLLLWLEQNLERVLPQPPKSSEWRD PAVATGAASDPAPPGRPQEMGPKLQARETPSLPTPIPLQPKEEP A PAPEPPQGSQAQTSSLPPTRDPARLVAVLHRLEMALPQPVHL KIGEQEPDSPGICDVQTISILPGGVQEPDLVLEEVEPWPEDAHQD VSPCGTTEVVPAYEEENKAVEKMPRELRSRIEEKEDEEEEEEEE EEEEEVTEVLLDSCVVSQVGQSEEDGTRPQSTS DQLWEEVGE AKKEAEEKAKEEAEVAAAEEAEKEPQDWAEKKEEPAEAEAASS GVPATKQHPEVQVEDTDADSCPMLMAEENPPSTVLPPPSPAKSDTLI VPSSASGTHRKKLPSDEDAEELKALSPAESPVVAWSDPTTPKD GDRAASTASTNSAIINDRQLVELKLFKERTBEVKKEKLIDPDT EESPCKPSPAKKAPEPAPDTKPAEAEVPVEEEHYCDMLCCKFKHRPW KKYQFPQSIDPLTNLMVWLWFFVVMAWNWNWCWLIPVRWAFPY QTPDNIIHHWLLMDYLCDLIYFLDITVQTRLQFVRGGDIITDKDM RNNYLKSRRFKMDLSSLLPLDFLYLKVGVPNPLLRLPRCLKYM EFNSRLESILSKAYVYRVIRTTAYLLYSLHLSCLYYWASAYQGL GSTHWVYDGVGNSYIRCYYFAVKTLTIGGLPDPKTLFEIVFQLLN YFTGVFAFSVMIQMRDVVGAAATAGQTYRSCMDSTVKYMFY KIPKSVQNRVKTWEYTWHSQGMLDES ELMVQLPDKMRLDIA VNINIVSKVALFQGCDRQMI FDMLKRLRSVYLPNDYVCKKGEI GREMYIIQAGQVQVLGGPDGKSVLVTLKAGSVFGEISLLAVGGGN RRTANVAHGFNLFILDKKDNEILVHYPESQKLLRKARRMLR SNNKPKEEKSVLILPPRAGTPKLFNAALAMTGMGGKA AHLRRLKELAALEAAAKQQELVEQAKSSQDVKGEEGSA THPKEAATDPAPRTPPEPPGSPPSSPPASLGRPEGE SVRICMSPGPEPGEQILSVKMP EEEREKAE

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
THPKEAATDPAPRTPPEPPGSPPSSPPPASLGRPEGEEEGPAEPEEH SVRICMSPGPEPGEQIILSVKMPEREKEA		
42	Sequence of 5' ITR- hRHO promoter- CNGB1a- SV40polyA- 3' ITR	CTCGCGCTCGCTCGTCACTGAGGCCGCCGGCAAAGCCG GGCGTCGGCGACCTTGTGTCGCCCTCATGAGCGAGGG AGCGCGAGAGGAGTGGCAACTCCATCACTAGGGTTCC TTGAGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCC ATGCTCTAGGAAGATCGGAATTGCCCTTAAGCCTCTCCCT GACCTCAGGCCCTCCCTAGTGTACCTTGCCCCCTTAGAAG CCAATTAGGCCCTCAGTTCTGCAGCGGGGATTAATGATTAT GAACACCCCCAAATCTCCAGATGCTGATTCAGCCAGGAGCTTA GGAGGGGGAGGTCACTTTAAAGGTCAGGCTCTGGGGGGTCAGAAC CAGAGTCATCACTAGTAACGCCGCCAGTGTCTGGAATTCC CCTCTCCACCGCCATGTTGGCTGGGTCAGAGGGTGTGCTCC CAGCCCCCAGGGACCCCTCGGAAGAACCAAGATGCAGGAGGA GAGGAAGTGGAAACCAGAGCCAGAGATGGAGGGAGGTGGA CCAGAACCGAATCTGGAGGGCCAGACAGAGTCCGAGTCCA TGCCCCCGAAGAGTCATTCAAGGAGGAGAACAGTGGCTG AGACCAAAAGCCCTCAGGAGAACCAAGGGAGCTGCCCTACT ACCTCTCCACCGCCATGTTGGCTGGGTCAGAGGGTGTGCTCC AAGCATATCCCTCGGGCCAGGGCCTGAGGATTTCTGAAATGA ATACTCCCAGCCACAGGGTACTGACCTGCTCATGAAAGGTGT AGAGAAGGTGATCCCGCAGCTGTTCACAGCATCACGGAGGAC CCGGCTCAGATCTGGGGCATGGCAGCACTGGGGACACAGGGT GCACAGATGAAACCAATGAGGCCCTTGAGGGCCAAAGACACTAG GCTGGGCTGCGCTGCTCTGAGCTGGAGCAGAATCTGGA AGAGTGTCTCTAGGCCCAACAGGGCCTGCCAGGCTGGGATGG ATGAGCCTGAGTTGCTACAGGCCCTCAGGACGCCCAAGGA AATGGGGCCAAGCTGAGGCCGGAGACCCCTCCCTGCCC ACACCCATCCCCCTGCAAGCCAAGGAGGAACCCAAGGAGGCAC CAGCTCAGAGCCCAAGGCCCTCAGGCCAGACCTCTC CCTGCCACCAACCAGGGACCTGCCAGGCTGGGATGGTC CTGACAGGCTGGAGATGGCTTGCCAGGCTACAGAGTGGTCC GGAAAATAGGGAAACAGGGCTGACTCCCTGGGATATGTGA TGTGCAAGCATCAGCATCTTCTGGAGGAAGTGGAGGCT GACCTTGTCTAGAGGAGGTGAACCGCCCTGGGAGGATGCC ACAGGAGTGTCACTACAGGCCACAGGGTACAGAGTGGTCC ACCTTATGAAAGAGAACAAAGCTGTGAGAACATGCCAG AGAGCTGTCCGGATTGAAGAGGAGAAAGAACATGAGGAGGA GGAAGAGGAAGAGGAGGAGGAGGAGGAAGAGGGAGGAGGTGA CTGAGGTCTGCTGGATAGCTGTGTTGTCAGGTTGGGGCT GGCCAGAGTGAAGAACAGGCCCTGAGGGCTGCGAGGCT AGATCAGAACAGCTGGAGGAAGTTGGGAGGAGGCAAGAA GGAGGCTGAAGAGAACAGGCCAGGAGGAGGCCAGGGAGGTGG TGAAGAGGAGGCTGAAAAGGAGGCCAGGACTGGCGAGAAC CAAGGAGGAGGCTGAGGGCTGAGGGCTGCGAGGCT AGTGCCTGCCAACAGCACCCAGAACAGTGCAGGTGAAAGAT ACTGATGCTGATAGCTGCCCTCATGGCAGAACAGAACATCC CCTCAACCGTGTGCGCCACCATCTCTGCCAAATCAGAACCC CTTATAGTCCAAGCTCAGCTCGGGGACACAGGAAGAAC TGCCCTCTGAGGATGATGAGGCTGAAGAGCTCAAGGCGTT ACCAGCAGAGTCCCAGTGGTGCCTGGTCTGACCCACACC CCGAAGGGACACTGATGCCAGGACCTGCGGCCACGGCCA GCACAAATAGGCCCATCATCACAGGCCCTCAGGAGCTGG GAAGCTCTCAAGGAGCGACAGAGAACAGTGAAGGGAGAAC CATTGACCTGACGTACCTCTGATGAGGGAGGCCAACAGCC TCCCCAGCCAAGAACAGGCCAGGCCAGCTCCAGAACAAAGC CGCCTGAAGGCCAGTGGAGAGGAGGCACTATTGCGACAT GCTCTGCTGCAAGTTCAACACGCCCTGGAGAACAGTACAG TTTCCCCAGAGCATGACCCGCTGACCAACTGATGTATG ATGCTGTTCTGTTGATGCCCTGGAATTGAACTGTTG TGATTCCTGGCTGGCTGGGCTTCCCTACAGACCCGGACA ATCCACCACTGGCTGCTGATGGATTACCTATGCCACCT CTTCTGGACATCACCGTGTCCAGACAGCCTGCAGTTG GAGGCAGGGACATCATTACGGACAAAAGGACATGCGAA ACTACCTGAAGTCTGCCGCTTCAAGATGGACCTGCTCAGGCC CTGCCCTGGATTTCCTATTTGAAAGTCGGTGTGAACCC CCTCCGCTGCCCTGGATCCATCCTCAGCAAGCCTACGT TTAACAGCCGCCCTGGAAATCCATCCTACAGCCTGCATT CAGGGTCATCAGGACACAGCCTACCTCTACAGCCTG TGAATTCTGTCTTATTACTGGGATCGGCCATCAGGGC GGCTCCACTCAGGGTTACGATGGCGTGGAAACAGTTATA

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
		TTCGCTGTACTACTTTGCTGTGAAGACCCCATCACCATCGGG GGGCTGCCTGACCCAAGACACTCTTGAATTGTCTTCAGCT GCTGAATTATTTACAGGGCCTTGTGCTTCTGTGATGATCG GACAGATGAGAGATGTGGTAGGGGCCACCAGGGACAGA CCTACTACCGCAGCTGCATGGACAGCACGGTAAGTACATGAA TTTCTACAAGATCCCCAAGTCCGTGCAAGAACCGCGTCAAGACC TGTTACGAGTACACCTGGCACTGGCAAGGCATGCTGGATGAGT CAGAGCTGATGGTGCAGCTCCAGACAAGATGCGGCTGGACCT CGCCATCAGCTGAACACTAACATCGTTAGCAAAGTGCACCTC TTTCAGGGCTGTGACCGGAGATGATCTTGACATGCTGAAGA GGCTTCGCTCTGTGCTACCTGCCAACGACTATGTGTGCAAG AAAGGGGAGATCGGCGCTGAGATGATCATCCAGGCAGGGC AAAGTCAGGTCTGGCGCCCTGATGGAAATCTGTGCTGTT GACGCTGAAAGCTGGATCTGTGTTGGAGAAATAAGCTGCTG GCTGTTGGGGCGGGAACCGGCCACGCCAACGTCGGTGGCGC ACGGGTTAACCAACCTTCTGAGATAAGAAGGACCTGAA TGAGATTTGGTCATTATCCTGAGTCAGAAAGTTACTCCGA AGAAAGCCAGGCGCATGCTGAGAACAAATAAGCCAAAGG AGGAGAAAGACGCTGCTGATCTCCACCCCGGGCGGGCACCCC AAAGCTCTCAACGCTGCCCTCGCTATGACAGGAAAGATGGGT GGCAAGGGGCCAAAAGGGGCAAAACTTCTCACCTCGGGCCC GGCTCAAAGAACTGGCGCGCTGGAGGGCTGCAAAGCAGC AAGAGTTGGTGAACAGGCCAAGAGCTGCGAAGACGTCAGG GAGAGGAAGGGCTCGCCGCCAGAGCCAGCACCGCACCCCA AGGAGGCCGCCACCGACCCACCGCGCCCCGAGGCCCGCGA GCCCGCGGGCTCCACCGAGCTCTCACCGCCTGCGCTCCCTG GGAGGCCGGAGGGAGAGGAGGGAGGGCGGGCGAGGCCGAAG AGCACTCGGTGAGGATCTGATGAGGCCGGCGAGGCCGG AGAGCAGATCTGCTGGTAAGATGCGGGATCATGGCGCAG GAAGCGGAGTAAGGTGGGTGAGGCCGATCATGGCGCAG ACATGATAAGATACTTGATGAGTTGGACAAACCACAATAG AATGCACTGAAAAAAATGCTTATTGTGAATTGTGATGCTA TTGCTTATTGTGAAACATTATAAGCTGCAATAAAAGTTAAC AAACAACATTGCAATTATTTATGTTTCAGGTTCAAGGGGAGGT GTGGGAGGTTTTAAAGCAAGTAAACCTCTACAAATGTGGT ACTCGAGTTAACGGCAATTCCCGATAAGGATCTCTAGAGC ATGCTACGTAGATAAGTACATGGCGGTTAATCATTAACCA CAAGGAACCCCTAGTGTGAGTTGGCACTCCCTCTGGCC GCTCGCTCGTCACTGAGGCCGGCGACCAAGGTCGCCGAC GCCGGGTTGCCCCGGCGCTCAGTGAGCGAGCGAGCG CAG
43	Sequence of 5' ITR- hRHO promoter- CNGB1a- SV40polyA- 3' ITR (NGS)	CTCGCGCGCTCGCTCGTCACTGAGGCCGCCGGCAAAGCCCG GGCCTCGGGCGACCTTGTGCGCCGCCCTCAGTGAGCGAGGG AGCAGCAGAGAGGGAGTGGCCAACCTCATCATAGGGGTTC TTGTTAGTTAATGATTAACCCGCGATGCTACTTATCTACGTA ATGCTCTAGGAAGATCGGAATTGCCCTTAAGCTCTCCCTCC GACCTCAGGCTCTCTCTAGTGTGACCTTGCCCCCTTAAAG CCAATAGGCGCTCAGTTCTGAGCGGGGATTAATATGATTAT GAACACCCCCAAATCTCCAGATGCTGATTCAAGCCAGGAGCTTA GGAGGGGAGGTCACTTATAAGGTCTGGGGGGTCAGAAC CAGAGTCATCACTAGTAACGCCGCAAGTGTCTGAAATTCC CCTTCCACCGCCATGGCTGGGTCAGAGGGTCTGCC CAGCCCCAGGGACCCCTGGAAAGACCAAGATGCAAGGGGAA GAGGAAGTGGAAACAGAGCCAGAGATGGAGGGAGGGTGAA CCAGAACCGAATCTGAGGGAGGCCAGACAGAGTCCGAGTCC TGCCCCCGAAGAGTCAAGGAGGGAGAGTGGCTGTGG AGACCCAAGCCCTCAGGAGACCAAGGGAGCTGCCCTACTTC ACCATATCCCTCGGGGCCAGGGCGTGAGATTCTGAAATGA ATAGTCCCAAGCCACAGGGTACTGACCTGGCTCATGAAGGGTGT AGAGAACGGTGAATCCCAGCCGAGCTGTTCAAGGAGTCA CCGGCTCAGATCTGGGCATGGCAGCACTGGGGACACAGGGT GCACAGATGAACCCAATGAGGCCCTTGAGGGCCAAGACACTAG GCTGGGCTGCCCTGCTTGTGGCTGGAGCAGAATCTGAA AGAGTGGCTCTCAGGCCCTCAAGGGGAAATCTCTGAGGTCTGGAGAG ATAGGCTCGAGTTGCTACAGGTGCTGCCCTCAGACCCAGCGC TCCAGGAGCCCCCAGGAAATGGGGCCAAGCTGCAGGCCCG GAGACCCCCCTCTGCCACACCCATCCCCCTGCAAGGCCAAG AGGAACCCAAGGGAGGCACCAAGCTCCAGAGCCCCAGGCCGCTC CAGGCCAGACCTCCCTGCCACCAACCAGGGACCCCTGCC AGGCTGGTGCATGGGCTCTGCAAGGCTGGAGATGCCCTTG

TABLE 1-continued

Table of select sequences of the invention

SEQ ID NO:	Description	Sequence
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TABLE 1-continued

Table of select sequences of the invention

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44	Sequence of 5' ITR- hRHO promoter- CNGB1a- SV40polyA- 3' ITR (GenBank)	GGCACTCCCTCTGCGCGCTCGCTCGCTACTGAGGCCGCC GGCAAAAGCCGGCGTCGGCGACCTTGGTCGCCGCCCTC AGTGAGCGAGCGCAGAGGAGGTGGCAACTCCAT CACTAGGGGTCTCTCAGATCGTAGCCATGCTCTAGGAAGATCG GAATTGCGCCCTTAAGCCTCTCTCCCTGACCTCAGGTTCTCC TAGTGTACCTTGGCCCTCTTAAAGCCAATTAGGCCCTCAGT TTCGCAGGGGATTAAATGATTATGAAACACCCCAATCTCC CAGATGCTGATTCAAGGCCAGGGACTTAGGAGGGGAGGTCACTT TATAAGGGTCTGGGGGGTCAGAACCCAGAGTCATCACTAGTA ACGGGCGCAGTGTGGAAATTGCGCCCTTCTCCACCGCCATGT TGGGCTGGGTCAGAGGGTGTCCCTCAGCCCCCAGGGACCCC TCGGAAGACCAAGATGCAGGAGGAAGAGGAAGTGAACAGA GCCAGAGATGGAGGGCGGGAGGTGGAAACCGAATCTGA GGAGGCCAGAGACAGTCGAGTCCATGCCCGGAAGAGTCA TTCAAGGGAGGAAGGTGCTTGGCAGACCCAAGCCTCAGG AGACCAAGGAGGCTGCCCTAATTCACCATATCCCTCGGGC CAGGGCGTGAAGATTCTGAAATGAATAGTCCAGCCGAGGG TACTGACTGGCTCATGAAGGGTGTAGAGAAGGTGATCCCCA GCCCTGTTCACAGCATCACGGAGGACCCGGCTCAGATCTGGG CATGGCAGCACTGGGACACAGGTGCACAGATGAACCCAATG AGGCCCTTGAGGCCAAGACACTAGGCCTGGCTGCGGCTGCT TCTGTGGCTGGAGCAGATCTGAAAGAGTGTCTCTCAGGCC CCCCAATCTCTGAGGTCTGGAGAGATGAGCTGCACTGCTA CAGGTCTGCCTCAGACCCAGGCCCTCAGGAGGCCAGGAGA AATGGGCCCCAAGCTGAGGCCAGGGAGACCCCTCCCTGCC ACACCCATCCCCCTGAGGCCAGGGAGACCCAGGAGGAC CACCTCCAGCCCCCACCCCTCCAGGAGACCTCTC CCTGCCACCAACAGGACCTTGCCAGGCTGGCATGGTC CTGCACAGGCTGGAGATGGCTTGCGCAGCAGTGCACATG TGTGCAGACCATCAGCATCTTCTGGAGGACAAGTGGAGGCT GACCTTGCTCTAGAGGAGGTGAACCGCCCTGGAGGATGCC ACCAGGATGTCAGTACAGCCACAGGGTACAGAGGTGGTCC AGCTTATGAAGAAGAGAACAAAGCTGTGGAGAGATGCCAG AGAGCTGTCCCGGATTGAAGAGGAGAACAGATGAGGAGGA GGAGAGGAAGAGGAGGAGGAGGAGGAGAACAGGAGGAGGTGA CTGAGGTGCTGGATAGCTGTGGTGTGCGCAGGTGGCGT GGGCCAGAGTGAAGAACAGGGACCCGGCCAGAGCACTC AGATCAGAAGCTGTGGAGGAAAGTTGGGGAGGAGGCCAAGAA GGAGGCTGAAGAGAACGGCAAGGAGGAGGCCAGGAGGTGGC TGAAGAGGAGGCTGAAAGAGGAGGCCAGGACTGGCGGAGAC CAAGGAGGAGGCTGAGGCTGAGGCCAGGGCTGCCAGTTCAGG AGTGCCTGCCACGAAACAGCACCCAGAAGTGCAGGTGGAAAGAT ACTGATGCTGATAGCTGCCCTCATGCCAGAACATCAC CCTCAACCGTGTGCCGCCACCGCTCTCTGCCAAATCAGACACC CTTATAGTCCCAAGCTCAGCCTGGGACACACAGGAAGAAGC TGCCTCTGAGGATGATGGCTGAAGAGCTCAAGGCGTGTGTC ACCAAGCAGTCTCCAGGGCTGGCTGCTGACCCACCC CCGAAGGACACTGATGCCAGGACCGTGCAGGCCACGGCCA GCACAAATAGCGCCATCATCAACGACCCGCTCCAGGAGCTGGT GAAGCTCTCAAGGAGGGACAGAGAACAGTGAAGGAGAACACT CATGACCTTGAGCTCACCTCTGATGAGGAGGAGGCCAACCCC TCCCCAGCCAAGAACGCCAGGCCAGCTCAGACACAAAGC CCGCTGAGGCCAGGCAAGTGGAGAGGAGCACTATTGCGACAT GCTCTGCTGCAAGTTCAAAACACCGGCCCTGGAAGAAGTACCAAG TTTCCCCAGAGCATTGACCCGCTGACCAACCTGATGTATGTCCT ATGCGCTGTTCTGCTGGTGTGGCTGGATTACCTATGCGACCTCATCTA CTTCTGGACATCACCGTGTCCAGACACGCCCTGCGAGTTGTCA GAGGCGGGGACATCATTACGGACAAAAGGACATGCGAATAA

TABLE 1-continued

Table of select sequences of the invention

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45	Sequence of human RPE65 protein	MSIQVEHPAGGYKKLFETVEELSSPLTAHTVGRIPWL TGSSLRCG PGLFEVGSEPFYHLDQGALLHKFDKEGHVTHRRFIRTDAYVR AMTEKRIVITEFGTCAPPDPCKNIFSRSFFSYFRGVETDNLNVY PVGEDYYACTETNFITKINPTELTIKVQLCNVYVSNNGATAHPhi ENDGTVVNIGNCFGKNFSIAYNIVKIPPLQADKEPIKSSEIVVQFP CSDRFKPSPVHSPGLTPNYIVFVTPVKINLPKFLSSWSLWGANYM DCFESNETMVGVLHIADKKRKLYLNNKYRTSPFNLFHHINTYED NGFLIVDLCCWKGFVFVNNYLILANLRNWEVKKNARKAPOP VRRYVLPNIDKADTGKNLVTLPNTTATAILCSDETIWLEPEVLFS GPROAFEPFPQINQKYCKPYTYAYGLGLNHFPDRLLKLNVKT KETWVWQEPDSYPSEPIFVSHDALEEDDGVVLSVVSPGAGQKP AYLLILNAKDLSEVARAEVEINIPVTFHGLFKKS

EXAMPLES

Example 1: Nucleic Acid Vector

[0210] In this exemplary embodiment, the rAAV.hCNGB1 vector is a hybrid AAV-based vector carrying the cDNA of the human CNGB1 gene encoding the B subunit of the rod photoreceptor cyclic nucleotide-gated (CNG) channel. The

hCNGB1 cDNA expression is under the control of the rod-specific Rhodopsin promoter (hRHO) and is enhanced using a SV40 pA sequence. The expression cassette is flanked by the AAV serotype 2 inverted terminal repeats (ITRs) and the recombinant genome is packaged in the AAV serotype 8 capsid. The expression cassette comprises the following elements:

- [0211] Promoter of the human rhodopsin gene: 0.194 Kb.
- [0212] cDNA of the human CNGB1a subunit of the rod photoreceptor cGMP phosphodiesterase: 3.74 Kb
- [0213] Polyadenylation signal of the Simian-Virus 40 (SV40): 0.23 Kb
- [0214] AAV serotype 2 inverted terminal repeats (ITRs): 0.13 KbThe structure of the rAAV.hRHO194. hCNGB1 vector genome is depicted in FIG. 1.

Example 2: pGL2.0-hRHO194-hCNGB1a-SV40
Cis Vector Plasmid

[0215] In one exemplary embodiment, the pGL2.0-hRHO194-hCNGB1a-SV40 cis vector plasmid with the nucleotide sequence depicted in SEQ ID No. 7 is used which contains an expression cassette comprising a 194 bp rod photoreceptor-specific human rhodopsin (hRHO) promoter and the full-length (3738 bp) human CNGB1 cDNA. The expression cassette also contains a 227 bp Simian-Virus 40 polyadenylation signal (SV40 pA). The 5591 bp vector backbone containing a kanamycin resistance (KanR) positioned 1943 bp from the L-ITR and 2853 bp from the R-ITR and 2024 bp from a pUC18 ori. The rAAV.hCNGB1 vector is produced using transient co-transfection of the cis vector plasmid and trans helper plasmid(s) encoding rep and cap sequences and adenoviral genes in the human embryonic kidney 293 T cells (HEK293T). The rAAV.hRHO194. hCNGB1 is harvested from the culture medium and/or the cell lysate using standard purification methods, e.g. cesium chloride gradient ultracentrifugation, ion exchange chromatography and/or tangential flow filtration. The resulting rAAV.hRHO194.hCNGB1 vector suspension is then sterile-filtered, filled and stored as drug product.

Example 3: Activity and Specificity of the hRHO194 Promoter

[0216] To verify the activity and specificity of the novel hRHO194 promoter the inventors constructed a version of the AAV cis vector which contains the eGFP cDNA instead of the hCNGB1 cDNA. The resulting pGL2.0-hRHO194-eGFP-SV40 cis vector plasmid map is shown in FIG. 2. Delivery of rAAV.hRHO194.eGFP vector into the subretinal space of 4-week-old wild type mice resulted in strong expression of eGFP protein 4 weeks after injection in rod photoreceptors only (FIG. 3A) thereby confirming the retinal cell type specificity of this promoter. For representative results see FIGS. 3A-3B. The rAAV.hRHO194.eGFP vector treatment resulted in strong eGFP protein expression in the treated eye reflected by native eGFP fluorescence in rod photoreceptors only.

Example 4: Biological Activity and Transgene Expression Conferred by the rAAV.hRHO194.hCNGB1

[0217] To verify biological activity and transgene expression the inventors delivered the AAV.hRHO194.hCNGB1 vector into the subretinal space of 4-week-old CNGB1 (-/-) mice. The delivery procedure was similar to the one described in Koch et al., Gene therapy restores vision and delays degeneration in the CNGB1 (-/-) mouse model of retinitis pigmentosa. *Hum Mol Genet.* 2012; 21 (20): 4486-96. PubMed PMID: 22802073. The mice received a subretinal injection in the treated eye (TE), whereas the other,

untreated eye (UE) served as control. The vector efficacy was evaluated at 4 months following the injection by means of electroretinography (ERG), an objective functional in vivo assay (FIGS. 4A and 4B). CNGB1 (-/-) mice lack normal rod photoreceptor function. Secondary to rods, non-affected cone photoreceptors also degenerate resulting in loss of cone function at later stages of the disease. Therefore, ERG protocols specifically testing for rod and cone function are suitable as an indirect measure for CNGB1 function and for the assessment of biological activity (BAA) of the rAAV hRHO194.hCNGB1 vector.

Example 5: In Vivo Optical Coherence Tomography (OTC) for the Determination of BAA

[0218] In another set of experiments BAA was determined by in vivo optical coherence tomography (OCT) imaging followed by quantification of the photoreceptor layer thickness. For this, the mice received a subretinal injection in the treated eye (TE), whereas the other, untreated eye (UE) served as control. Photoreceptor layer thickness measurement was performed at 4 months following the injection by means of OCT (FIGS. 5A-5C). Rod photoreceptors of CNGB1 (-/-) mice degenerate over time resulting in thinning of the photoreceptor cell layer (FIGS. 5B and 5C). Therefore, biological activity (BAA) of the rAAV. hRHO194.hCNGB1 vector can be indirectly measured by determining the photoreceptor layer thickness in treated CNGB1 (-/-) mice using OCT. The rAAV.hRHO194. hCNGB1 vector treatment resulted in a clear therapeutic effect in the treated eye reflected by preservation of the photoreceptor layer thickness. In particular, more than 45% increase in photoreceptor layer thickness was observed (FIG. 5C).

Example 6: In Vivo CNGB1 Gene Augmentation in Cngb1^{-/-} Mice

[0219] Cngb1^{-/-} mice were treated with 1×10¹⁰ viral genomes (1 e 10 vgs) of AAV8-hRHO 194-hCNGB1-SV40 or AAV5-hRHO194-hCNGB1-SV40 subretinally at 4 weeks of age. Structural outcome measures included SD-OCT at 1 and 3 months post injection, histology, and immunohistochemistry.

[0220] General vector design is shown in FIG. 7. 1 e 10 total viral genomes in 1 ul was injected subretinally in 4 week old Cngb1^{-/-} mice (postnatal week 4; PW4).

[0221] AAV8-hRHO194-hCNGB1-SV40 gene augmentation was found to result in restoration of rod function post subretinal injection in Cngb1^{-/-} mice. Efficacy was found to persist out to 8 months post-treatment. Dark adapted ERG B wave amplitudes were found to be significantly improved in the treated mice (FIGS. 8A-8B). Scotopic electroretinography (ERG) at rod-specific stimulus Cngb1^{-/-} at 9 months (8 months post treatment in treated mice) is shown in FIG. 8A. ERG of wild-type and Cngb1^{-/-} mice before treatment showed that ERG B wave was absent in Cngb1^{-/-} mice at time of injection (FIG. 8B). CNGB1 channel expression in rod outer segments was found to be restored (FIGS. 9A-9B). A rabbit polyclonal anti-CNGB1 antibody that recognizes aa 1078-1168 of human CNGB1a (Sigma-Aldrich) was used for transgene expression assays. Immunohistochemistry was performed at 9 months in Cngb1^{-/-} mice treated with AAV8-hRHO194-hCNGB1-SV40 (8 months post treatment; FIG. 9A) and in untreated Cngb1^{-/-} mice (FIG. 9B), and

showed restoration of CNGB1 channel expression in treated Cngb1^{-/-} mice. OCT analysis revealed a significant delay in retinal degeneration (FIGS. 10A-10C). General injection schedule is shown in FIG. 10A. In vivo optical coherence tomography (OCT) images were collected at 9 months in Cngb1^{-/-} mice treated with AAV8-hRHO194-hCNGB1-SV40 (8 months post treatment; FIG. 10B) and in untreated Cngb1^{-/-} mice (FIG. 10C). As shown in FIG. 10, it was found that at 9 months, treated Cngb1^{-/-} mice had a thicker photoreceptor layer compared to untreated Cngb1^{-/-} mice.

[0222] AAV5-hRHO194-hCNGB1-SV40 gene augmentation was found to result in restoration of rod function by two months post subretinal injection in Cngb1^{-/-} mice. Dark adapted ERG B wave amplitudes were found to be significantly improved in the treated mice (FIGS. 11A-11E). Scotopic ERG was measured in treated and untreated Cngb1^{-/-} mice at 3 months of age (2 months post subretinal treatment in treated mice) and results are shown in FIG. 11A. B-wave amplitude in response to a light stimulus of -0.5 log (cd s/m²) measured in treated and untreated Cngb1^{-/-} mice (n=8) at 3 months of age (2 months post subretinal treatment in treated mice) is shown in FIG. 11B. OCT analysis revealed a significant delay in retinal degeneration. In vivo optical coherence tomography (OCT) images were collected at 3 months in Cngb1^{-/-} mice treated with AAV5-hRHO194-hCNGB1-SV40 (2 months post treatment; FIG. 11C) and in untreated Cngb1^{-/-} mice (FIG. 11D). Measurement of the photoreceptor layer thickness showed a significant delay in retinal degeneration in treated Cngb1^{-/-} mice at 3 months (2 months post treatment) compared to wild-type Cngb1^{-/-} mice (n=6; FIG. 11E).

Example 7: Mutant Dog Study Design

[0223] Cngb 1^{-/-} dogs have a mutation in exon 26 that leads to a truncated and non-functional protein, resulting in loss of rod function and retinal degeneration. Three Cngb1^{-/-} dogs were treated with AAV5-hRHO₁₉₄-hCNGB1a subretinally in both eyes at 3 months of age. For each animal, eye 1 was treated at a dose of 5 e 11 vgs (aiming for 2×100 ul blebs; "low dose") and eye 2 was treated at a dose of 1 e 12 vgs (aiming for 2×100 ul blebs; "high dose"). Structural outcome measures included SC-OCT at 1 and 3 months post injection, histology and immunohistochemistry.

Functional outcome measures included vision testing and ERG at 1 and 3 months post injection.

Example 8: Results of Mutant Dog Studies

[0224] AAV5-hRHO194-hCNGB1a-SV40 gene augmentation was found to result in restoration of rod function by one month post subretinal injection in Cngb 1^{-/-} dogs.

[0225] Dark adapted ERG waveforms were found to be significantly improved post treatment at both doses evaluated. Comparable injections were performed in both eyes. Obvious ERG rescue was observed in both eyes of treated dogs compared to untreated dogs, using both rod-specific stimulus (FIG. 12A) and flicker response (FIG. 12B). Larger ERG amplitudes were observed in eyes treated with the higher dose.

[0226] Vision testing showed that treated dogs had rod-mediated vision and improved performance in a four-choice vision testing device. FIGS. 13A-13B shows the results of vision testing of treated dogs at 1 month post injection and untreated dogs. A four-choice vision testing device was used. Untreated Cngb1^{-/-} dogs were found to have normal cone vision at this age, but lack rod-mediated vision. Untreated Cngb1^{-/-} dogs are blind at lower light levels (e.g., 5.7 e -2 cd/m²) and make fewer correct exit choices and take longer to exit from the testing device. Both treatment groups (high and low dose) were found to have restored rod vision as indicated by the significantly improved performance in correct exit choice (FIG. 13A) and time to exit (FIG. 13B), at the lowest lighting level.

[0227] The mean ERG A- and B-wave amplitudes in the high dose group were found to be higher compared to the low dose group. A- and B-wave amplitudes in treated eyes were found to be about 80% of wild-type levels. FIGS. 14A-14B shows ERG amplitude measurements one month post injection in each treatment group and the untreated group. A highly significant increase in A-wave amplitude for both treatment groups was observed compared to untreated controls. Improvement in response threshold in treated eyes was found to be greater than 1.5 log units (FIG. 14A). A highly significant increase in B-wave amplitude for all stages in the high dose group and all but the second and third strongest stimuli for the low dose group was found, compared to untreated controls. Improvement in response threshold in treated eyes was found to be greater than 2 log units (FIG. 14B).

SEQUENCE LISTING

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mol_type = other DNA
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SEQ ID NO: 7 moltype = DNA length = 10243

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gcctcgggga	caacacggaa	gaatgtccc	tctggatgt	atggggctga	agagctcaag	1560
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ggcgctggaa	acagttatat	tcgctgttac	tactttgcgt	tgaagaccct	catcaccatc	2520
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gaggagaagg	cgggatggaa					3738

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SEQ ID NO: 10          moltype = AA    length = 1065
FEATURE                Location/Qualifiers
REGION                 1..1065
note = MISC_FEATURE - Abca4 (ATP binding cassette subfamily
                           A member 4)
source                 1..1065
mol_type = protein
organism = Homo sapiens
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SEQUENCE :	10	Organism	- Homo sapiens	
MDVVVLHHVPE	AKLVECIGQE	LIFLLPNKNF	KHRAYASLFR ELEETLADLG LSSFGISDTP	60
LEEEIFLKVT	DSDSGPLFLAG	GAQQKREVN	PRHPCLGPRE KAGOTPQDSN VCSGPAPAAH	120
PEGQPPPEPE	CPGPQLNTGT	VLQLQHVQAL	LVRKFQHTIR SHKDPLAQIV LPATFVFLML	180
MLSIVIPFPF	EYPALTLHPW	IYGQOYTFFS	MDEPGSEOFQ VLADVLNNKP GFCNRCLKEG	240
WLPEYPCGNS	TPWKTPSPVSP	NITQLFQKQK	WTQVNPSSPSC RCSTREKLT M LPECPEGAGG	300
LPPPQRTQR	TEILQDLTDR	NISDPLVKT	KFWVNEQRYG GISIGGKLPV	360
VPIGEALV	FLSDLGRMIM	VSGGPI	TREA SKEIPDFLKH LETEDVNLVW FNNKGWHALV	420
SFLNVHNAAI	LRASLPLKDRS	PEEYGITIVS	QPLNLTKEQL SEITVLTTSV DAVAIIACVIF	480
SMSFVPASFV	LYLIQERVNK	SKHLQFISGV	S PTTYWVTFN LWDIMNYSVS AGLVVGIFIG	540
FQKKAYTSPE	NLPALVALLL	LYGWAVIPMM	Y PASFLFDVP STAVVALSCA NLFIGINSSA	600
ITFILELFEN	NRTLLRFNAV	LRKLLIVFPH	FCLRGRLIDL ALSQAVTDVY ARFEGHEHSAN	660
PFPHWLIGK	LFAMVVEGVV	FYLLTLLVQR	F HFLSQSWIAE TPKIEPVDED DDVAEERQR	720
ITGGNKTDIL	RLHELTKIYP	GTSSPAVDRL	CVGVPRGECE F GLLGVSAGK TTTFKMLTG	780
TTVTSGDATV	AGKSILTNIS	EVHQNMGYCP	QFDAIDELLT GREHLYLAR LRGVPAEEIE	840
KVANWSIKSL	GLTVYADCLA	GTYSGGNKR	LSTAIALIGC PPLVLLDEPT TGMDPQARM	900
LWNVIIVSI	EGRAVVLTSM	SMEECALST	R LAIMVKQAF RCMGTIQHLK SKFGDGYIVT	960
MKIKPSKDDL	LPDLNVMVQE	FQGNFGPSVQ	R ERHYNMLQF QVSSSLARI FQLLSHKDS	1020
LLIEEYSVTQ	TTLDQVFVN	AKQOTESHDL	PLHPRAAGAS RQAQD	1065

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SEQ ID NO: 11          moltype = AA    length = 384
FEATURE                  Location/Qualifiers
REGION                   1..384
note = MISC_FEATURE - AIPL1 (Aryl-hydrocarbon-interacting
                           protein-like 1)
source                   1..384
mol_type = protein
organism = Homo sapiens
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SEQUENCE: 11
MDAALLNNEV GVKKTILHGG TGELPNFTG SRVIFHRTM KCDEERTVID DSRQVGQPMH 60
IIIGNMFKLE VWEILNTSMR VHEVAEFWCD TIHTGVYPL SRSRLRQMAQG KDPTEWHVHT 120
CGLANPMAYH TLGYFEDLDEL QKEPQOLIVPEV TELLOVADPS DYORETWNLIS NHEKMKAPVY 180

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LHGEGNRLFK	LGRYEEASSK	YQEAIIICLRN	LQTKEKPWEV	QWLKLEKMIN	TLILNYCQCL	240
LIKKEEYEV	EHTSDILRHH	PGIVKAYYVR	ARAHAEVWNE	AEAKADLQKV	LELEPSMQKA	300
VRRELRRLLEN	RAEKQEEER	LCRNMMLSQG	ATQPPAEPPT	EPPAQSSTEP	PAEPPTAPSA	360
ELSGAGPPAEP	ATEPPPSPGH	SLQH				384

SEQ ID NO: 12	moltype = AA length = 585	
FEATURE	Location/Qualifiers	
REGION	1..585	
	note = MISC_FEATURE - BEST1 (Bestrophin-1), isoform 1	
source	1..585	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 12		
MTITYTSQLA NARLGSFSRL	LLCWRSIYK LLYGEFLIFL LCYYIIRFIY RLALEEQQL	60
MFEKLKLYCD SYIQLIPSF	LGFLYVTLLV TRWWNQYENL PWPDRLMSLV SGFVEGKDEQ	120
GRLLRRRTLIR YANLGNVLIL	RSVSTAVYKR FPPSAQHLVQA GFMTPAEHKQ LEKLSLPHN	180
FWVPWVWFAN LSMKAWLGGR	IRDPILLQL LNEMNTLRTQ CGHLYAYDWI SIPLVYTQVV	240
TVAVYSFLT CLVGRQFLNP	AKAYPGHEDL LVVPVFTRFLQ FFFYVGWLKV AEQLINPFGE	300
DDDDFETNW1 VDRNLQVSLL	AVDEMHDQLP RMEPDMYWNK PEPPQPYTAA SAQFRRASFM	360
GSTFNISLNK EEMEFQPNQE	DEEDAHAQII GRFLGLQSHD HHPPRANSRT KLLWPKRESL	420
LHEGLPKNH AAKQNVRGQE	DNKAWKLAV DAFKSAPLYQ RPGYYSAPQT PLSPTPMFFF	480
LEPSAPSCHKL SVTGDITKDK	SLKTVSSGAK KSPELLSESD GALMEHPEVS QRRRKTVEFN	540
LTDMPPEIPEN HLKEPLEQSP	TNIHTTLKD MDPYWALENR DEAHS	585

SEQ ID NO: 13	moltype = AA length = 1977
FEATURE	Location/Qualifiers
REGION	1..1977
	note = MISC_FEATURE - CACNA1F (Voltage-dependent L-type calcium channel subunit alpha-1F), isoform 1
source	1..1977
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 13	

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AVASAQRSPR ALFCCLTLANP	LRRSCISIVE WKPFIDLILL TIFARNVALG VYIPPFEDDS	120
NTANHNLLEQV EVVFLVIFTV	ETVLKIVAYG LVLHPSAYIR NGWNLLDFII VVVLGFSVLL	180
EQGPGRGDA PHTGGKPGGF	DVKALRAFPV LRPLRLVSGV PSLHIVLNSI MKALVPLHI	240
ALLVLVFLVIII YAIIGLELFL	GRMHKTCYFL GSDEMAEEDP SPCASSGSGR ACTLNQTECR	300
GRWPGPNGGI TNFDNPFFFAM	LTVFQCVTME GTWDVLYWMQ DAMGYELPWV YFVSLVIFGS	360
FFVFLNVLGV LGSEFSKERE	KAKARGDFQK QREKQQMEED RGRYLDWITQ AEELDMEDPS	420
ADDNLGSMAE EGRAGRHRPQL	AELTMRRRGR LRWFSSHSTRS THSTSSHASL PASDTGSMTE	480
TQGDEDEEEG ALASCTRCNL	KIMKTRVCRR LRRANRVLRA RCRRAVKNSA CYWAVLLL	540
LNTLTIASEH HGQPVWLTQI	QYEYANVKKL LFTVEMLLKL YGLGPSAYVS SFFNRFDCCV	600
VCGGILETTL VEVGAMQPLG	ISVLRVCVLL RIFKVTRHWA SLSNLVASSL NSMKSIASSL	660
LILLFLIIIF SLLGMQLFGG	KFNFNDQTHTK RSTFDTFPQA LLTVFQILTG EDWNVMYDG	720
IMAYGGPFFP GMLVCIYFII	LFICGNYIIL NVFLAIAVDN LASGDAGTAK DKGGEKSNEK	780
DLPQENEGLV PGVEKEBEEG	ARREGADAME EEEEEEEEEE EEEEEEAGGGV ELLQEVVPKE	840
KVVPipeGLSA FPLCSQTNP	RKGCHTLIH HVFTNLLL VF IISSVSLLA EDPIRAHSFR	900
NHILGYFDYA PTSIFTVEIL	LKMTVFGAFL HRGSFCRCSWF NMNLDLUVSV SLISPGIHSS	960
AISVVVKILRV LRLVRLPRAI	NRAKGLKHVV QCVFVAIRI GNIMIVTTLL QFMMACIGVQ	1020
LFKGKFYTCT DEAKHTPQEC	KGSFLVYPDG DVSRLPVRER LWVNNSDFNFD NVLSAMMALF	1080
TVSTFEGWPA LYKAIDAYA	EDHGFIYNYR VEISVFFIVY IIIIAFFMMN IFVGFVIITF	1140
RAGEQEYQNC QELCDNQRCQ	VEYALKAQPL RRYIPKPNHQ YRVWATVNSA AFEYLMFLII	1200
LLNTVALAMQ HYEQTAPFNY	AMDILNMVFT GLFTIEMVLK IIIFKPKHYF TDAWNTFDAL	1260
IVVGSIVDIA VTEVNNGGHL	GESSEDDSSRI SITFFRLLFRV MRLVKLLSKG EGIRTLLWTF	1320
IJKSFQALPYV ALLIAMIFFI	YAVIGMOMFG KVALQDGTOQI NRNANNFQTFP QA VALLLFRCA	1380
TGEAWQEIML ASLPGNRCDP	ESDFCPGEFF TCGSNFAIAY FISFFMLCAF LIINLFLVAVI	1440
MDNFIDYLTRD WSILGPHHLD	EFPKRIWEYD PGAKGRIKHL DVVALLRRIQ PPLGFLGKLC	1500
HRVACKRLVA MNMPLNSDGT	VTFNATLFL VRDSLKIKTE GNLEQANQEL RIVIKKIWK	1560
MKQKLLDEV1 PPPDEEEVTV	GKFYATFLIQ DYFRKFRRRN EKGLLGNDAA PSTSSALQAG	1620
LRSLQDLGPE MRQALTCDE	EEEEEEQGEVG EEEDEKDLER NKATMVSQPS ARRSGSGISVS	1680
LPVGDRLPDS LSFGPSDDDR	GTPTSSQPSV PQAGSNTHRR GSGALIFTIP EEEGNSQPKGT	1740
KGONKQDEDE EVPDRLSYLD	EQAGTPPCSV LLPPHRAQRY MDGHLVPRR LLPPPTPAGRK	1800
PSFTIQCLQR QGSCEDLPIP	GTYHGRGRNSG PNRAQGSWAT PPQRGRLLYA PLLLVEEGAA	1860
GEGYLGRSSG PLRTFTCLHV	PGTHSDPLSH KRGSDADS LVE AVLISEGLL FARDPRFVAL	1920
AKQEIAADACR LTLDDEMDDNAA	SDLLAQGTSS LYSDEEISL RFDEEGLGDE MACVHAL	1977

SEQ ID NO: 14	moltype = AA length = 438
FEATURE	Location/Qualifiers
REGION	1..438
	note = MISC_FEATURE - CLN3 (Battenin), isoform 1
source	1..438
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 14	

MGCGAGSRRR PSDSEGEETV	PEPRLPLLDH QGAHWKNAV FGWLGLCNMF SYVVMLSAAH	60
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DILSHKRTSG	NQSHVDPGPT	PIPHNSSSRF	DCNSVSTAAV	LLADILPTLV	IKLLAPLGLH	120
LIPYSPRLV	SGICAAGSFV	LVAFSHSVT	SLCGVVFAASI	SSGLGEVTFI	SLTAFYPRAV	180
ISWWSSGTGG	AGLLGALSYL	GLTQAGLSPQ	QTLLSMLGIP	ALLASFYFL	LTSPEAQDPG	240
GEEEAESAAR	QPLIRTEAPE	SKPGSSSSLS	LRERWTVFKG	LLWYIVPLVV	VYFABYFINQ	300
GLFELLFFFWN	TSLSHAQQYR	WYQMLYQAGV	FASRSSLRC	RIRFTWALAL	LQCLNLVFLL	360
ADVWFGLPLS	IYLVFLIILY	EGLLGGAAYV	NTFHニアLET	SDEHREFAMA	ATCISDTLGI	420
SLSGLLALPL	HDFLCQLS					438
 SEQ ID NO: 15		moltype = AA	length = 232			
FEATURE		Location/Qualifiers				
REGION		1..232				
		note = MISC_FEATURE - CLRN1 (Clarin-1)				
source		1..232				
		mol_type = protein				
		organism = Homo sapiens				
 SEQUENCE: 15						
MPSQQKKIIF	CMAGVFSFAC	ALGVVTALGT	PLWIKATVLC	KTGALLVNAS	GQELDKFMGE	60
MQYGLFHFEG	VRQCGLGARP	FRFSFFPDL	KAIPVSIHVN	VILFSAILIV	LTMVGTAFFM	120
YNAFGKPFET	LHGPGLYLL	SFISGSCGCL	VMILFASEVK	IHHLEKIAN	YKEGTYYVYKT	180
QSEKYTTFSW	VIFFCFVFHV	LNGLLIRLAG	FQPPFAKSKD	AETTNVAADL	MY	232
 SEQ ID NO: 16		moltype = AA	length = 690			
FEATURE		Location/Qualifiers				
REGION		1..690				
		note = MISC_FEATURE - CNGA1 (cGMP-gated cation channel				
		alpha-1), isoform 1				
source		1..690				
		mol_type = protein				
		organism = Homo sapiens				
 SEQUENCE: 16						
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HARGSFSYKS	LRKGGPSQRE	QYLPGAIALF	NVNNSSNKQDQ	EPEEKKKKK	EKKSKSDKN	120
ENKNDPEKKK	KKKDKKEKKKK	EEKSKDKKEE	EKKEVVVIDP	SGNTYYNWLF	CITLPVMYNW	180
TMVIARACFD	ELQSDYLEYW	LILDYVSDIV	YLIDMFVTRR	TGYLEQGLLV	KEELKLINKY	240
KSNLQFKLDV	LSSIPLDLY	FKLGWNYPEI	RLNRLLRFSSR	MFEFFQRTET	RTNYPNIFRI	300
SNLVMYIVII	IHWNAVCVFYS	ISKAIGFGND	TWVYVDINDP	EFGRLARKYV	YSLYWSTLTL	360
TTIGETPPPV	RDSEYVFVVV	DFLIGVLIFA	TIVGNIGSMI	SNMNAARAES	QARIDAIKQY	420
MHPRNVSKDM	EKRVVIKFWD	LWTNKTKTDE	KEVLKYLDPK	LRAEIAINHV	LDTLKVRI	480
ADCEAGLLVE	LVLKLQPQVY	SPGDYRCKKG	DIGREMYIIK	EGKLAVVADD	GVTQFVVLSD	540
GSYFGEISIL	NIKGSKAGNR	RTANIKSIGY	SDLFCLSKDD	LMEALTEYPD	AKTMLEEKKG	600
QILMKDGLLD	LNIAAGSDP	KDLEEKVTRM	EGSVDLLQTR	PARILAEEYES	MQQKLKQRLT	660
KVEKFLKPLI	DTEFSSIEGP	GAESGPIDST				690
 SEQ ID NO: 17		moltype = AA	length = 2479			
FEATURE		Location/Qualifiers				
REGION		1..2479				
		note = MISC_FEATURE - CEP290 (centrosomal protein of 290				
		kDa), isoform 1				
source		1..2479				
		mol_type = protein				
		organism = Homo sapiens				
 SEQUENCE: 17						
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MKAQEVELAL	EEVEKAGEEQ	AKFENQLTKT	VMKLENELEM	AQQSAGGRDT	RFLRNEICQL	120
EKQLEKQDRE	LEDMEKELEK	EKKVNEQAL	RNEEAENENS	KLRRENKRKLK	KKNEOCLCQDI	180
IDYQKQIDSQ	KETLLSRGGE	DSDYRSQLSK	KNYELIQYLD	EIQQLTEANE	KIEVQNQEMR	240
KNLLEEVQEM	EKMTDEYNRM	KAIVHQTDNV	IDQLKKENDH	YOLQVQELTD	LLKSKNEEDD	300
PIMVAVNAVK	EEWKLILSSK	DDEIIEYQQM	LHNLREKLKN	AQLDADKSNV	MALQQGIQER	360
DSQIKMLTEQ	VEQYTKEMEI	NTCIIIEDLN	ELQRNKGAST	LSQQTHMKIQ	STLDILKEKT	420
KEAERTAELA	EADAREKDKE	LVEALKRLKD	YESGVYQLED	AVVEIKNCNK	QIKIRDREIE	480
IILTKEINKLE	LKISDFLDEN	EALRERVGLE	PKTMIDLT	RNSKHLKQQQ	YRAENQILLK	540
EIESLEEERL	DLKKKIRQMA	QERGKRSATS	GLTTEDLNLT	ENISQGDRIS	ERKLDDLSSK	600
NMSEAQSKE	PLSRELIEKE	RDLESRTVI	AKPQNLKEL	VEENKQLEEG	MKEILQAIKE	660
MQKDPDVKG	ETSLIIPSLE	RLVNAIESKN	AEGIFDASHL	LKAQVQDQLTG	RNEELRQELR	720
ESRKAEAINYS	QQLAKANLKI	DHLEKETSSL	RQSEGNSVVF	KGIDLPDGIA	PSSASIINSQ	780
NEYLIHLLQE	LENKEEKKLN	LEDSLDEYNR	KFAVIRHQOS	LKYKEYLSEK	ETWKTESKTI	840
KEEKRKLEQDQ	VQODAIKVKE	YNNLLNQALQM	DSDEMKKILA	ENSRKITVQ	VNEKSLIRQY	900
TTLVELERQL	RKENEKQKNE	LLSMEAECVE	KIGCLQRPK	MAIFKTAALQ	KVVDNSVSL	960
ELELANKQYN	ELTAKYRDIL	QDNMLVQRT	SNLEHLECEN	ISLKEQVEST	NKELEITKEK	1020
LHTIEQAWEQ	ETKLGNESSM	DKAKKSITNS	DIVSISKKIT	MLEMKELNER	QRAEHQCKMY	1080
EHLRTSLQKM	EERNFELETT	FAELTKINLD	AQKVEQMLRD	ELADSVSKAV	SDADRQRI	1140
LEKNEMELKV	EVSKLREISD	IARRQVEILN	AQQQSRDKEV	ESLRMQLDY	QAQSDEKSLI	1200
AKLHQHNQVSL	QLSSEATALGK	LESITISKLQK	MEAYNLRLEQ	KLDEKEQALY	YARLEGRNRA	1260
KHLRQTIQSL	RRQFSGALPL	AQQEKFSTKTM	IQLQNDKLKI	MQEMKNSQOE	HRNMENKTLE	1320
MELKLKGLEE	LISTLKDTC	AQKVINWHMK	IEELRLQELK	LNRELVKDKE	EIKYLNIIIS	1380
EVERTISSLE	EEIVQQNKFH	ERQMAWDQR	EVDLERQLDI	FDRQQNEILN	AAQKFEATG	1440

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SIPDPSLPLP	NQLEIALRKI	KENIRIILET	RATCKSLEEK	LKEKESALRL	AEQNILSRDK	1500
VINELRLRLP	ATAEREKLIA	ELGRKEMEPK	SHHTLKTAHQ	TIANMQARLN	QKEEVLKKYQ	1560
RLLEKAREEQ	REIVVKKHEED	LHILHHRLEL	QADSSLNKFK	QTAWDLMQQS	PTPVPTNKHF	1620
IRLAEMBQTV	AEQDDSLSSL	LVKLKKVSDQ	LEROREITTEL	KVKEFENIKL	QLQENHEDEV	1680
KVKVAEVEDL	KYLLDQSQKE	SQCLKSELQA	QEANSRAPT	TTMRNLVERL	KSQLALKEKQ	1740
QKALSRALLE	LRAENTAAAB	ERIIISATSQK	EAHLNVQQIV	DRHTRELKTQ	VEDLNENLLK	1800
LKEALKTSKN	RENSLTDLNL	DLNNELOKKQ	KAYNKILREK	EIIDQENDEL	KRQIKRLTSG	1860
LQGKPLTDNK	QSLIELQRL	VKKLENQLEG	KVEEVSDLKPM	KEKNAKEELI	RWEEGKKWQA	1920
KIEGIRNKLK	EKEGEVFTLT	KQLNLTLDLF	AKADKEKLT	QRKLKTTGMI	VDQVLGIRAL	1980
ESEKELEELK	KRNLLDLEN	LYMRAHQALP	RDSVVEDLHND	QNRYLQEKHL	ALEKQFSKDT	2040
YSKPSISGIE	SDDHCQREQE	LQKENLKLSS	ENIELKFQLE	QANKDLPRLK	NQVRDLKEMC	2100
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EKMANIEQEN	EKLKAELEKL	KAHLGHQLSM	HYESKTKGTE	KIIAENERLR	KELKKETDA	2220
EKLRIAKNNL	EILNEKMTVQ	LEETGKRLQF	AESRGPGQLEG	ADSCKSWKSIV	VTRMYETKLK	2280
ELETDIAKKN	QSITDLQKL	KEATEREQKV	NKYNEDLEQQ	I KILKHVPEG	AETEQGLKRE	2340
LOVRLRLANHQ	LDKEKAEELIH	QIEANKDQSG	AESTIPDADQ	LKEKIDLDET	QLKMSDLEKQ	2400
HILKEEIKKLK	KELENFDPSF	FEEIEDLKYN	YKEEVKKNIL	LEEKVKKLSE	QLGVELTSPV	2460
AASEEFEDEE	ESPVNFPPIY					2479

SEQ ID NO: 18 moltype = AA length = 1406
 FEATURE Location/Qualifiers
 REGION 1..1406
 note = MISC_FEATURE - CRB1 (protein crumbs homolog 1),
 isoform 1
 source 1..1406
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 18
 MALKNINYLL IFYLSFSLLI YIKNSFCNKN NTRCLSNSCQ NNSTCKDFSK DNDCSCSDTA 60
 NNLDKDCDNM KDPCFSNPQC GSATCVNTPG ERSFLCKCPP GYSGTICETT IGSCGKNSCQ 120
 HGGICHQDP1 YPVCICPAGY AGRFCEIDHD ECASSPCQNG AVCQDGIDGY SCFCVPGYQG 180
 RHDCLVEDDEC ASDPCKNEAT CLNEIGRYTC ICPHNYSGVN CELEIDECSWS QPCLNGATCQ 240
 DALGAYPCDC APGFLGDHCE LNTDECASQP CLHGGLCVGD ENRYSNCNTG SGFTGTHCET 300
 LMLPCWSKPC HNNATCEDSV DNYTCHCWPG YTGAQCEIDL NECNSNPCQS NGECVSELSE 360
 KQYGRITGLP SFFSYHEASG YVCICQPGFT GIHCEEDVNE CSSNPQCNGG TCENLPGNYT 420
 CHCPFDNLSR TFYGRDCCSD ILLGCTHQCC LNNGTCIPH QDGQHGFSC1 CPSGYTGSLC 480
 EIATTLSFEG DGFLWVKGSG VTTKGSVCNI ALRFQTVQPM ALLLFRSNRD VFVKLELLSG 540
 YIHLHSIQVNN QSKVLLFISH NTSDGEWHFV EVIFAEAVTL TLIDDSCKEK CIAKAPTPLE 600
 SDQSICAFQNF SFLGGLPVGM TSNGVALLNF YNMPSTPSFV GCLQDIKIDW NHITLENISS 660
 GSSLNVKAGC VRKDWCESQP CQSRRGCINL WLSYQCDCHR PYEGPNCLRE YVAGRFGQDD 720
 STGYVIPTLD ESYGDTISLS MFVRTLQPSG LLLALENSTY QYIRVWLERG RLAMLTTPNSP 780
 KLVVKFVLND CNVHLISLKI KPYKIELYQS SQNLGFISAS TWKIEKGDVI YIGGLPDKQE 840
 TEIENGFFKG CTQDVRLLNNQ NLEFFPNPTN NASLNPVLVN VTQGCAQDNS CKSNPCHNGG 900
 VCHSRWDDFS CSCPALTSKG ACEEVQWCGF SPCHGQAQCQ PVLGQFECIA NAVFNGQSGQ 960
 ILFRSRNGNIT RELTNITFGF RTRDANVILL HAAKEPEPLN ISIQDSSLFF QLQSGNSFYM 1020
 LSLTSLSQSVN DGTWHEVTLS MTDPLSQTSR WQMEVDNETP FVTSTIATGS LNFLKDNTDI 1080
 YVGDRADNI KGLQGCLSTI EIGGIYLSF ENVHGFINKP QEEQFLKIST NSVVIGCLQL 1140
 NVCNNSPCLH GGNCDIYSS HYSCSPLGWS GKHECLNIDE CFSPNCIHGN CSDRVAAYHC 1200
 TCEPGYTVN CEVDIDNCQS HQCANGATCI SHNGYSLC FGNFTGKFCR QSRLPSTVCG 1260
 NEKTNLTCYN GGNCTEFQTE LKCMCRPGFT GEWCEKDIDE CASDPCVNNG LCQDLLNKFQ 1320
 CLCDVAFAGE RCEVDSLADDL ISDIFTTIGS VTVALLLILL LAIVASVVTS NKRATQGTY5 1380
 PSRQEKEGSR VEMWNLMPPP AMERLI 1406

SEQ ID NO: 19 moltype = AA length = 1285
 FEATURE Location/Qualifiers
 REGION 1..1285
 note = MISC_FEATURE - CRB2 (protein crumbs homolog 2)
 source 1..1285
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 19
 MALARPPTD PQALASVLLL LLWAPALSLL AGTVPSEPPS ACASDPCAPG TECQATESGG 60
 YTCGPMERPRG CATQPCHHGA LCVPQGPDT GFRCYCVPGF QGPRCELDID ECASRPCHHG 120
 ATCRNLADRY ECHCPLGYAG VTCEMEVDEC ASAPCLHGGG CLDGVGFSFRC VCAPGYGGTR 180
 CQLDLDECQSF QPCAHHGGTQ DLVNGRHCDC AGTGYEGTH EREVLECASEA PCEHNASCLE 240
 GLGSFRCLCW PGYSGELCEV DEDECASSPC QHGGRCQLRS DPALYGGVQA AFPGAFSFRH 300
 AAGFLCHCPCP GFEGADCGVE VDECASRPCL NGGGCQDLPN GFQCHCPDGY AGPTCEEDVD 360
 ECLSDPCLHG GTCSDTVAGY ICRCPETWG RDCSVQLTGC QGHTCPLAAT CIPIFESGVH 420
 SYVCHCPGPT HGPFCGQNTT FSVMAGSPIQ ASVPAGGPLG LALRFRRTLQ AGTIAATRNDT 480
 KESLELALVA ATLQATLWSY STTVLVLRP DLALNDGHWH QVEVVLHLLT LELRLWHEGC 540
 PARLCVASGP VALASTASAT PLPAGISSAQ LGDATFAGCL QDVRVDGHLL LPEDLGENVL 600
 LGCERREQCR PLPCVHGGSC VDLWTHFRC CARPHRGPTC ADEIIPAATFG LGGAPSSASF 660
 LLIQELPGPNL TVSFLLRTRE SAGLLLQFAN DSAAGLTVEL SEGRIRAEVP GSPAUVLPGR 720
 WDDGLRHLMV LSFGPDQLQD LGQHVHVGGR LLAADSQPWG GFPRGCLQDL RLDGCHLPFF 780
 PLPLDNSSQP SELGGRQSWN LTAGCVSEDM CSPDPFCNNGG TCLVTWNDFH CTC PANFTGP 840
 TCAQQLWCPG QPCLPPATCE EVPDFGFCVVA EATFREGPPA AFSGHNASSG RLLGGSLA 900

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RTRDSEAWLL	RAAAGAALEGV	WLAVRNGSLA	GGVRGGHGLP	GAVLPPIPGR	VADGAWHRVR	960
LAMERPAATT	SRWLLWLDS	ATPVALRGLA	SDLGFLQPGP	AVRILLAENF	TGCLGRVALG	1020
GLPLPLARPR	PGAAPGAREH	FASWPGTPAP	ILGCRGAPVC	APSPCCLHDGA	CRDLFDFAAC	1080
ACCPGWEPR	CEAHVDPCHS	APCARCRHT	HPDGRFECRC	PPGFGGPRCR	LPVPSKECSL	1140
NVTCLDGSPC	EGGSPAANCS	CLEGLAGQRC	QVPTLPCEAN	PCLNNGTCRA	AGGVSECICN	1200
ARFSGQFCEV	AKGLPLPLPF	PLLEVAVPAA	CACLLLILLG	LLSGILAARK	RRQSEGTYSP	1260
SQQEVAGARL	EMDSVLKVPP	EERLI				1285

SEQ ID NO: 20	moltype = AA	length = 299				
FEATURE	Location/Qualifiers					
REGION	1..299					
	note = MISC_FEATURE - CRX (cone rod homeobox protein)					
source	1..299					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 20						
MMAYMNPMPGH YSVNALALSG	PSVDMHMQAV	PYPSAPRKQR	RERTTFTRSQ	LEELEALFAK	60	
TQYPDVPYARE EAVALKINLP	SRVQWFKNR	RAKCRQQRQQ	QKQQQOPPGG	QAKARPAKRK	120	
AGTSPRVPTSD VCPDPGLISD	SYSPPLPGS	GSPTTAVATV	SIWSPASESP	LPEAQRAGLV	180	
ASGPSTSAP YAMTYAPASA	FCSSPSAYGS	PSSYFSGLDP	YLSPMVPQLG	GPALSPLSGP	240	
SVGPPLAQS P TSLSGQSYGA	YSPVDSLEFK	DPTGTWKFTY	NPMPLDYKD	QSAWKFQIL	299	
SEQ ID NO: 21	moltype = AA	length = 6306				
FEATURE	Location/Qualifiers					
REGION	1..6306					
	note = MISC_FEATURE - GPR98 (G-protein coupled receptor 98)					
source	1..6306					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 21						
MSVFLGPMPG SASLLVNLLS	ALLLIFVFGE	TEIRFTGQTE	FVVNETSTTV	IRLIIERIGE	60	
PANVTAIVSL YGEDAGDFD	TYAAAFIPAG	ETNRTVYIAV	CDDDLPEPDE	TFIFHLTQK	120	
PSANVKLGWP RTVTVTILSN	DNAFGIISFN	MLPSIAVSEP	KGRNESMPLT	LIREKGTGYGM	180	
VMVTFFEVGG PNPPDEDLSP	VKGNTTFPPG	RATVIYNLTV	LDDEVPENDE	IFLIIQLKSVE	240	
GGAEITNSRN SIEEIIKKND	SPVRLFLQSIY	LVPEEDHILI	IPVVRGKDNN	GNLIGSDEYE	300	
VSISYAVTTG NSTAAHQCNL	DFIDLQPNTT	VVPPPFHIHES	HLKFQIVDDDT	IPEIAESFHI	360	
MLLKDTLQGD AVLISPSVQ	VTIKPNDKPY	GVLSFNSVLF	ERTVIIIDEDR	ISRYEEITVV	420	
RNGGTHGNVS ANWVLTRNST	DPSPVTA DIR	PSSGVLHFAQ	GQMLATIPLT	VVDDDLPEEA	480	
EAYLLQILPH TIRGGAEVSE	PAEELFYI QD	SDDVYGLITE	FFPMENQKIES	SPGERYLSLS	540	
FTRLGGTKGD VRLLYSVLYI	PAGAVDPLQA	KEGILNISR	NDLIFPEQKT	QVTTKLPIRN	600	
DAFLQNGAHF LVQLETVELL	NIIPLIPPI	PRGEICNMIS	LLVTPAIANG	EIGFLSNLP	660	
ILHEPEDFAA EVVYIPLH RD	GTDGQATVW	SLKPSGFNSK	AVTPDDIGPF	NGSVLFLSGQ	720	
SDTTINITIT GDDIPEMNET	VTLSLDRVN	ENQVLKSGYT	SRDLIILEND	DPGGVFEFSP	780	
ASRGPYVIKE GSEVLEHII R	SRGSLVKQFL	HYRVEPRD NS	EFYQNTGVLE	FKPGEREIVI	840	
TILLARLDGIP ELDEHYWWVL	SSHGERESKL	GSATIVNITI	LKNDDPHGII	EFVSDGLIVM	900	
INESKGDAI SAVYDVVRNR	GNFGDVS VSW	VVSPDFTQDV	FPVQGTVFG	DQEFSKNITI	960	
YSLPDEIPEE MEEFTVILLN	GTGAKAVGNR	TTATLRIRRN	DDPIYFAEPR	VVRVQEGETA	1020	
NFTVLRNGSV DVTCMVQYAT	KDGKATARA	DFIPVKEGET	LIFEVGSRQQ	SISIFVNEDG	1080	
IPETDEPFYI ILLNSTGDTV	VYQYGVATVI	IEANDDPNGI	FSLEPIDKAV	EEGKTNAFWI	1140	
LRHRGYFGSV SVSQWLQFND	SALQPQGEFY	ETSGTVNFMD	GEEAKPIILH	AFPDKIPEFN	1200	
EFFFLKLVNI SGGSPGPGGQ	LAETNLLQTV	MVFPNDDPFQ	VFILDPEC LE	REVAEDVLS	1260	
DDMSYITNFT ILRQQGVFGD	VQLGWLSS	EFPAGLPPMI	DFLVQGIFT	TVHLQHMRR	1320	
HHSGTDALYF TGLEGAFGTV	NPKYHPSRN	TIANFTFSAW	VMPNANTNG	IIAKDGN GS	1380	
IYYGVKIQTN ESHVTLSLHY	KTLGSNATYI	AKTTVMKYLE	ESVWLHLLII	LEDGIIEFYL	1440	
DGNAMPRIK SLKGEAIT	PGILRIGAGI	NGNDRFTGLM	QDVRSYERKL	TLEEIYELHA	1500	
MPAKSDLHPI SGYLEFRQGE	TNKSDFL	DDNDEE GEEL	FILKLVSVY	GARISEENT	1560	
ARLTIQKSDN ANGLFGFTGA	CIPEIAEEGS	TISCVVTER	GALDYVHV	FY TISQIETDGI	1620	
NYLVDDFANA SGTITFLPWQ	RSEV LNIYV	DDD IPELNEY	FRVTLVSAIP	GDGKLGSTPT	1680	
SGASIDEPEK TTDTITKASD	H PYGLLQFST	GLPQPKDAM	TLPASSVPHI	TVEEEDGEIR	1740	
LLVIRAQG LL GRVTA FERTV	SLATFAS PED	QNVAGTLEFQ	PGERYKYIFI	NITDNSIPEL	1800	
EKSFKVELLN LEGGVAELFR	VDGS GSGD GD	MEFLPLTIHK	RASLGVASQI	LVTIAASDH	1860	
HGVFEFSPES LFVSGTEPED	GYSTVTLN VI	RHHGTLSPV	LHWNIDSDPD	GDLAFTSGNI	1920	
TFFIGQTSAN ITVEILPDED	PELDKA FSVS	VLSVSSGSLG	AHINATLTVL	ASDDPYGIFI	1980	
FSEK NRPV KV EEA	TOMITL S	IIRLKGLMGK	V L VSYATLDD	MEKPYFPPM	LARATQGRDY	2040
IPASGFALFQ ANQSEATIAI	SIL DDE	SESVFIELLN	STL VAKVQSR	SIPNSPRLGP	2100	
KVETIAQLLI I AND DAFG TL	QLSAPIVRA	ENHV GP INV	TRTGGAFADV	SVKFKAVPIT	2160	
AIAGEDYSIA SSDV VLLEGE	TSKAVPI YVI	NDI YPELEES	FLVQLMNETT	GGARLGALTE	2220	
AVIIIEASDD PYGLFGFQIT	KLIVEEPEPN	SVKVNLP II	NSGT LGNVTV	QWV ATINGQL	2280	
ATGDLRVVSG NVT FAPGETI	QTLL LEVLA	DVPEIEEVIQ	VQLTDASGGG	TIGLDRIANI	2340	
I IPAN DD PYG TVAFA QM VYR	VQ EPLERSS C	ANITV RRS GG	HFG RLL FYS	TSD IDVV ALA	2400	
MEEGQ DLLS Y YES PIQGV P	PLW RTWM NVS	AVG EPLYCA	TL CLK EQAC S	AFSFF SASEG	2460	
PQC FWM TSWI SPA VNNS DFW	TYR K NMTR VA	SLF SGQ AVAG	SDY EPV TRQ W	AIM QEG DEFA	2520	
NLT VSI LPD DPEM D EFL	SLV E HLM NI	SAS LK NQ PTI	GOP NIST VVI	AL NGDA FG V	2580	
VIYN IS PNTS ED GLF VEV Q	Q P QTL VEL MI	H RTG G S L G QV	A VE WRV VGG T	ATE GLD FIG A	2640	
GEILT FAE GE TKK T VLT IL	DD SE P E DDES	I I VSL VY TEG	G SR IL PSS DT	VR VNI LAN D	2700	
VAG IV S PNT S R S VIG HE	I L QF H V I RT F	P GR GN VTV NW	KI GQ NLE N	FAN FSG QL FF	2760	

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PEGSLNNTLF	VHLLDDNIPE	EKEVYQVILY	DVRTQGVPPA	GIALLDAQGY	AAVLTVEASD	2820
EPHGVLNFAL	SSRFVLLQE	NITIQLFINR	EFGLGAINV	TYTTVPGMLS	LKNQTVGNLA	2880
EPEVDFVPII	GFLILEEGET	AAAINITILE	DDVPELEEFY	LVNLTYVGLT	MAASTSFPPR	2940
LDSEGLTAQV	IIDANDGARG	VIEWQQSREF	VNBETHGSLLT	VAQRSRERPLG	HVSLEFVYAQN	3000
LEAQVGLDYI	FTPMLHFAD	GERYKVNINM	ILDDDIPEGD	EKFQLILTNP	SPGLELGKNT	3060
IAIIVLANK	DGPGVLSFNN	SEHFFLREPT	ALYVQESVAV	LYIVREPAQG	LFGTVTQFQ	3120
VTEVNNSNES	KDLTPSKGYI	VLEEGVRFKA	LQISAILDT	PEMDEYFVCT	LFNPTGGARL	3180
GVHVQTLITV	LQNQAPLGLF	SISAVENRAT	SIDIEEANRT	YVLNVSRTNG	IDLAVSVQWE	3240
TVSETAFGMR	GMDVVFSVFO	SFLDESASGW	CFFTLENLIY	GIMLRKSSVT	YVRWQGIFIP	3300
VEDLNIENPK	TCEAFNIGFS	PYFVITNEER	NEEKPSLNSV	FTFTSGFKLRL	LVQTIIILES	3360
SQVRYFTSDS	DDSELTQVFR	WNGGSFVLHQ	KLPVGRVLTV	ALFNKGGSVF	3420	
LAISQANARL	NSLLFRWSGS	GFINFQEVPV	SGTTEVEALS	SANDIYLIFA	ENVFLGDQNS	3480
IDIFIWEMQG	SSFRYFQSVD	FAAVNRIHSF	TPASGIAHIL	LIGQDMMSALY	CWNSERNQFS	3540
FVLEVPSAYD	VASVTVKSLN	SSKNLIALVG	AHSHIYELAY	ISSHSDFIPS	SGELIFEPGE	3600
REATIAVNL	DDTVEPEKEES	FKVQLKNPKG	GAEIGINDSV	TITILSNDDA	YGIVAFQAQNS	3660
LYKQVEEMEQ	DSLVTLNVER	LKGTYGRITI	AWEADGSIID	IPFTSGVILF	TEGOVLSTIT	3720
LTIADNIPE	LSEVVIVTLT	RITTEGVEDS	YKGATIDQDR	SKSVITTLPN	DSPFGLVGVWR	3780
AASVFIRVAE	PKENTTQLQ	QIARDKGLLG	DIAIHLRAQP	NFLLHVDNQA	TENEDYVVLQE	3840
TIIIMKENIK	EAHAEVSIILP	DDLPELEEGF	IVTITEVNLL	NSDFSTGQPS	VRRPGMEIAE	3900
IMIEENDPPR	GIFMFHVTRG	AGEVITAYEV	PPPLNVLQVP	VVRLAGSFGA	VNVYWKASPD	3960
SAGLEDFKPS	HGILEFADKQ	VTAMIEITII	DDAEFELETET	FNISLISVAG	GGRLGDDVVV	4020
TVVIPQNDSP	FGVFGFEKK	VMIIDESLSSD	DPSDVITLTV	VRSPGKGTV	RLEWTIDEKA	4080
KHNLSPNLNTG	LHFDETESQK	TIVLHTLQDT	VLEEDRRFTI	QLISIDEVEI	SPVKGASII	4140
IRGDKRASGE	VGIAPSRRH	LIGEPSAKYN	GTAIIISLVRG	Pgilgevttf	WRIFPPSVGE	4200
FAETSGKLTM	RDEQSAVIVV	IQALNDDIPE	EKSFYEFQLT	AVSEGGVLSE	SSSTANITVV	4260
ASDSPYGRFA	FSHEQLRVSE	AQRVNITIIR	SSGDFGHVRL	WYKTMGSTAE	AGLDPVPAAG	4320
ELLFEAGEM	KSLHVEILDD	DYPEGPEEFS	LTTKVELQG	RGYDFTIQEN	GLQIDQPEI	4380
GNISIVRIII	MKNDNAEGII	EFDPKYTAPE	VEEDVGLIMI	PVVRHLGTYG	YVTADFISQS	4440
SSASPGGVDVY	ILHGSTVTFQ	HGQNLNSFINI	SIIDDNESEF	EEPIEILLTG	ATGGAVLGRH	4500
LVSRIIIAKS	DSPFVGIRFL	NQSKLISIANP	NSTMILSLLV	ERTGGLLGEI	QVNWETVGPN	4560
SQEALLPQNR	DIADPVGSLF	YFGEGEVGVR	TIIILTYPHE	EIEVTFII	KLHLVKGEAK	4620
LDSRAKDVTL	TIQEFGDPNG	VVQFAPETLS	KKTYSPELAL	EGPLLITFFV	RRVKGTFGEI	4680
MVWELSSEF	DITEDFLSTS	GFFTIADGES	EASFDVHLLP	DEVPEIEEDY	VIQLVSVEGG	4740
AELDLEKSIT	WFSVYANDDP	HGVFALYSR	QSLIIGQNLRI	RSIQINITRL	AGTFGDVAVG	4800
LRISSDHKEQ	PIVTENAERQ	LVVKDGATYK	VDVVPPIKNOV	FLSLGSNFTL	QLVTVMVLVGG	4860
RFYGMPTILQ	EAKSAVLVPS	EKAANSQVGF	ESTAFQLMNI	TAGTSVMIS	RRGTYGALSV	4920
AWTTGYAPGL	EIPEFIVVGN	MTPTLGSLSF	SHGEQRKGVF	LWTFPSPGWP	EAFVLHLSGV	4980
QSSAPGGAQI	RSGFIVAEIE	PMGVQFSTS	SRNIIIVSEDT	QMIRLHVQLR	FGFHSDLIKV	5040
SYQTAGTASAK	PLEDFEPVQ	GELFQFQFQ	EVDFEITIIN	DQLSEIEEFF	YINLTSVEIR	5100
GLQKFDVNWS	PRLNLDPSVA	PRLNLDPSVA	VITILDNDDL	AGMDISFPET	TVAVADTTL	5160
LSTSCKTTIL	QPTNVAIVT	EATGVSAIPE	KLVTLHGTPA	VSEKPDVATV	TANVSIHGTF	5220
SLGPSIVYIE	EEMKNGTFNT	AEVLIRRTGG	FTGNVSVITVK	TRGERCAQME	PNALPFRGIY	5280
GISNLNTWAE	EEDFEEQTLT	LIFLDGERB	KVSVQILDDD	EPEQGEFFYV	FLTNPQGGAQ	5340
IVEEKDDTGF	AAFAMVIIITG	SDLHNGIIGF	SEESQSGLEL	REGAVMRRLL	LIVTRQPNRA	5400
FEDVKVFWRV	TLNKTVVVLQ	KDGVNLVEEL	QSVSGTTCT	MQOTKCFISI	ELKPEKVPQV	5460
EVYFFVELYE	ATAGAAINNS	ARFAQIKILE	SDESQSLVYF	SVGSRLAVAH	KKATLISLQV	5520
ARDSGTGLMM	SVNFSTQELQ	SAETIIGRTII	SPAISGKDFV	ITEGTLVFP	GQRSTVLDVI	5580
LTPETGSLNS	FPKRFQIVLF	DPKGKARIDK	VYGTANITLV	SDADSQAIWG	LADQLHQPVN	5640
DIDLNRVLHT	ISMKVATENT	DEQLSAMMH	IEKITTEGKI	QAFSVASRTL	FYEILCSLIN	5700
PRKRKDTRGFS	HFAEVNTENFA	FSLLNTVNTCG	SPGEKSKTIL	DSCPYLSILA	LHWYPQQING	5760
HKPEGKEGDI	IRIPERLLDVY	QDAEIMAGKS	TCKLVQFTEY	SSQQWFISGN	NLPTLKNKVL	5820
SLSVKGQSSQ	LLTNDNDLVY	RIYAAEPRII	PQTSCLLWN	QAAASWLSDS	QFCKVVEETA	5880
DYVECACSHM	SVYAVYARTD	NLSSYNEAFF	TSGFICISGL	CLAVLHSIFC	ARYSMFAAKL	5940
LTHMMAASLG	TQILFLASAY	ASPQLAEEESC	SAMAATVTHYL	YLCQFWSWMLI	QSVNFWYVVL	6000
MNDEHTTERY	LLFFLSSWGL	PAFVWILLIV	ILKGIVYHQS	SQIYGLIHG	LCFIPNVYAA	6060
LFTAALVPLT	CLVVVFVVF	HAYQVKPQVK	AYDDVFRGRT	NAAEIPILLY	LFALISVTWL	6120
WGLLHMAYRH	FWMLVLFVIF	NSLQGLYVFM	VYFILHNQMC	CPMKASYTVE	MNGHPGPSTA	6180
FFTPGSGMPP	AGGEISKSTQ	NLIGAMEEV	PDWERASFQQ	GSQASPDLK	SPQNGATFPS	6240
SGGYGQGSLLI	ADEESQEFDD	LIFALKTGAG	LSVSDNESGQ	GSQEGGTLTD	SQIVELRRIP	6300
IADTHL						6306

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SEQ ID NO: 22          moltype = AA  length = 201
FEATURE
REGION
source
SEQUENCE: 22
MGNVMEGKSV EELSSTECHQ WYKKFMTCEP SGQLTLYEFP QFFGLKNLSP SASQYVEQMF 60
ETFDFNKDGY IDFMEYVAAL SLVLKGKVEQ KLRWYFKLYD VDGNGCIDRD ELLTIIQAIR 120
AINPCSDTTM TAAEFTDTVF SKIDVNGDGE LSLEEFIEGV QKDQMLLDTL TRSLDLTRIV 180
RRLQNGEQDE EGADEAAEAA G 201

SEQ ID NO: 23          moltype = AA  length = 200

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FEATURE REGION	Location/Qualifiers
	1..200
	note = MISC_FEATURE - GUCA1B (guanylyl cyclase-activating protein 2)
source	1..200
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 23	
MGQEFSWEEA EAAGEIDVAE LQEWFYKKFVM ECPGFTLFWH EFKRRFFKVTD DEEASQYVEG	60
MFRAFDKNGD NTIDFLEYVA ALNLVLRGTL EHKLKWTPKI YDKDGNGCID RLELLNIVEG	120
IYQLKKCRR ELQTEQGQLL TPEEVVDRIF LLVDENGDGQ LSLNEFVEGA RRDKWVMKML	180
QMDMNPSSWL AQQRKRSAMF	200
SEQ ID NO: 24	moltype = AA length = 2213
FEATURE REGION	Location/Qualifiers
	1..2213
	note = MISC_FEATURE - MYO7A (unconventional myosin-VIIa), isoform 1
source	1..2213
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 24	
MVILQQGDHV WMDLRLGQEF DVPIGAVVKL CDSGQVQVVD DEDNEHWISP QNATHIKPMH	60
PTSVHGVEDM IRLGDLNEAG ILRNLLIRYR DHLYIYTYYGS ILVAVNPYQL LSIYSPEHIR	120
QYTNKKIGEM PPHIFAIADN CYFNMKRNSR DQCCIISGES GAGKTESTKL ILQFLAAISG	180
QHSWIEQVQL EATPILEAFQ NAKTRNDNS SRPGKYIDH FNKRGIAIEGA KIEQYLLEKS	240
RVCQALDER NYHVFYCMLE GMSEDQKKKL GLGQASDINYV LAMGNCITCE GRVDSQEYAN	300
IRSAMKVLMF DTENWEISK LLAIALHGN LQEYARTPEN LDACEVLFSP SLATAASLLE	360
VNPPDLMSCS TSRTSLITRGE TVSTPLSREQ ALDVRDAFVVK GIYGRFLVWI VDKINAAIYK	420
PSPSQDVKNSR RSIGLLDIFG FENFAVNSFE QLCINFANEH LQQFFVRHVF KLEQEYDLE	480
SIDWLHNFID DNQDALDMIA NKPMMNIISLI DEESKFPKG DTTMLHKLNS QHKLNNANYIP	540
PKNNHETQFG INHHFAGIVYY ETQGPFLKEKNR DTLHGDIIQL VHSSRNKFHK QIFQADVAMG	600
AETRKRSPLT SSQFKRSLEL LMRTLGLACQP FFVRCIKPNE FKKPMLFDRH LCVRQLRYSG	660
MMETIRIRRA GYPIRYSFVE EVERYRVLLP GVKPAYQGD LRGTQCRMMAE AVLGHDDWQ	720
IGKTKIPLKD HHDMLEVER DKAITDRVIL LOKVIRGFK RSNFLKLKNA ATLIQRHWRG	780
HNCRKNYGLM RLGFRLRLQAL HRSRKLHQQY RLARQRIIQF QARCRAYLVR KAFRHLWAV	840
LTVQAYARGM IARRLHQRLK AEYLWRLAE KMRLAEEEKL RKEMSAKKAK EEAERKHQER	900
LAQLAREDAD RELKEKEAAR RKKEELQE RARHEPVNHS DMVDKMPGFL GTSGGLPGQE	960
GQAPPSGFEDL ERGRREMVER LDALDAALPLD EDEEDLSEYK FAKFAATYFQ GTTTHSYTRR	1020
PLKQPLLYHD DEGDDQALAALA WVIITLRFMG DLPEPKYHTA MSDGSEKIPV MTKUYETLGK	1080
KTYKRELQAL QGEGEAQOLPE GQKKSNSVRHK LVHLLTCKKS KLTEEVTKRL HDGESTVQGN	1140
SMLEDRPTSN LEKLUHPIIGN GILRPALRDE IYCQISKQLT HNPSKSSYAR GWILVSLCVG	1200
CFAPSEKFKV YLRLNFIHGGP PGYAPYCEER LRLRTFVNTR TOPPSWLELQ ATKSKKPIML	1260
PVTFMDGTTK TLTDTSATTA KELCNALADK ISLKDRFGVS SLGSGSDHVM	1320
DAISQCBEYA KEQGQAQERNA PWRLFFRKEV FTPWHSPSED NVATNLLIYQQ VVGRGKFGEY	1380
RCEKEDELLAE LASQQYFVDY GSEMILERLL NLVPTYIPDR EITPLKTLEK WAQLAIAAHK	1440
KGIIYAQRRTD AOKVKBDDVS YARFKWPPLF SRFYEAJKFS GSPSLPKNDVI VAVNWNTGVYF	1500
VDEQEQLVLE SSRECRWVLSS LGCSDLGCACAA PHSGWAGLTP AGPCSPCWSC	1560
RGAKTTAPSFL TLATIKGDEY TFTSSNAEDI RDLVVTFLLEG LRKRSKYVVA LDQDNPNPAGE	1620
ESGFLSFAKG DLIILDHDTG EQVMNSGWAN GINERTKQRG DFPTDSVYVM PTVTMPPREI	1680
VALVUTMPDQ RQDVVRLLQL RTAEPEVRAK PYTLEEFSYD YFRPPPCKHTL SRVMVSKARG	1740
KDRLWSHTRE PLKQALLKKL LGSEELSQEA CLAFIAVLKY MGDYPSKRTR SVNELTDQIF	1800
EGLKLAEPLK DEAYQVILKQ LTDNHIRYSE ERGWELLWLC TGLFPPSNIL LPHVORFLQS	1860
RKHCPLAIDC LQRLQKALRN GSRKYPPHLV EVEAIQHKTQ QIFHKVYFPD DTDEAFEVES	1920
STKAKDFCQN IATRLLKL EGFLSFVKA DKVLSVPEND FFFDFVRHLT DWIKKARPIK	1980
DGIVPSLTYQ VFFMKKLWTT TVPGKDPMD SIFHYYQELP KYLGRYHKCT REEVQLQLGAL	2040
IYRVKFEEDK SYFPSPIPKLL RELVPQDLIR QVSPDDWKRS IVAYFNKHAG KSKEEAKLAF	2100
LKLIFKWPTF GSFFEVKQT TEPNFPEILL IAINKYGVSL IDPDKTDILT THPFTKISNW	2160
SSGNTYFHIT IGNLVRGSKL LCETSLGYKM DDLLTSYISQ MLTAMSQORG SRS	2213
SEQ ID NO: 25	moltype = AA length = 236
FEATURE REGION	Location/Qualifiers
	1..236
	note = MISC_FEATURE - NRL (neural retina-specific leucine zipper protein), isoform 1
source	1..236
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 25	
ALPPSPLAME YVNDFDLMKF EVKREPSEGR PGPPTASLGS TPYSSVPPSP TFSEPGMVGA	60
TEGTRPGLEE LYWLATLQQQ LGAGEALGLS PEEAMELLQG QGPVVPDGPY GYYPGSPEET	120
GAQHVQLAER FSDAALVMSMS VRELNRLRG CGRDEALRLK QRRTTLKNRG YAQACRSKRL	180
QQRGGLEAER ARLAAQLDAL RAEVARLARE RDLYKARCDR LTSSGPGSGD PSHLFL	236
SEQ ID NO: 26	moltype = AA length = 860
FEATURE	Location/Qualifiers

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REGION	1..860	
	note = MISC_FEATURE - PDE6A (rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha)	
source	1..860	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 26		
MGEVTAEEVE KFLDSNIGFA KQYYNLHYRA KLISDLLGAK EAAVDFSNYH SPSSMEESEI	60	
IFDLRLRDFQE NLQTEKICIFN VMKKLCFLLQ ADRMSLFWMYR TRNGIAELAT RLFNVHKDAV	120	
LEDCLVMPDQ EIFVPLDMGI VGHVAHSKKI ANVPNTEEDFE HFCDFVDILT EYKTKNILAS	180	
PMNGKDVVA IMAVNKVKG SHFTKRDEEI LLKYLNFANL IMKVKYHLSYL HNCETRRGQI	240	
LWWSGSKVFE ELTDIERQFH KALYTVRAFL NCDRYSVGLL DMTKQKEFFD WVPVLMGEVP	300	
PYSGPRTPDG REINFYKVID YILHGKEDIK VIPNPPDHW ALVSGLPAYV AQNGLICNIM	360	
NAPAEDFFAF QKEPLDESGW MIKVNLSMPI VNKKCEEIVGV ATFYNRKDGF PFDEMDETLM	420	
ESLTQFLGPI VLNPDTYESM NKLENRKDIF QDIVKYHVKC DNEEIQKILK TREVYGKEPW	480	
ECCEEEELAEWI LQAELPDADY YEINKFHFSD LPLTELELVK CGIQMYEELK VVDKPHIPQE	540	
ALVRPFMYSLS KGYRKITYHN WRHGFNVGQT MFSLLVTGKL KRYFTDLEAL AMVTAACFHD	600	
IDHRGTNNLY QMKSONPLAI LHGSILERH HLEFGKTLLR DESLNIFQNL NRRQHEHAIH	660	
MMDIAIIATD LALYFKKRTM FQKIVDQSQT YESEQEWQTQY MMLEQTRKEI VMAMMMTACD	720	
LSAITKPWEV QSQVALLVAA EFWEQGDLER TVLQQNPIMP MDRNKADEL P KLQVGFIDFV	780	
CTFVYKEFSR FHEEITPMLD GITNNRKEWK ALADEYDAKM KVQEEKKKQKQ QSAKSAAAGN	840	
QPGGNPSPGG ATTSKSCCIQ	860	
SEQ ID NO: 27	moltype = AA length = 854	
FEATURE	Location/Qualifiers	
REGION	1..854	
	note = MISC_FEATURE - PDE6B (rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta), isoform 1	
source	1..854	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 27		
MSLSEEQARS FLDQNPDFAR QYFGKQLSPE NVAACEDGC PPDCDSLRLD CQVEESTALL	60	
ELVQDMQESI NMERVVFKV RRLCTLLQAD RCSLFMYQR NGVAELATRL FSVQPDSVLE	120	
DCLVPPDSEI VFPLDVGVG HVAQTKMVN VEDVAECPHF SSFADELTDY KTKNMLATPI	180	
MNGKDVVAVI MAVNKLNPGF FTSEDEDVFL KYLNFAFLYL KIYHLSYLN CETRRGQVLL	240	
WSANKVPEEL TDIERQFHKA FYTVRAYLNC ERYSVGLLDM TKEKEFFDVW SVMGESQPY	300	
SGPRTPDGRE IVFYKVIDYV LHGKEEIKVI PTPSADHWAL ASGLPSYVAE SGFICNIMNA	360	
SADEMPKFQE GALDDSGWLK KNVLSPMIVN KKEEIVGVAT FYNRKDGKPF DEQDEVLMES	420	
LHQFLGWSVM NTDTYDKMKN LENRKDIQD MVLYHVVKCDR DEIQLILPTR ARLGKEPADC	480	
DEDELGEILK EELPGPTTFD IYEFHFSDE CTELDLKVCG IQMYYELGVV RKFOIPQEV	540	
VRLFLSISKG YRRIYHNWR HGFNVAQTMF TLLMTGKLKS YYTDLEAFAM VTAGLCHDID	600	
HRTGTTNQYM KSQNPLAKLH GSSILERPLH EFGKFLLSEE TLNIYQNLNR RQHEHVINLM	660	
DIAIIATDLA LFKKKRAMFQ KIVDESKNYQ DKKSWVEYLS LETTRKEIVM AMMMTACDLS	720	
AITKPWEVQS KVALLVAAEF WEQGDLERV LDQQPIPMMD RNKAELPKL QVGFIDFVCT	780	
FVYKEFSRFH EEILPMFDRL QNNRKEWKAL ADEYEAKVKA LEEKEEEERV AAKVGTEIC	840	
NGGPAPKST CCIL	854	
SEQ ID NO: 28	moltype = AA length = 346	
FEATURE	Location/Qualifiers	
REGION	1..346	
	note = MISC_FEATURE - PRPH2 (peripherin-2)	
source	1..346	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 28		
MALLKVKFDQ KKRVKLAQGL WLMNWFSVLA GIIIFSLGLF LKIELRKRSV VMNNSESHFV	60	
PNSLIGMGVL SCVFNSLAGK ICYDALDPAK YARWKPWLPK YLAICVLFNI ILFLVALCCF	120	
LIRGSLENTL QOGLKNGMKY YRDTDTPGRM FMKKTIDMLQ IEFKCCGNNG FRDWPEIOWI	180	
SNRYLDFSSK EVKDRIKSNV DGRYLVDPGV FSCCNPSSPR PCIQYQITNN SAHYSYDHQT	240	
EELNLWVRGC RAALLSYSS LMNSMGVVTI LIWLFEVITI IGLRQLQTSV DGVSNPEESE	300	
SESEGWLLEK SVPETWKAFL ESVKLGKGN QVEAEGAGAG QAPEAG	346	
SEQ ID NO: 29	moltype = AA length = 865	
FEATURE	Location/Qualifiers	
REGION	1..865	
	note = MISC_FEATURE - PROM1 (prominin-1), isoform 1	
source	1..865	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 29		
MALVLGSLLL LGLCGNSFSG GQPSSTDAPK AWNYELPATN YEQDSHKAG PIGILFELVH	60	
IFLYVVQPRD FPEDTLRKFL QKAYESKIDY DKPETVILGL KIVYYEAGII LCCVLGLLFI	120	
ILMPLVGYFF CMRCRCCNKCG GEMHQRQKEN GPFLRKCFAI SLLVIIIS IGIFYGFVAN	180	
HQVRTRIKRS RKLADSNFKD LRTLLNETPE QIKYILAQYN TTKDKAFTDL NSINSVLLGG	240	
ILDRLRPNII PVLDEIKSMA TAIKETKEAL ENMNSTLKSL HQQSTQLSSS LTSVKTSLRS	300	

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S1NDPLCLVH PSSETCNSIR LSLSQLNSNP ELRQLPPVDA ELDNVNNVLR TDLDGLVQQG YQSLNDIPDR VQRQTTVVV GIKRVLNSIG SDIDNVTORL PIQDILSAFS VYVNNTESYI HRNLPTLEEV DSYWWLGGLV ICSLLTLIVI FYYLGLLCGV CGYDRHATPT TRGCVSNTGG VFLMVGVLGS PLFCWILMII VVLTTFVFGAN VEKLICEPYT SKELFRVLDT PYLLNEDWEY YLSGKLFNKS KMKLTFEQVY SDCCKNRGTY GTLHLQNSFN ISEHLNINEH TGSISSELES LKVNLNIFLL GAAGGRKNLQD FAACGIDRMM YDSYLAQTGK SPAGVNLLSF AYDLEAKANS LPPGNRLNSL KRDAQTIKTD HQQRVLPIEQ SLSTLYQSVM ILQRTGNGLL ERVTRILASL DFAQNPFITNN TSSVIIETK KYGRTIIGYF EHYLQWIEBS ISEKVASCKP VATALDTAVD VFLCSYIIDP LNLFWFHGIGK ATVFLLPALI FAVKLAKYYR RMDSEDVYDD VETIPMKNME NGNNGYHKDH VYGIHNPVMT SPSQH	360 420 480 540 600 660 720 780 840 865
 SEQ ID NO: 30	molttype = AA length = 348
FEATURE	Location/Qualifiers
REGION	1..348
	note = MISC_FEATURE - RHO
source	1..348
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 30	
MNGTEGPNFY VPFSNATGVV RSPFEYPQYY LAEPWQFSML AAYMFLLIVL GFPINFLTLY VTVQHKKLRT PLNYILLNLA VADLFMVLGG FTSTLYTSLH GFYFVFGPTGC NLEGFFATLG GEIALSLV LAIERYVVVCK KPMPSNRFGE NHAIMGVAFT WVMALACAAP PLAGWSRYIP EGLQCSCGID YTTLKPEVNN ESFVYMFVV HFTIPMIIIF FCYQGLVFTV KEAAAQQES ATTQKAKEV TRMVIIMVIA FLICWVPYAS VAFYIFTHQG SNFGP1FMTI PAFFAKSAAI YNPVIYIMMN KQFRNCMLTT ICCGKNPLGD DEASATVSKT ETSQVAPA	60 120 180 240 300 348
 SEQ ID NO: 31	molttype = AA length = 351
FEATURE	Location/Qualifiers
REGION	1..351
	note = MISC_FEATURE - ROM1 (rod outer segment membrane protein 1)
source	1..351
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 31	
MAPVLPVLVP LQPRIRLAQG LWLLSWLLAL AGGVILLCSL HLLVQLRHG TFLAPSCQFP VLPQAALAAG AVALGTGLVG VGASRASLNA ALYPPWRGVL GPLLVAGTAG GGGLLVVGLG LALALPGSLD EAEEGLVTA LAHYKDTEVP GHQCQAKRLWD ELQLRYHCCG RHGYKDWFVG QWSSRQLWA GDRDVADRIQ SNVEGGLYLD GVPFSCCNPH SPRPCLQNRL SDSYAHPLFD PRQPQNQLWA QGCHEVLLEH QDLAGTLLGS MLAFTLQLA LVLLGLRQLQ TALEGLGGVI DAGGETQGYL FPSGLKDMRK TAWLQGGGVAC RPAPEEAPPG EAPPKEDLSE A	60 120 180 240 300 351
 SEQ ID NO: 32	molttype = AA length = 2156
FEATURE	Location/Qualifiers
REGION	1..2156
	note = MISC_FEATURE - RP1 (oxygen-regulated protein 1)
source	1..2156
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 32	
MSDTPSTGF5 1IHPTSSEGQ VPPPRHLSLT HPVVAKRISF YKSGDPQFGG VRVVVNPRSF KSFDALLDNL SRKVPLPFGV RNISTPRGRH SITRLEELED GESYLCSHGR KVQPVLDKA RRRPRPWLSS RAISAHSPPH PVAVAAKGMP RPPRSLVVFR NGDPKTRRAV LLSRRVTQSF EAFLQHLTEV MQRPVVKLYA TDGRRVPSLQ AVILSSGAVV AAGREPFKPG NYDIQKYLLP ARLPGISQRV YPKGNAKSES RK1STHMSSS SRSQIYSVSS EKTHNNDCYL DYSFVPEKYL ALEKNDQSNL KS1PYSEDDIE KS1IHFQDGT MTVEMKVRFR IKEEETIKWT TTVSKTGPSN NDEKSEMSFP CRTERSSSGL KLAACSFSAV VSPMERSSNQ EGSLAEINI QMTDQVAETC SSASWENATV DTDIIQGTQD QAKHFRYRPP TPGLRRVRQK KSVIGSVTLV SETEVQEAKMI GQFSYSEERE SGENKSEYHN FTHCSKSMSS VSNKPVLVQI NNNDQMEESS LERKKENSLL KSSAISAGVI EITSQKMLEM SHNNGLPSI SNNSIVEEDV VDCVQLDNKT GIKNFKTYGN TNDRFSPISA DATHFSSNN SGTDKNISEAP ASEASSTVTA RIDRILINEFA QCGLTKLPKN EKKILSSVAS KKKKKSRQQA INSRYQDGQL ATKIGLKNNE RINTKGRTK EMIVQDSDSP LKGGLCEED LQKSDTIVIES NTFCSKSNNL STISKNFHRN KLNTTQNSKV QGLLTKRKSR SLINKSILGAP KKREIGQRD VFPHNESKYC KSTFENKSLK HVFNILEQKQ KDFYAPQSQA EVASGYLRGMA AKKSLSVSKVT DSHITLKSQK KRKGDKVKS AILSQKQHATT RANSLASLKK PDFPEAIAHH SIQNYIQSQL QNINPYPTLK PIKSAPVCRN ETSVVNCNN SFSGNDPHTN SGKISNFVME SNKHITKIAG LTGDNLCKEG DKSFIAANDTG EEDLHETQVG SLNDAYLVPL HEHCTLSQSA INDHNTKSHI AAEKSGPEKK LVYQEINLAR KRSVVEAAIQ VDPIEEETPK DLLPVMLHQ LQASVPGIHK TQNGVVQMPG SLAGVPPHSA ICNSSTNLLL AWLLVVLNLKG SMNSFCQVDA HKATNKSSET LALLEILKHI AITEEADDLK AAVANLVEST TSHFGLSEKE QDMVPIDLSSA NCSTVNIQSV PKCSENERTQ GISSLDGGCS ASEACAPEVC VLEVTCSPCE MCTVNKAYSP KETCNPSDTF FPSDGYGVQDQ TSMNKACFLG EVCSLTDYFV SDKACAQKEN HTYEGACPID ETYVPVNVCN TIDFLNSKEN TYTDNLNSTE ELERGDDIQK DLNLITDPEY KNGFNTLVSH QNVSNLSSCG LCLSEKEAEL DKKHSSLDDF ENCSLRKFQD ENAYTSFDME EPRTSEEPGS ITNSMTSSER NISELESFEE LENHDTDIFN TVVNGGEQAT EELIQEEVEA SKTLELIDIS SKNIMEEKRM NGIIYEIISK RLATPPSLDF CYDSKQNSEK ETNEGETKVM	60 120 180 240 300 360 420 480 540 600 660 720 780 840 900 960 1020 1080 1140 1200 1260 1320 1380 1440 1500 1560

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KMMVKTMETG	SYSESSPDLK	KCIKSPVTSD	WSDYRPDSDS	EQPYKTSSDD	PNDSGELTQE	1620
KEYNIGFVKR	AIEKLHYGKD	IICKPSFFPGS	TRKSQVCPYN	SVEFQCSRKA	SLYDSEGQSF	1680
GSSEQVSSSS	SMLQEFQEER	QDKCDVSAVR	DNYCRGDIVE	PGTKQNDDSR	ILTDIEEGVL	1740
IDKGKWLLKE	NHLLRMSSSEN	PGMCGNADTT	SVDTLDDNNS	SEVPYSHFGN	LAPGPTMDEL	1800
SSSELEELTQ	PLELKCNYFN	MMPHGDSEPF	HEDILLDVRNE	TCAKERIANH	HTEEKGSQHS	1860
ERVCTSVTHS	FISAGNKVYP	VSDDAIKNQF	LPGSNM1HGT	LQEADSLDKL	YALCQHQCFI	1920
LTVIIQPMNE	EDRGFAYRK	SDIENFLGFY	LWMKIHOPYLL	QTDKNVFREE	NNKASMQRQNL	1980
IDNAIGDIFD	QFYFSNTFDL	MGKRRKQKRI	NFLGLEEEGN	LKKFQPDLLKE	RFCMNFLHTS	2040
LLVVGNVDSN	TQDLSGQTNE	IFKAVDENNN	LLNNRFQGSR	TNLNQVVRREN	INCHYFFEML	2100
GQACLLDICQ	VETSLNISNR	NILELCMFEG	ENLF1WEEDD	ILNLNLTDELESS	REQEDL	2156

SEQ ID NO: 33	moltype = AA length = 350					
FEATURE	Location/Qualifiers					
REGION	1..350					
	note = MISC_FEATURE - RP2 (protein XRP2)					
source	1..350					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 33						
MCGFFSKRK	ADKESRPENE	EERPKQYSWD	QREKVDPKDY	MFSGLKDETV	GRPLPGTVAGQ	60
QFLIQDCENC	NIYIFDHSAT	VTIDDCNCI	IIFLGPVKGSN	FFRNCRDCKC	TLACQQFRVR	120
DCKLKVFLC	CATQPIIESS	SNIKPGCFOW	YYPELAQFK	DAGLSIFNNT	WSNIHDFTPV	180
SGELNWSLAP	EDAIVVQDYVP	IPTVWLSKAV	RVSTEANRSI	VPISRGQRQK	SSDESCLVVL	240
FAGDGYTIANA	RKLIDEMVGK	GFFLVTQTKEV	SMKAEDDAQRV	FREKAPDFLP	LLNKGTVIAL	300
EFNGDGAVEV	CQLIVNEIFN	GTKMFVSESK	ETASGVDSF	YNFADIQMGI		350
SEQ ID NO: 34	moltype = AA length = 1020					
FEATURE	Location/Qualifiers					
REGION	1..1020					
	note = MISC_FEATURE - RPGR (X-linked retinitis pigmentosa GTPase regulator), isoform 1					
source	1..1020					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 34						
MREPEELMPD	SGAVFTFGKS	KFAENNPGKF	WFKNDDPVVHL	SCGDEHSAAV	TGNNKLYMFG	60
SNNWQQLGLG	SKSAISKPTC	VKALKPEVK	LAACGRNHTL	VSTEGGNVVA	TGGNNNEGQLG	120
LGDTTEERNTF	HVISFFTSEH	KIKOLSGASN	TSAALTEDGR	LFMWGDNSEG	QIGLKNVNSV	180
CVPPQVTTIGK	PVSWISCGYY	HSAFVTTDGE	LYVFGEPENG	KLGLPNQLLG	NHRTPQLVSE	240
IPEKVIQVAC	GGEHTVVL	NAVYTFGLGQ	FGQLGLGTFL	FETSEPKVIE	NIRDQTISYI	300
SCGENHTALI	TDIGLMLYTFG	DGRHGKLGGL	LENFTNHFIP	TLCNSFLRFI	VKLVACGGCH	360
MUVFAAPHRG	VAKIEBFDEI	NDTFLCSVATF	LPYSSLTSGN	VLRQRTLSARM	RRRERERSPD	420
SFSMRRLLPP	IEGTLLGLSAC	FLPNNSVFPRC	SERNLQESVL	SEQDLMQPEE	PDYLLDEMTK	480
EAEIDNSSTV	ESLGETTDIL	NMTHIMSLNS	NEKSLKLSPW	QKQKKQQTIG	ELTQDTALTE	540
NDDSDYEYEM	SEMKEGACK	QHVSQGIFMT	QPATTIEAFS	DEEVGNDTGQ	VGPQADTDGE	600
GLQKEVYRHE	NNNGVDQLDA	KEIEKESDGG	HSQKESEABE	IDSEKETKLA	EIAGMKDLRE	660
REKSTKKMSP	FFGNLKPDRGM	NTSEENKDF	VKKRESCQDF	VIFDSERESV	EKPDSYMEGA	720
SESEQQGIADG	FQQPEAIEFS	SGEKEDEVVE	TDQNIRYGRK	LIEQGNEKET	KPIIISKSMAK	780
YDFKCDRLSE	IPEEEKGAAED	SKGNGIEEQE	VEANEENVKV	HGGRKEKTEI	LSDDLTDKAE	840
DHEFSKTEEL	KLEDVDEEIN	AENVESKKKT	VGDDESVPVG	YHSKTEGAER	TNDDSSAETI	900
EKEKEKANLEE	RAICEYENNP	KGYMLDDADS	SSLEILENSE	TPPSKDMKKT	KKIFLFKRV	960
SINQKIVKNN	NEPLPEIKSI	GDQIILKSDN	KDADQNHMSQ	NHQNIPPTNT	ERRSKSCTIL	1020
SEQ ID NO: 35	moltype = AA length = 405					
FEATURE	Location/Qualifiers					
REGION	1..405					
	note = MISC_FEATURE - SAG (S-arrestin)					
source	1..405					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 35						
MAASGKTSKS	EPNHVIFKKI	SRDKSVTIYL	GNRDYIDHVS	QVQPVDGVL	VDPDLVKGKK	60
VVVTLTCAFIR	YGQEDIDVIG	LTFRDRLYFS	RVQVYPPVGA	ASTPTKLQES	LLKKLGNTY	120
PFLLTFPDYL	PCSVMLQAP	QDSGKSCGVD	FEVKAFATDS	TDAEEDKIPK	KSSVRLLIRK	180
VQHAPLEMGP	QPRAEAAWQF	FMSDKPLHLA	VSLNKEIYFH	GEPIPVTVT	TNNTEKTVKK	240
IKAFFVEQVAN	VVLYSSDDYYV	KPVAMEEAQF	KVPPNSTLTK	TLLTLLPLAN	NRERRGIALD	300
GKIKHEDTNL	ASSTIIKEGI	DRTVGLILVS	YQIKVKLTVS	GFLGELTSSE	VATEVPFRLM	360
HPQPEDPAKE	SYQDANLVFE	EFARHNLKDA	GEAEEGKRDK	NDVDE		405
SEQ ID NO: 36	moltype = AA length = 552					
FEATURE	Location/Qualifiers					
REGION	1..552					
	note = MISC_FEATURE - USH1C (Usher syndrome type-1 C protein), isoform 1					
source	1..552					
	mol_type = protein					

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SEQUENCE: 36	organism = Homo sapiens
MDRKVAREFR HKVDFLIED AEKDYLYDVL RMYHQTMDVA VLVGDLKLVI NEPSRLPLFD	60
AIRPLIPLKH QVEYDQLTPR RSRKLKEVRL DRLHPEGLGL SVRGGLEFGC GLFISHLIKIG	120
GQADSVGLQV GDEIVRINGY SISSCTHEEV INLIRTKKTV SIKVRHIGLI PVKSSPDEPL	180
TWQYVQDFVS ESGGVGRGSLQ SPGNRENKEK KVFISLVGSR GLGCSSISSGP IQKPGIFISH	240
VKPGSLSAEV GLEIGDQIVE VNGVDFSNLD HKEAVNVLK SRSLTISIVA AAGRELFMTD	300
RERLAEARQR ELQRQELLMQ KRLAMESNKI LQBQQEMERQ RRKEIAQKAA EENERYRKEM	360
EQIVEEEEEKF KKQWEEDWGS KEQLLLPKTI TAEVHPVPLR KPKYDQGVEP ELEPADLDG	420
GTEEQGEQDF RKYEEGFDPV SMTPEQIMG KVDRLLRIKK EGSSLDALEG GVDSPIGVVV	480
VSAYVYERGA ERHGGIVKGD EIMAINGKIV TDYTLLAEAEA ALQKAWNQGG DWIDLVVAVC	540
PPKEYDDELT FF	552
 SEQ ID NO: 37	 moltype = AA length = 461
FEATURE Location/Qualifiers	
REGION 1..461	
source note = MISC_FEATURE - USH1G (Usher syndrome type-1G protein)	
1..461	
mol_type = protein	
organism = Homo sapiens	
SEQUENCE: 37	
MNDQYHRAAR DGYLELLKEA TRKELNAPDE DGMPPTLWAA YHGNLESRLR IVSRGGDPDK	60
CDIWGNTPHL LAASNGHLHC LSFLVSGAN IWCLDNDYHT PLDMAAMKGH MECVRYLDSI	120
AAKQSSLNPK LVGKLKDCAF REAERRIREK AKLQRHHRRHMER MERRYRREL ERSDTLSFSS	180
LTSSTLSRRL QHLALGSHLP YSQATLHGTA RGKTMQKQL ERRKQGEGT FKVSEDFGRKS	240
ARSLSLQLQG SDVMFVRQGT YANPKEWGRA PLRDMFLSDE DSVSRSATLAA EPAHSEVSTD	300
SCHDSLTFP GLGTMVFRNN YLSSGLHGLG REDGGLDGVG APRGRHQSSP SLDDDSLGS	360
NSLQDRSCGE ELPWDDELGLG LDLEDPEP TS PLETFLASHL MEDFAALLRQ EKIDLEALML	420
CSDLDLRSIS VPLGPRKKIL GAVRERRRQAM ERPPALEDTE L	461
 SEQ ID NO: 38	 moltype = AA length = 5202
FEATURE Location/Qualifiers	
REGION 1..5202	
source note = MISC_FEATURE - USH2A (Usherin), isoform 1	
1..5202	
mol_type = protein	
organism = Homo sapiens	
SEQUENCE: 38	
MNCPVLSLG GFLFQVIEML IFAYFASISL TESRGLFPRL ENVGAFKKVS IVPTQAVCGL	60
PDRSTFCHSS AAAESIQFCQ QRCFICQDCPY RSSHPTYTAL FSAGLSSCIT PDKNDLHPNA	120
HNSNASFIG NHKSCFSSPP SPKLMASFTL AWLKPSEQQ VMCVIEKTVG GQIVFKLTIS	180
EKETMFYRT VNGLQPPIKV MTLGRILVKK WIHLSVQVHQ TKISFFINGV EKDHTPFNAR	240
TLSGSITDFA SGTVQYQGSQ NGLFQFVGRM QDFRLYQVAL TNREILEVFS GDLLRLHAQS	300
HCRCPGSHPR VHPLAQRYCI PNDAGDTADN RVSLRNPEAH PLSFVNNDV GTSWVSVNFT	360
NITQLNQGVT ISVLDENGQY QVFYIIQFF SPQPTEIRQ RKKENSLDWE DWQYFARNCG	420
AFGMKNNGDL EKPDVSNLQ LSNFTPYSRG NVTFSILTPG PNYRPGYNF YNTPSLQEJV	480
KATQIRFHFD CQYYTTETAV NLRHRYYAVD EITISGRQCQ HGHADNCDDT SQPYRCLCSQ	540
ESPTEGLRHFD RCLPLYNDKP FRQGDQVAF NCKPCQCNSH SKSCHYNSIV DPFPFEHFHRG	600
GGGVCDDEH NTTGRNCELC KDYFFRQVGA DPSAIDVCKP CDCDTVGETRN GSILCDQIGG	660
QCNCKRHVSG RQCNQCQNGF YNLQELDPDG CSPCNCNTSG TVDGDITCHQ NSGQCKCKAN	720
VIGLRCDHFC PGFKFLRSFN DVGCEPCQCN LHGSVNPFCN PHSGQCECKE EAKGLQCDTC	780
RENFYGLDVT NKACACDCTA GSLPGTVCNA KTGCICKPN VEGRQCNKCL EGNFYLQRNN	840
SFLCLPCNCD KTGTINGSLL CNKSTGQCPK KLGVTLRCN QCEPHRYNLT IDNFQHQCQMC	900
ECDSLGLTPG TICDPISGQC LCVPNRQGRR CNQCQPGFYI SPGNATGCLP CSCHTTGAVN	960
HICNSLTLQG QCQDASIAGQ RCDQCKDHYF GFDPQPTGRQC PCNCNHSAL NETCHLVTGQ	1020
CFCQKFVFTGS KCDACDCAAS HLDVNNLGC SKTPFQQPCCP RGQVQSSSAI NLSWSPPDSP	1080
NAHWLTYSLR RDGFETYTT DQYPSIYQF LD'TDLLPYTK YYSYIETTNV HGSTRSVAVT	1140
YKTKPGVPEG NLTSYIIP1 GSDSVTLWT TLSNQSGPIE KYILSCAPLA GGQPCVSYEG	1200
HITSATIWNL VPFAKYDFSV QACTSGGCLH SLPITVITAQ APPQRQLSPPK MQKISSTELH	1260
VEWSPPAELN GIIYELYLM RRLRSTKETT SEESRVPFVSE SANENALKPP	1320
QTMTTITGLE PYTKYEFTRV AVNMAGVSSS AWNSERTQFSE AVPVMIPPSV FPLSSYSLNI	1380
SWEKPADNVT RGKVVGYDIN MLSEQSPQQS IPMAFSQLHH TAKSQELSYT VEGLKPYRIY	1440
EFTITLCSV GCVTASAGAG QTAAAPAPL RPPLVKGINS TTIIHLRWFFF EELNGPSPYI	1500
QLERRESSLP ALMTMMKGI RFINGYCF PSSTHPVNTD FTGIKASFRT KVPEGLIVFA	1560
ASPQNGEEYF WQQLKKGRY FLFDPQGSPV EVTTTNDHKG QYSDGKWHWEI IAIRHQAFGQ	1620
ITLDGIFTYGS SAILNGSTV GDNTGVFLGG LPRTSYTILRK DPEIIQKGFV GCLKDVFHM	1680
NYNPSAIWEP LDWQSSEEQI NVYNSWEGCP ASLNEGAQFL GAGFLELHPY MFHGGMNFEI	1740
SFKFRTDQLN GLLLTVYNAK GPDFLAMELK SGILTFLRNT SLAFTQV DLL LGLSYCNKGW	1800
NKVIIKKEGS FISASVNGLM KHASSESGDQP LVVNSPVYVG GIPQELLNST QHLCLCQGFG	1860
GCMKDVKFTR GAVVNLASVS SGAVRVNLNDG CLSTDSAVNC RGNDISILVYQ GKEQSVYEGG	1920
LQFTEYLYR VIASHEGGSV YSDWSRGRRTT GAAPQSVPTP SRVRSNLNGYS IEVTWDEPVV	1980
RGVIEKYILK AYSEDSTRPP RMPSASAECV NTSNLGTILT GLLPKFKNYAV TLTACTLAGC	2040
TESSHANLIS TPQEAPQEVQ PPVAKSLPSS LLLSWNPNNPKK ANGIITQYCL YMGRILYSG	2100
SEENYIVTDL AVFTPHQFLL SACTHVGCTN SSWVLLYTAQ LPPEHVDSPV LTVIDSRTH	2160
IQWKQPRKIS GILERVLYM SNHHDFTIW SVIYNSTELF QDHMLQYVLP GNKYLIKLG	2220
CTGGGCTVSE ASEALTDEDI PEGVPAPKAH SYSPDSFNVS WTEPEYPNVG ITSGLYLDG	2280

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ILIHNSSELS	YRAYGFAPWS	LHSFRVQACT	AKGCALGPLV	ENRTLEAPPE	GTVNVFVKTO	2340
GSRKAHWRWE	APFRPNGLLT	HSVLFITGIFY	VDPVGNNYTL	LNVTKVMYSG	EETNLWVLID	2400
GLVPFTNYTV	QVNISNSQGS	LITDPITIAM	PPGAPDGVL	PRLSSATPTS	LQVVWSTPAR	2460
NNAPGPSRYQ	LQMRSGDSTH	GFLELFSNPS	ASLSYEVDL	QPYTEYMFLR	VASNGFGSAH	2520
SSWIOPMTEA	DKPGPVPPI	LLDVKSRMML	WTWQHPRKSN	GVITHYNIYL	HGRLYLRTPG	2580
NVTNCTVMHL	HPYTAYKFQV	EACTSKGCSL	SPESQTVWTL	PGAAPEGIPSS	ELFSDPTPSV	2640
IISWQPPTHP	NGLVEVFNTIE	RRVKGKEEV	TLLTLPRSSH	MRFIDKTSAL	SPWTKYEYRV	2700
LMSTLHGGTN	SSAWEVTTT	PSRPAGVQPP	VVTVLEPDAV	QVTWKPLIQ	NGDILSYEIH	2760
MPDPHILTN	VTSAVLSQLV	THLIPFTNYS	VTIVACSGGN	GYLGGCTESL	PTYVTTHPTV	2820
PQNVGPLSVI	PLSESVVVIS	WQPPSKPKNP	NLRYELLRK	IQQPLASNPV	EDLNRNWHNIY	2880
SGTQWLWYEDK	GLSRFTTYEY	MLFVHNSVGF	TPSREVTVTT	LAGLPERGAN	LTASVLNHTA	2940
IDVRWAKPTV	QDLQGEVEYY	TLFWSSATSN	DSDLKILPDVN	SHVIGHLKP	TEYWFISVF	3000
NGVHSINSAG	LHATTCDGE	QGMLPPEVVI	INSTAVRVI	TSPSNPNGVV	TEYSIYVNNK	3060
LYKTGMNVPG	SFILRDLSPF	TIYDQVCEC	TIYACVKSNG	TQITTVEDTP	SDIPTPTIRG	3120
ITSRSLQIDW	VSPRKPGII	LGYDLLWKTW	YPCAKTQKLV	QDQSDELCKA	VRCQKPEVIC	3180
GHICYSSEAK	VCCNGVLYNP	KPGHRCCEEK	YIPFVLNSTG	VCCGGRIQEA	QPNHQCCSGY	3240
YARILPGEVC	CPDEQHNRVS	VGIGDSCCGR	MPYSTSGNQI	CCAGRLHDGH	GQKCCGRQIV	3300
SNDECCCGE	EGVGVNRLPG	MFCCQDYVN	MSDTICCSAS	SGESKAHIKK	NDPVPVKCCE	3360
TELIPKSQKC	CNGVGYNPLK	YVCSDKISTG	MMMKTKECR	ILCPASMEAT	EHCGRCDFNF	3420
TSHICTVIRG	SHNSTGKAST	EEMCSSEAET	IHTGSVNTYS	YTDVNLKPYM	TYEYRISAWN	3480
SYGRGLSKAV	RARTKEDVPQ	GVSPPWTWTKI	DNLEDTIVLN	WRKPIQSNGP	IIYYILLRNG	3540
IERFRGTSLS	FSDKEGIQPV	QEYSYQLKAC	TVAGCATSSK	VVAATTQGVP	ESILEPSSITA	3600
LSAVALHLSW	SPVEKSNGV	KEYQIRQVGK	GLIHTDDTTDR	RQHTVTGLQP	YTNYNSFTLTA	3660
CTSAGCTTSE	PFLGQTLQAA	PEGWVVTPRH	IIINSTTVEL	YWSLPEKPN	LVSQYOLSRN	3720
GNLLFLGGSE	EQNFTDKNLE	PNSRYTYKLE	VKTGGGSSAS	DDYIVQTPMS	TPEEIYPYNN	3780
ITVIGPYSIF	VAWIPPGIL	PEIPVEYNVL	LNDGSVTPLA	FSGVHHQSTL	LENLTPFTQY	3840
EIRIQAQCNQ	CGCVSSRMFV	KTPPEAAPMDL	NSPVLKALGS	ACIEIKWMPP	EKPNGIIINY	3900
FIYRRPAGIE	EESVLPFWSE	GALEMFMDG	TLPRTFLIYEY	RVRACNSKGS	VESLWSLTQT	3960
LEAPPQDFPA	PWAQATSAAHS	VLLNWTKPES	PNGIISHYRV	VYQERPPDPT	FNSPTVHAFT	4020
VKGTSQHQAHL	YGLEPFTTYR	IGVVAANHAG	EILSPWTLIQ	TLESSPPSLR	NFIVEQKENG	4080
RALLLQWSEP	MRTNGVIKTY	NIFSDQFLR	SGLNRQFLR	RLDPTFLYTL	TLEACTRAGC	4140
AHSAPQPLW	DEAPPDSQAL	PTVHSVKSTS	VELSWSEPVN	PNGKIIYREV	IRRCFEGKAW	4200
GNQTIQADEK	IVFTEYNTTER	NTFMYNDTGL	QPWTQCEYKI	YTWNNSAGHTC	SSNVNRVTLQ	4260
APPAGLSPPV	ISYVSMNPQK	LLISWIPPEQ	SNGIIQSYRL	QRNEMLYPFS	FDPVTFNYTD	4320
EELLPFSTYS	YALQACTSGG	CSTSKPTST	TLEAAPSEVS	PPDLWAVSAT	QMNVCWSPPT	4380
VQNGKITVY	VRYDNKESLA	GQGLCLLVSH	LQPYSQYNFNS	VLACTNGCCT	ASVSKSAWTN	4440
EALPENMDSP	TLOVGTGSESI	EITWKPPRNP	NGQIRSYELR	RDGTIVYTGL	ETRYRDFTLT	4500
PGVEYSYVT	ASNSQGGILS	PLVKDRTSPS	APSGMEPPKL	QARGPQEILV	NWDPPVRTNG	4560
DIINYTLFIR	ELFERETKII	HINTTHNSFQ	MQSIVINQLK	PFHRYEIRIQ	ACTTLGCASS	4620
DWTFIQTPLI	APLQMPPPHL	EVQMAPGGFQ	PTVSLLWTGP	LQPNGKVLYY	ELYRRQIATQ	4680
PRKSNPVTLI	NGSSTSFIGS	ELLPTFTEYEY	QWAVANSAGK	APSSWTWCRT	GPAPPEGLRA	4740
PTPHVISSTQ	AVVNISAPGK	PNGIVSLYRL	FSSSAHGAET	VLSEGMMATQ	TLHGLQAFNT	4800
YSIGVEACT	FNCCSKGPTA	ELRTHPAPP	GLSSPQIGTL	ASRTASFRWS	PPMFNGVIIH	4860
SYELQFHVCAC	PPDSALPCPT	SQIETKTYGL	GQKASLGGQL	PTTYKLRVV	AHNEVGSTAS	4920
EWISFTTQKE	LPQYRAPFSV	DSNLSSVVCVN	WSDTFLLNGQ	LKEYVLTDGG	RRVYSGLDTT	4980
LYIPRTADKT	FFFQVICTTD	EGSVKTPLIQ	YDTSTGLGLV	LTPPGKKGS	RSKSTEFYSE	5040
LWFIVLMAML	GLILLLAIFL	LILQRKIHKE	PYIRERPPLV	PLQKRMSPLN	VYPPGENHMG	5100
LADTKIPRSG	TPVSI	RSNR	ACVLRIPSON	QTSVLYSQGS	LHRVSQSLMD	5160
SLWEAIMGHN	SGLYVDEEDL	MNAIKDFSSV	TKERTTFTDT	HL		5202

SEQ ID NO: 39 moltype = AA length = 410
 FEATURE Location/Qualifiers
 REGION 1..410
 note = MISC_FEATURE - NR2E3 (photoreceptor-specific nuclear receptor), isoform long
 source 1..410
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 39
 METRPTALMS STVAAAAPAA GAASRKESPG RWGLGEDPTG VSPSLQCRVC GDSSSGKHYG 60
 IYACNGCSGF FKRSVRRRLI YRCQVQGAGMC PVDKAHRNQC QACRLKKCLQ AGMNQDAVQN 120
 ERQPRSTAQV HLDMSMESNTE SRPESLVAPP APAGRSPRGP TPMSAARALG HHFMASLITA 180
 ETCAKLEPED ADENIDVTSN DPEFPSSPVS SSSPCGLDSI HETSARLLFM AVKWAKNLPV 240
 FSSLPFIRDQV ILLEEAWSL FLLGAIQWSL PLDSCPPLAP PEASAAGGAQ GRLTLSMET 300
 RLQETISRF RALAVDPTEF ACMKALVLFK PETRGLKDPE HVEALQDQSQ VMLSQHSKAH 360
 HPSQPVRFGK LLLLLPSLRF ITAERIELLF FRKTIGNTPM EKLLCDMFKN 410

SEQ ID NO: 40 moltype = AA length = 1250
 FEATURE Location/Qualifiers
 REGION 1..1250
 note = MISC_FEATURE - human CNGB1 protein (NGS)
 source 1..1250
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 40
 MLGWVQRVLP QPPGTPRKTQ MQEEEVEPE PEMEAEVEPE PNPEEAETES ESMPEESFK 60

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EEEEEAVADPS	PQETKEAALT	STISLRAQGA	EISEMNSPSH	RVLTLWMKGV	EKVIPQPVHS	120
ITEDPAQILG	HGSTGDTGCT	DEPNEALEAQ	DTRPGLRLLL	WLEQNLERVL	PQPPKSSEVW	180
RDEPAVATGA	ASDPAPPGRP	QEMGPKLQAR	ETPSLPTPIP	LQPKEEPKEA	PAPEPQPGSQ	240
AQTSSLPPTR	DPARLVAWVL	HRLEMALPQP	VLHGKIGEQE	PDSPGICDVQ	TISILPGGQV	300
EPDLVLEEEVE	PPWEDAHQDV	STSPQGTEVV	PAYEEENKAV	EKMPRELSRI	EEEKEDEEEE	360
EEEEEEEEE	EVTEVLLDSC	VVSQVGVGQS	EEDGTRPQST	SDQLWEEEVGE	EAKKEAEKA	420
KEEAEEVAEE	EAEKEPQDW	ETKEEPEAEA	EAASSGVPAT	KQHPEVQVED	TDADSCPLMA	480
EENPPSTVLP	PPSPAKSDTL	IPVSSASGTH	RKKLPSEDDE	AEELKALSPA	ESPVVAWSDP	540
TPPKDTDQGD	RAASTASTNS	AIINDRLQEL	VKLFKERTEK	VKEKLIDPDV	TSDEESPKPS	600
PAKKAPEPAP	DTKPABAEPV	EEEHYCDMLC	CKPFKHRPWKK	YQFPQSIDPL	TNLMLYVWLW	660
FVVMAWNWN	WLIPVRWAPP	YQTPDNIHHW	LIMDYLCDLI	YFLDITVFQ	RLQFVRGGDI	720
ITDKDKDMRN	YLKSRRFKMD	LLSLPLDFL	YLKVGVNPL	LRPRLCKYMA	FFEFNSRLES	780
ILSKAYVYRV	IRTTAYLLYS	LHLNSCLYYW	ASAYQGLGST	HWVYDGVGNS	YIRCYYFAVK	840
TLITIGGLPD	PKTLEIVFQ	LLNYFTGVFA	F SVMIGQMRD	V VGAATAGQT	YYRSCMDSTV	900
KYVMNFYKIP	SQVNRRVKTW	EYTWHSQML	DESELMVQLP	DKMRLLDAID	VNYNIVSKVA	960
LFQGCDRQMI	FDMLKRLRSV	VYLPNDYVC	KGEIGREMYI	I IQAGQVQLG	GPDGKSVLV	1020
LKAGGSVFGEI	SLLAVGGGNR	RTANVVAHGF	TNLFLILDKD	LNEILVHYPE	SQKLLRKAR	1080
RMLRSNNKPO	E EKSVLILPP	RAGTPKLFNA	ALAMTGMGG	KGAKGGKLH	LRARLKELAA	1140
LEAAAKQQEL	VEQAKSSQDV	KGEEGSAAPD	QHTHPKEAAT	DPPAPRTPPE	PPGSPPSSPP	1200
PASLGRPEG	EEGPAPEEH	SVRICMSPGP	EPGEQILSVK	MPEEREKAE		1250

SEQ ID NO: 41	moltype = AA	length = 1251
FEATURE	Location/Qualifiers	
REGION	1..1251	
	note = MISC_FEATURE	- human CNGB1 protein (GenBank)
source	1..1251	
	mol_type = protein	
	organism = Homo sapiens	

SEQUENCE: 41						
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EEEEEAVADPS	PQETKEAALT	STISLRAQGA	EISEMNSPSH	RVLTLWMKGV	EKVIPQPVHS	120
ITEDPAQILG	HGSTGDTGCT	DEPNEALEAQ	DTRPGLRLLL	WLEQNLERVL	PQPPKSSEVW	180
RDEPAVATGA	ASDPAPPGRP	QEMGPKLQAR	ETPSLPTPIP	LQPKEEPKEA	PAPEPQPGSQ	240
AQTSSLPPTR	DPARLVAWVL	HRLEMALPQP	VLHGKIGEQE	PDSPGICDVQ	TISILPGGQV	300
EPDLVLEEEVE	PPWEDAHQDV	STSPQGTEVV	PAYEEENKAV	EKMPRELSRI	EEEKEDEEEE	360
EEEEEEEEE	EVTEVLLDSC	VVSQVGVGQS	EEDGTRPQST	SDQLWEEEVGE	EAKKEAEKA	420
KEEAEEVAE	EAEKEPQDW	ETKEEPEAEA	EAASSGVPA	TKQHPEVQVE	DTDADSCPLM	480
AEEENPPSTVLP	PPPSPAKSDT	LIVPSSASGT	HRKKLPSEDDE	AEELKALSP	AESPVVAWS	540
PTTPKDTDQGD	RAASTASTNS	SAIENDRLQE	VLKLFKERTE	KVKEKLIDPD	VTSDEESPKP	600
SPAKKAPPAPE	PDTKPAEAE	VEEEHYCDMLC	CCKFKHRPWK	YQFPQSIDPL	LTNLMYVWLW	660
FFVVMAWNWN	CWLIPVRWAF	PYQTPDNIHH	WLLMDYLCDL	IYFLDITVFQ	TRLQFVRGGD	720
ITDKDKDMRN	NYLKSRRFKM	DLLSLPLDF	LYLKGVVNPL	LRPRLCKYMA	AFFEFNSRLE	780
SILSKAYVYR	IRTTAYLLYS	SLHLNSCLYY	WASAYQGLGS	THWVYDGVGNS	SYIRCYYFAV	840
TLITIGGLPD	PKTLEIVFQ	DPKTLFEIVF	AFSVMIGQMRD	DVVGAAATAGQ	YYRSCMDST	900
KYVMNFYKIP	SQVNRRVKTW	YEYTWHSQML	LDESELMVQLP	PDKMRLLDAI	VNYNIVSKVA	960
ALFQGCDRQMI	FDMLKRLRSV	VYLPNDYVC	KKGEIGREMYI	I IQAGQVQLG	GGPDGKSVLV	1020
LKAGGSVFGEI	SLLAVGGGNR	RRTANVVAHGF	FTNLFLILDKD	DLNEILVHYP	ESQKLLRKKA	1080
RMLRSNNKPO	E EKSVLILPP	PRAGTPKLFNA	ALAMTGMGG	KGAKGGKLH	LRARLKELAA	1140
LEAAAKQQEL	VEQAKSSQDV	KGEEGSAAPD	QHTHPKEAAT	DPPAPRTPPE	PPGSPPSSPP	1200
PASLGRPEG	EEGPAPEEH	SVRICMSPGP	EPGEQILSVK	MPEEREKAE		1250

SEQ ID NO: 42	moltype = DNA	length = 4651
FEATURE	Location/Qualifiers	
misc_feature	1..4651	
	note = 5' ITR-hRHO promoter-CNGB1a-SV40polyA-3' ITR	
source	1..4651	
	mol_type = other DNA	
	organism = synthetic construct	

SEQUENCE: 42						
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gttcgcgcgg	cctcaagttag	cgagcgagcg	cgcagagagg	gagtgcccaa	ctccatcaact	120
aggggttct	tgttagtaat	gattaaccgc	ccatgtact	tatctacgta	gccatgtct	180
aggaagatcg	gattcgcgc	ttaaggctct	cctccctgac	ctcaggctc	ctccctagtgt	240
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cactttataa	gggtctgggg	gggtcagaa	ccagagtc	cactgttaac	ggccggccagt	420
gtgtctggat	tgcgcctct	ccacccgc	gttgggctgg	gtccagagg	tgctgcctca	480
gccccccagg	acccctcgga	agaccaagat	gcaggaggaa	gaggaatgtt	aaccagagcc	540
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gtccatgc	cccgaaaggat	cattcaagg	ggaggaatgt	gtgtggcag	acccaaggccc	660
tcaggagacc	aaggaggctg	cccttacttc	cacatccat	ctccggccccc	agggcgctga	720
gatttctgaa	atgaatagtc	ccagccacag	ggtactgacc	tggctcatga	agggtgtaga	780
gaaggtgtac	ccgcagcctg	ttcacagcat	cacggaggac	ccggctcaga	tcctggggca	840
tggcagcact	ggggacacag	ggtgacacaga	tgaacccaaat	gaggcccttg	aggcccaaga	900
cactaggct	gggctgcggc	tgcttctgt	gctggagacg	aatctggaaa	gagtgttcc	960
tcagcccccc	aaatcctctg	aggtctggag	agatgacgcct	gcagttgc	cagcgccctcc	1020

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aggacgcccc	cagggaaatgg	ggcccaagct	gcaggcccgg	gagaccctc	ccctgcccac	1080
accatcccc	ctgcgcgcca	aggaggaaacc	caaggaggcca	ccagctccag	agcccccagcc	1140
cggctcccg	gccccagact	cctccctgcc	accaaccagg	gaccctgcca	ggctgggtggc	1200
atgggtctcg	cacaggctgg	atagggcctt	gcccgcagcca	gtgctacatc	ggaaaatagg	1260
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aggacaagt	gagccgtgacc	ttgtctctaga	ggagggttga	ccgccttggg	aggatgccta	1380
ccaggatgtc	agtaccagcc	cacagggtac	agaggtgttt	ccagcttatg	aagaagagaa	1440
caaaggctgt	gagaqatgc	ccagagact	gtcccgatt	gaagaggaga	aagaqatgt	1500
ggaggaggaa	gagggaggag	aggaggagga	ggaagaggaga	gagggtactg	agggtctgt	1560
gtatagctgt	gtgggtcgcc	aggtgggtgt	ggggccagact	gaagaqacg	ggacccggcc	1620
ccagagact	tcagatcaga	agetgtgggg	ggaaggttggg	gaggaggcca	agaaggaaaggc	1680
tgaagagaag	gccaaggagg	aggccggaga	gggtggctgaa	gaggaggctg	aaaaggagcc	1740
ccaggactgg	cgccggagcca	aggaggagcc	tgaggctgag	gcccggggctg	ccagttcagg	1800
agtgcctgcc	acggaaacagc	acccagaagt	gcagggtggaa	gatactgtat	ctgatagctg	1860
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tgaggatgt	gaggctgaag	agctcaaggg	gttgcacca	gcagagtccc	cagtgggtgc	2040
ctggctcgac	cccacccac	cggagacac	tgatggccag	gaccgtgggg	cctccacggc	2100
cagcacaaat	agccggatca	taacgcggcc	gctccaggag	ctgggtgaagc	tcttcaagga	2160
gccccacagag	aaagtgtgaa	agaaaatcat	tgaccctgtac	gtcaccctctg	atgaggagag	2220
cccccaagccc	tcccccggcca	agaaaaagccc	agagccacgt	ccagacacaa	agccggctga	2280
agccgagoca	gtgggaagg	agcaacttgc	tgctgcaagt	tcaaaccac	2340	
ccccctggaa	aaagtaccatg	ttccccagag	cattgaccatc	ctgaccaacc	tgatgtatgt	2400
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aggcggggac	atccatccg	acaaaaaaagg	catggaaat	aacttgcgtg	2640	
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1. A polynucleotide comprising in this order:
 - a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising, consisting essentially of or consisting of the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and
 - b) at least one transgene (TG) operably linked to the promoter of a);

wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1.
 2. The polynucleotide according to claim 1, wherein: the 5' end of the hRPSPE is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 290 to 310 of SEQ ID NO: 2 or variants thereof; the CP comprises a TATA-box and/or an initiator (Inr); the 5' end of the promoter is at a nucleic acid position from 1 to 160 and the 3' end at a nucleic acid position from 340 to 350 of SEQ ID NO: 2 or variants thereof; and/or
 - the at least one transgene comprises a nucleic acid encoding a protein or RNA that maintains or improves the physiological function of rods.
- 3-5. (canceled)**
6. The polynucleotide according to claims-1 to 5, wherein at least one transgene:
 - (i) comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, AIPL1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MYO7A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USH1C, USH1G, USH2A or functional fragments or variants thereof, optionally wherein the hCNGB1 comprises an amino acid sequence according to SEQ ID NOS: 3, 40, or 41, or variants thereof;
 - (ii) comprises a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof;
 - (iii) comprises a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof; or
 - (iv) comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, optionally wherein the protein is a toxin; a prodrug converting enzyme, e.g. thymidine kinase; or a cell cycle inhibitor, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2;
 - (v) comprises a nucleic acid encoding a mRNA encoding a dominant negative mutant of a cell cycle inhibitor; and/or
 - (vi) comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor.
- 7. (canceled)**
8. The polynucleotide of claim 1, comprising one or more further nucleotide sequence elements selected from the group consisting of:
 - (i) a polyadenylation signal (PAS), optionally wherein the PAS comprises or consists of a Simian-Virus 40 (SV40) PAS and/or the PAS comprises or consists of a nucleic acid according to SEQ ID NO: 4 or functional variants thereof;
 - (ii) one or two inverted terminal repeat (ITR) sequences, optionally wherein:
the ITR sequence is an adeno-associated virus (AAV) ITR,
the ITR sequence is an AAV ITR wherein the AAV is AAV serotype 2, 5, 8, or 9, and/or
the polynucleotide is flanked at the 5' end with an L-ITR and at the 3' end with an R-ITR, optionally wherein the L-ITR comprises or consists of the sequence according to SEQ ID NO: 5 or variants thereof and/or the R-ITR comprises or consists of the sequence according to SEQ ID NO: 6 or variants thereof; and

(iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

9-14. (canceled)

15. The polynucleotide of claim **1**, wherein the total length of the polynucleotide is 5200 bases or less, preferably 5100 bases or less, more preferably 5000 bases of less.

16. A plasmid comprising the polynucleotide of claim **1**, optionally wherein the plasmid comprises a nucleic acid sequence according to SEQ ID NOS: 7, 42-44, or variants thereof.

17. (canceled)

18. A viral vector comprising the polynucleotide of claim **1**, optionally packaged in a virus selected from the group consisting of AAV2, AAV5, AAV8, AAV9 or variants thereof.

19-20. (canceled)

21. A pharmaceutical composition comprising the polynucleotide according to claim **1**, and a pharmaceutically acceptable carrier.

22. A method for treating a disease of the retina, comprising administering the polynucleotide according to claim **1** to a patient in need thereof, optionally wherein the disease of the retina is retinal degeneration.

23-26. (canceled)

27. A polynucleotide comprising from 5' to 3':

- a) a human rhodopsin promoter comprising the nucleic acid sequence according to SEQ ID NO: 9 or variants thereof; and
- b) at least one transgene (TG) operably linked to the promoter of a).

28. The polynucleotide according to claim **27**, wherein:

- (i) the transgene comprises a nucleic acid encoding a protein that maintains or improves a physiological function of rods;
- (ii) the transgene comprises a nucleic acid encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1), ABCA4, AIPL1, BEST1, CACNA1F, CLN3, CLRN1, CNGA1, CEP290, CRB1, CRB2, CRX, GPR98, GUCA1A, GUCA1B, MYO7A, NRL, PDE6A, PDE6B, PRPH2, PROM1, RHO, ROM1, RP1, RP2, RPE65, RPGR, SAG, USH1C, USH1G, USH2A or functional fragments or variants thereof;
- (iii) the transgene comprises a nucleic acid encoding a miRNA or shRNA targeting a mRNA encoding a dominant negative mutant thereof;
- (iv) the transgene comprises a nucleic acid encoding an antibody or antibody binding fragment that specifically binds to a dominant negative mutant thereof;
- (v) the transgene comprises a nucleic acid encoding a protein that inhibits proliferation of rod cells, optionally wherein the protein is a toxin; a prodrug converting enzyme, e.g. thymidine kinase; or a cell cycle inhibitor, e.g. retinoblastoma protein (pRB), p53, p21CIP1, p27KIP1 and p57KIP2;
- (vi) the transgene comprises a nucleic acid encoding a mRNA encoding a dominant negative mutant of a cell cycle inhibitor; and/or
- (vii) the transgene comprises a nucleic acid encoding a dominant negative mutant of a cell cycle inhibitor.

29. (canceled)

30. The polynucleotide of claim **27**, comprising one or more further nucleotide sequence elements selected from the group consisting of:

- (i) a polyadenylation signal (PAS), optionally wherein the PAS comprises or consists of a Simian-Virus 40 (SV40) PAS;
- (ii) one or two inverted terminal repeat (ITR) sequences, optionally wherein: the ITR sequence is an adeno-associated virus (AAV) ITR, and/or the ITR sequence is an AAV ITR wherein the AAV is AAV serotype 2, 5, 8, or 9; and
- (iii) viral nucleotide sequences necessary to form an infectious viral vector, preferably an adenovirus, a retrovirus, a lentivirus, a vaccinia/poxvirus, or a herpesvirus vector, in particular herpes simplex virus (HSV) vector.

31-33. (canceled)

34. A viral vector comprising the polynucleotide of claim **27**, optionally packaged in a virus selected from the group consisting of AAV2, AAV5, AAV8, AAV9 or variants thereof.

35. (canceled)

36. A method for treating retinal degeneration or retinitis pigmentosa in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polynucleotide according to claim **27**, optionally wherein the polynucleotide comprises the nucleic acid sequence set forth in SEQ ID NO: 43.

37-38. (canceled)

39. A method for treating retinal degeneration in a subject in need thereof, wherein the retinal degeneration is characterized by a defect or absence of CNGB1 in the retinal cells of the subject, the method comprising administering to the subject a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43, optionally wherein the retinal degeneration is CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45).

40. (canceled)

41. A method for treating CNGB1-linked retinitis pigmentosa or retinitis pigmentosa type 45 (RP45) in a subject in need thereof, comprising subretinal administration to the subject a therapeutically effective amount of a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43.

42. A polynucleotide comprising from 5' to 3':

- a) a promoter comprising a human rod photoreceptor-specific promoter element (hRPSPE) comprising the nucleic acid sequence according to SEQ ID NO: 1 or variants thereof and a core promoter (CP); and
- b) a transgene encoding the human rod cyclic nucleotide-gated channel beta subunit (hCNGB1) operably linked to the promoter of a), wherein the variant of SEQ ID NO: 1 comprises one or more nucleic acid substitutions outside nucleotide positions 6 to 13, 32 to 40, 70 to 83, and 87 to 94 of SEQ ID NO: 1.

43. A pharmaceutical composition comprising the polynucleotide of claim **42**, and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising a viral vector comprising the nucleic acid sequence set forth in SEQ ID NO: 43, and a pharmaceutically acceptable carrier.