REVIEW ARTICLE

Gene therapies for retinal dystrophies: potential in the Chinese population

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Abstract

Retinal dystrophies (RD) refer to a group of clinically and genetically heterogenous degenerative conditions of the retina. We aim to summarize emerging gene therapies for RD and their efficacy in restoring photoreceptor or bipolar cell functions. In patients with retinitis pigmentosa, injection of adeno-associated virus containing *RPE65*, *RPGR* or *MERTK* results in improvements in outcomes of the multi-luminal mobility test and full-field light sensitivity threshold test. In animal models of congenital stationary night blindness, gene augmentation of *Cacn1f*, *LRIT3* or *Nyx* increases ON-bipolar cell signaling cascade and preserves retinal morphology. Patients with achromatopsia show improved visual acuity, contrast sensitivity, and cone responses after injection of a vector comprising *CNGA3* or *CNGB3*. In patients with Leber congenital amaurosis, administration of a vector containing *RPE65* or *RDH12* results in improved full-field sensitivity to white light and photoreceptors responses, particularly in pediatric populations. Some patients have improved dark-adapted spectral sensitivities and pupillary light responses after injection of vectors. For choroideremia, *REP1* gene therapy has been shown to improve visual acuity and retinal sensitivity. Nonetheless, voretigene neparvovec-ryzl (Luxturna) remains to be the only approved gene therapy in patients with biallelic *RPE65* mutation. In the Chinese population, *RPGR*, *Lrit3*, *Nyx*, *CNGA3*, *RPE65*, *RDH12*, and *CHM* gene therapies may be beneficial, because the mutated genes are compatible with the genes investigated in previous clinical trials. A thorough understanding of gene therapies for different RD subtypes may allow more personalized management of retinal degeneration.

Key words: Choroideremia; Color vision defects; Gene therapy; Leber congenital amaurosis; Night blindness, congenital stationary; Retinitis pigmentosa

Introduction

Retinal dystrophies (RD) refer to a group of clinically and genetically heterogenous degenerative conditions of the retina. RD have a prevalence of 1 in 4000 and affect >2 million people wordwide.[1,2] RD may be inherited with an autosomal dominant, autosomal recessive, or X-linked mode, whereas some cases may be sporadic in nature.[3] Disease onset varies from neonatal to early adolescence or adulthood. Clinical presentations range from poor peripheral or dim vision and tunnel vision to complete blindness, depending on the gene affected and the disease severity.[3] Visual impairment is associated with reduced independence, resulting in mental and financial burden.[4]

The retina consists of photoreceptors, mainly rod and cone cells, which are reactive to dim and bright light, respectively. Light signals are then phototransduced into electric signals, which are sent via the optic nerve to the occipital lobe of the central nervous system for image processing.[5] Phototransduction requires the integrity of retinal pigmental epithelium (RPE), a single layer found below

the photoreceptors. RPE stores nutrients for photoreceptors and phagocytoses, the oldest portion of photoreceptor outer segment. RPE is the main site of vitamin A storage, which helps the isomerization of retinoids in the classical visual cycle.[6] 11-*cis*-retinal first bounds to cone opsins or rhodopsin, which is then photoisomerized to all-*trans*-retinal. All-*trans*-retinal is then reduced to all-*trans*-retinol and transported to RPE. Inside RPE, an enzyme RPE65 is responsible for the *trans*-to-*cis* isomerization to regenerate the visual chromophore.[7] The underlying cause of RD can be attributed to >270 genes involved in the retinoid cycle, photoreceptor survival, and phototransduction.[8] Depending on the cell types involved, RD can be classified into different phenotypes such as rod-dominated disease (retinitis pigmentosa [RP], congenital stationary night blindness [CSNB]), cone-dominated disease (achromatopsia), generalized retinal degeneration involving both cells (Leber congenital amaurosis [LCA] and choroideremia), and vitreoretinopathies.[3]

Currently, there is no effective treatment for RD. However, gene therapies have shown to restore vision and cell-based therapies (embryonic stem cells, induced pluripotent stem cells, and retinal progenitor cells) have been performed in mouse models.[9-11] Gene therapy uses exogenous DNA to treat genetically mutated disease.[12] It has been applied to retinal pathologies; the therapeutic amount requirement is small, and the presence of the blood-retinal barrier helps avoid immunological responses.[1]

We aim to review the emerging gene therapies for RD (RP, CSNB, achromatopsia, LCA, and choroideremia) and their effectiveness in preserving vision. The gene defects found in Chinese patients with RD and the potential use of gene therapies for such patients are also discussed.

Rod-dominated diseases

Retinitis pigmentosa

RP is the most common subtype of RD. RP results in loss of rods and subsequently cones and RPE functions. RP involves the mutations of *RHO*, *ROM1*, *PRPH2*, and *RPE65*.[13] Patients with RP first manifest with nyctalopia, followed by a loss of peripheral vision and eventually blindness. Subretinal injection of adeno-associated virus (AAV)–carrying genes that affect RP including AAV2-hRPE65, AAV8.coRPGR, and rAAV2-VMD2-hMERTK has been reported to improve rod functions in clinical trials (**Table 1**).

AAV2-hRPE65v2

RPE65 gene encodes all-*trans* retinyl ester isomerase that helps the conversion into 11-*cis*-retinol in the visual cycle for chromophore regeneration and phototransduction.[13] In a phase 1 trial of 11 individuals with *RPE65* mutations,[14] unilateral subretinal injection of voretigene neparvovec (AAV2-hRPE65v2), an AAV2 vector containing human RPE65 cDNA, resulted in a robust improvement in the functions of rods and cones (measured by full-field light sensitivity threshold [FST] testing) at day 30 and until 3 years ($p<0.0001$ for all timepoints). Six patients had increased sensitivity to white and blue light by at least 10 dB. Nonetheless, no clinically significant improvement in visual acuity was reported, although no adverse event was reported either.

In a phase 3 trial of 31 patients with biallelic *RPE65* gene mutation who were randomized to receive placebo or subretinal injection of voretigene neparvovec in the worse-seeing eye for 1 year,[15] the intervention group showed higher improvement in the bilateral multi-luminance mobility test (MLMT) mean score (1.8 vs 0.2), improvement of a mean of >2 log units in the FST testing by day 30 ($p=0.0004$) and until 1 year, higher improvement in mean LogMAR (8.1 vs 1.6 letters), and doubling of the mean sum total degrees of Goldmann visual field (compared with a decrease in the control group).

In 29 patients with *RPE65* mutation in a phase 1 follow-up study at year 4 and a phase 3 study at year 2,[16] unilateral subretinal injection of voretigene neparvovec-ryzl (AAV2-hRPE65v2) resulted in an improvement in the mean MLMT lux score at day 30 and the score remained stable over 4 years (2.4 at 4 years, 1.9 at 2 years, and 2.1 at 1 year), compared with 0.2 in the control group ($p=0.004$) and an improvement in the mean white light FST at 1 year, with a gain of >2.3 $\log^{10}$ units. All patients with an increase of the MLMT score of 1 had FST improvement. Seven of 11 patients who had MLMT improved by 1 light score achieved maximum lux score, which reflects the ceiling effect of MLMT score at minimal measurable light level.

In a phase 3 randomized controlled trial of 31 patients with biallelic *RPE65* mutation who received subretinal injection of voretigene neparvovec in both eyes,[17] the improvement in the MLMT score in both eyes was 1.8 at year 3 and 1.7 at year 4. 71% of patients were able to pass MLMT at the lowest light level at year 3. The mean change in FST was -2.04 $\log_{10}$ (cd.s/m^2) at year 3 and -1.90 $\log_{10}$ (cd.s/m^2) at year 4. There was a clinically significant improvement of visual acuity of binocular vision by ≥-0.3 logMAR at year 3.

In six pediatric patients with biallelic *RPE65* mutation who received subretinal injection of rAAV2-CB-hRPE65 in the worse-seeing eye,[18] four patients had improvement in visual acuity during the first 2 years and until subsequent years. Two of them had improved visual acuity in the untreated eye as well. Four patients had no change in the V4e target from the normal baseline, whereas three patients had no change in visual field or III4e or II4e targets based on the kinetic perimetry. Despite that, three patients showed improved central 30° and total hill of vision in the treated eye based on static perimetry during the first 2 years. However, five adult patients in the same study showed no significant improvement in visual acuity or static perimetry. This demonstrates the effectiveness of gene therapy in the pediatric group in improving visual acuity and visual field.

Table 1. Gene therapies for retinitis pigmentosa

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2-hRPE65v2					
Bennett et al, 2016[14]	United States	*RPE65*	11 patients with *RPE65* mutation had subretinal administration of AAV2-hRPE65v2 in one eye, followed up for 3 years.	Goldmann visual field test, full-field light sensitivity threshold testing, white, blue and red stimuli, visual acuity.	Visual field tests showed islands of responding retina and expansion of visual field by day 30 corresponded to injection area. Full-field light sensitivity threshold testing showed improvement in rod and cone function by day 30.
Russell et al, 2017[15]	United States	*RPE65*	31 patients with biallelic *RPE65* mutations divided into intervention group with subretinal injection of voretigene neparvovec for 1 year or control group (2:1).	Multi-luminance mobility testing performance, full-field light sensitivity threshold, BCVA, visual field.	Intervention group had mean bilateral MLMT change of 1.8 while that of control group was 0.2. No control patients passed MLMT at the lowest luminance level but 65% of the intervention group passed it. Mean full-field light sensitivity threshold in the group with gene therapy had a rapid and greater improvement by day 30.
Maguire et al, 2019[16]	United States	*RPE65*	29 *RPE65*- mutated subjects with 20 having bilateral subretinal injection of vector and 9 serving as control group.	Change in performance on multi-luminance mobility test, full-field light sensitivity threshold, BCVA, visual field.	Mean MLMT lux score showed improvement by day 30 visit and remained stable for 4 years in the interventional group. 72% of the patients passed MLMT at the lowest illuminance level. Mean full-field light sensitivity threshold improved at 1 year.
Maguire et al, 2021[17]	United States	*RPE65*	31 patients with *RPE65* mutation randomized 2:1 to intervention with voretigene neparvovec subretinal injection or control.	Multiluminance mobility test, full-field light sensitivity threshold white light, visual field, visual acuity.	Mean MLMT at year 4 for intervention group was 1.7 and that of control group was 2.4, having 71% of patients being able to pass MLMT at the lowest light level. Full-field light sensitivity threshold white light showed a mean change of -2.04 log10 and -2.91 log10 in interventional and control group respectively.
Pennesi et al, 2018[18]	United States	*RPE65*	11 subjects with *RPE65* mutation received rAAV2-CB-hRPE65 subretinal injection in the worse-seeing eye, followed up for 5 years.	BCVA, static perimetry hill of vision measurements, kinetic perimetry, visual field area.	Paediatric patients showed improved BCVA and static perimetry results but not in the kinetic perimetry. Adult subjects had no consistent changes in the parameters measured.
AAV8.coRPGR					
Cehajic-Kapetanovic et al, 2020[19]	United Kingdom and United States	*RPGR*	18 patients with *RPGR* gene mutation received subretinal AAV8. *coRPGR*, another eye as the fellow eye.	Visual acuity, microperimetry, central corneal thickness.	VA returned to baseline by 3 months post-treatment. Mean visual field change was +0.5 dB in treated eye while that in control eye was +0.1 dB.
rAAV2-VMD2-hMERTK					
Ghazi et al, 2016[21]	Saudi Arabia	*MERTK*	6 patients with *MERTK*-related RP received subretinal injection of rAAV2-VMD2-hMERTK for 2- year follow up.	BCVA, intraocular pressure, full-field stimulus threshold test.	50% of the patients showed improved visual acuity in the treated eye. No significant difference in mean FST values between operated and non-operated eyes.

AAV8. coRPGR

RP GTPase regulator (*RPGR*) gene mutation is associated with X-linked RP. In the first phase 1 and 2 trials of 18 patients with genetically confirmed variants in *RPGR* who were randomized to receive subretinal injection of codon-optimized serotype 8 vector (AAV8. coRPGR) in three different concentrations,[19] six patients with mid-dose (5×10^{11} gp/mL) achieved an improvement in retinal sensitivity and visual field at month 1, which persisted to month 6. The mean change in microperimetry at month 6 was +0.5 dB in treated eyes and +0.1 dB in untreated eyes. The mean change of LogMAR was -0.1 letters in treated eyes and +0.8 letters in untreated eyes; the treated eyes had less improvement because the outcome of gene therapy involves the interplay of neurodegeneration, vector dosage, and injection-related inflammation in the early phase. Foveal central retinal thickness revealed a decrease of 10.8 μm in treated eyes and 10.9 μm in untreated eyes. Optical coherence tomography showed similar retinal morphology. These findings suggest that gene therapy preserves the degeneration of the outer retinal structure.

rAAV2-VMD2-hMERTK

MER proto-oncogene, tyrosine kinase (MERTK) gene

involves in the phagocytosis of RPE and prevents accumulation of toxic debris, and thus its mutation may result in RP.[20] In a phase 1 study of six patients with *MERTK* mutation who received subretinal injection of rAAV2-VMD2-hMERTK,[21] three patients showed improved visual acuity, with one of them achieving 20/125 at day 8 (compared with <20/6400 at baseline). The mean FST testing results improved over time (p=0.01) and better in treated eye at day 10 (p=0.02). There was no major change in the central macular or foveal thickness of the treated eyes. This shows the efficacy and safety of *MERTK* gene therapy on the retina.

Congenital stationary night blindness

CSNB is an inherited and non-progressive disease affecting photoreceptors, mainly rods, and bipolar cells. It can be classified based on electroretinogram (ERG) pattern, fundus appearance, and mode of inheritance.[22] CSNB is mainly caused by defects in four genes including *PDE6B*, *CACNA1F*, *NYX*, and *SLC24A1*.[22] Patients often present with poor vision under dim light, delayed adaptation of the dark, and photophobia. Injection of AAV-carrying genes that affect CSNB including iZEG:Cacna1f, AAV2-7m8-*Lrit3*, and AAV2(quadY-F+T-V)-Ple155 has been reported to improve photoreceptor and bipolar cell responses in animal studies (**Table 2**).

iZEG:Cacna1f vector

CSNB with disrupted phototransduction within the bipolar cells is referred to as type 2 CSNB or incomplete CSNB. CSNB2A, the most common form of CSNB, results in poor visual acuity, strabismus, and nystagmus.[23] In a *Cacna1f*-knockout mouse model of CSNB2A that has a loss-of-function mutation of a gene coding for calcium channel CaV1.4,[24] overexpression of *iZEG:Cacna1f* resulted in rescue of visual function, with a well-delineated b-wave on scotopic ERG, which is an indicator of ON-bipolar cells (ON-BC) signaling. This reflects the re-establishment of photoreceptor-bipolar cell synapses.[24] Photopic ERG showed distinct b-wave in all background intensities, compared with no b-wave component in controls. Retinal morphology was preserved in areas with transgenic *Cacna1f* expression. This indicates α1F immune-positive ribbon synapse and preserved cone morphology, which is similar to wild-type photoreceptors. There were also reduced bipolar cells dendritic sprouting and restored mature lamination of cone pedicles. This reveals that high expression of *Cacna1f* may rescue retinal morphology and functions in CSNB2A models.

AAV2-7m8-Lrit3

Leucine-rich repeat immunoglobulin-like transmembrane domain 3 (*LRIT3*) gene is responsible for the protein in the outer plexiform layer of the retina, which affects transmission of signals between photoreceptors and ON-BC.[25] The disrupted signal transmission leads to complete CSNB. In *LRIT3*-knockout mice subjected to right eye intravitreal injection of AAV2-7m8-*Lrit3* (a vector containing *LRIT3* gene),26 LRIT3 proteins were found in rod-to-rod bipolar cells and cone-to-cone bipolar cells synapse. This confirms the effective protein synthesis in the outer plexiform layer. ERG showed a significant b-wave with sustained amplitude under scotopic conditions at 4 months after treatment, compared with no b-wave signals in controls. In addition, transient receptor potential melastatin 1 (TRPM1) was localized at the dendritic tips of the ON-

Table 2. Gene therapies for congenital stationary night blindness

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
iZEG:Cacna1f					
Waldner et al, 2020[24]	Canada	*Cacna1f*	iZEG:Cacna1f transgenic mice were used by injecting vector DNA into egg of wild type mice.	Immunohistochemical labels, electrophysiological studies, optokinetic response analysis.	Transgenic mice showed a well-delineated b-wave of normal implicit time and subnormal amplitude. Gene transduction rescued α1F immune-positive ribbon synapse, preserved cone morphology, reduced bipolar cells dendritic sprouting, and restored mature lamination of cone pedicles.
AAV2-7m8-*Lrit3*					
Varin et al, 2021[26]	France	*LRIT3*	*LRIT3*$^{-/-}$ mice received intravitreal injections of recombinant AAVs.	Electroretinogram, immunolocalized study, optomotor test.	Mice with gene therapy revealed a partial scotopic b-wave, where b-wave amplitude corresponded to 45% compared to that of *LRIT3*$^{+/+}$ mice. Treated retina showed transient potential receptor melastatin 1 localized at the dendritic tips of rod bipolar cells instead of cell bodies. Optomotor reflexes improved in treated mice under scotopic conditions.
AAV2(quadY-F+T-V)-Ple155					
Scalabrino et al, 2015[28]	United States	*Nyx*	*Nyx*^{nob} mouse model of CSNB1 received subretinal injections of AAV vector plasmid containing Ple155-GFP and Ple155-YFP_NYX.	Electroretinogram, immunohistochemistry, quantitative polymerase chain reaction.	Injected eye of the mice showed improved ERG b-wave. TRPM1 localization was restored to the dendritic tips of bipolar cells and TRPM1 channel gating was completely rescued. AAV-mediated Nyx transcript was found in treated eye.

BC instead of cell bodies. This indicates the restoration of ON-BC signaling cascade. A higher proportion of retinal ganglion cells was found to display ON-responses in treated eyes, indicating a functional rescue. Optomotor responses were improved in treated mice. This reflects that visual perception is rescued together with the transmission defect between photoreceptors and ON-BC.

AAV2(quadY-F+T-V)-Ple155

Apart from *LRIT3* gene, nyctalopin (*Nyx*) is another leucine-rich repeat protein that contributes to complete CSNB. NYX is necessary for the correct localization of TRPM1, for the signaling pathway in ON-BC and light-evoked depolarization.[27] In a study of Nyx-knockout mice that received trans-corneal subretinal or intravitreal injection of AAV vector plasmid containing Ple155-GFP and Ple-YFP_NYX,[28] intravitreal injection of AAV2(quadY-F+T-V)-Ple155 resulted in a strong expression of *Nyx* on the dendritic tips, soma, and axonal terminals of ON-BC. However, subretinal delivery resulted in inefficient transduction in both wild-type or transgenic retina. Subretinal delivery may only promote transduction in the area of surgically induced bleb, whereas intravitreal delivery can induce panretinal expression. Moreover, *Nyx* gene replacement partially rescued b-wave on ERG. The pattern was similar in wild-type mice, with a waveform deflection. Similar to the *Lrit3* gene therapy, *Nyx* gene replacement resulted in co-expression of NYX and TRPM1 in the retina, where TRPM1 was found in both cell bodies and the dendritic tips of the ON-BC. This demonstrates that gene therapy promotes the correct localization of TRPM1 and thus improves signaling pathway of the bipolar cells. Appropriately sized amplicons of *Nyx* transcript were produced in treated retina at days 2 and 30. This demonstrates the potential of *Nyx* gene replacement therapy in human complete CSNB.

Cone-dominated disease

Achromatopsia

Achromatopsia is an autosomal recessive disease that mainly affects the cone photoreceptors, with a lack of all three types of cones. Patients usually present with day blindness, poor visual acuity, photophobia, nystagmus, and poor discrimination of chromatic contrast. Mutation of *CNGA3*, *CNGB3*, *GNAT2*, *PDE6H*, *PDE6C*, and *ATF6* is responsible for >90% of achromatopsia cases.[29] Injection of AAV-carrying genes that affect achromatopsia including AAV8.CNGA3, AAV-hCNGB3, AAV2.GL, and AAV2.NN has been reported to ameliorate cone cell responses in animal and human studies (**Table 3**).

Table 3. Gene therapies for achromatopsia

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV8. CNGA3					
Ofri et al, 2018[30]	Israel	*CNGA3*	9 day-blind sheep treated with subretinal injection of AAV5 vector carrying transgene for 6 years.	Periodic photopic maze testing, electroretinogram, immunohistochemistry.	Mean maze navigation time and number of collisions with obstacles significantly dropped after treatment. ERG showed improvement in cone function. Staining showed expression of CNGA3 protein colocalized with red/ green opsin in eye with AAV-injected.
Fischer et al, 2020[31]	Germany	*CNGA3*	9 *CNGA3*-linked achromatopsia patients had unilateral subretinal injection of AAV8.CNGA3 with escalating doses, followed up for one year.	BCVA, contrast sensitivity, full-field stimulation threshold, flicker fusion frequency.	Improved mean BCVA of 2.9 letters and mean log contrast sensitivity of 0.33 log were shown comparing to the baseline. Contrast sensitivity testing improved to 0.328 and critical fusion frequency increased by 5 Hz.
Reichel et al, 2021[32]	Germany	*CNGA3*	9 *CNGA3*-mutated patients had subretinal injection of AAV8. CNGA3 in 3 escalating doses, followed up for 1 year.	BCVA, contrast sensitivity, Roth 28-hue color test.	BCVA of the treated eye at year 3 showed an improvement of 4.6 letters with contrast sensitivity improved by 0.23 log. However, color test showed no improvement after year 2.
AAV2. GL and AAV2. NN					
Pavlou et al, 2021[33]	Germany	*CNGA3*	*Cnga3*$^{-/-}$ mice, dogs and non-human primates with subretinal and intravitreal injection of AAV2.GL or AAV2. NN.	Electroretinogram, immunohistochemistry.	Mice with intravitreal injection showed restoration of cone-mediated light responses, and cone-mediated flicker and single-flash responses. Sections proximally and distally to injection site showed positive Cnga3 staining showing the widespread transduction of vector over the retina.
AAV-hCNGB3					
Ye et al, 2016[34]	United States	*CNGB3*	*CNGB3* knockout mice and non-human primates had subretinal injection of AAV-GFP vector containing PR1.7 promotor.	Electroretinogram, quantitative polymerase chain reaction, immunohistochemistry.	Cone-deficient mice showed rescued cone ERG b-wave responses after vector administration for 3 months. Promotors resulted in strong green fluorescence protein expression in photoreceptors especially cones.

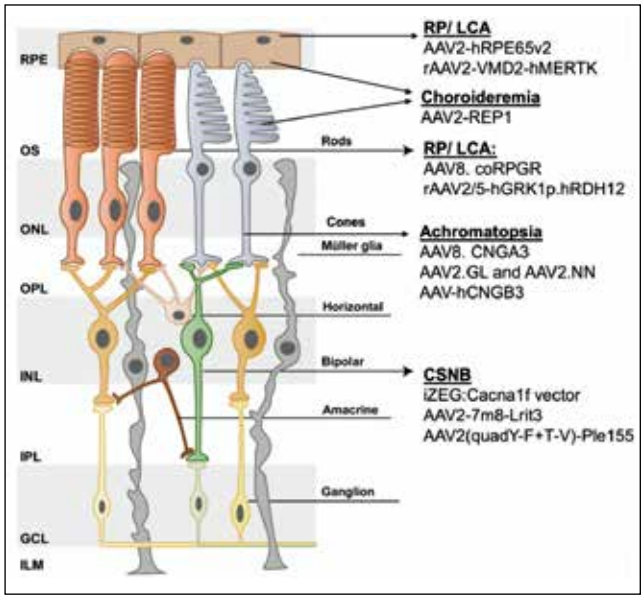

Figure. Schematic diagram showing the targets of various gene therapies. Copyright 2019. MDPI. Copyright under the terms of the Creative Commons CC-BY license.
Abbreviations: RPE retinal pigment epithelium, OS outer segment, ONL outer nuclear layer, OPL outer plexiform layer, INL inner nuclear layer, IPL inner plexiform layer, GCL ganglion cell layer, ILM inner limiting membrane, RP retinitis pigmentosa, LCA Leber congenital amaurosis, and CSNB congenital stationary night blindness.

AAV8. CNGA3

Preclinical studies of day-blind sheep demonstrated the efficacy of cyclic nucleotide-gated channel alpha subunit (*CNGA3*) gene replacement. Nine sheep with *CNGA3* mutation received unilateral subretinal injection of AAV5 vector containing *CNGA3* transgene for 6 years.[30] There was a significant reduction in the mean maze navigation time (p=0.001) and the mean number of collisions with obstacles (p<0.001). This shows an improved visual behavior. The mean navigation time was significantly longer when the treated eye was patched than when the untreated eye was patched (p<0.05). ERG resulted in a significant improvement in cone functions, with a higher critical flicker fusion frequency at 30 and 40 Hz at all four light intensities (p<0.0001). This supports the usage of gene therapy for robust rescue of cone functions in the long term.

In a non-randomized controlled trial of nine patients with *CNGA3*-linked achromatopsia who received a single unilateral subretinal injection of AAV8. CNGA3 (a vector to transduce photoreceptors) in three different doses,[31] at 1 year the mean best-corrected visual acuity (BCVA) improved up to 2.9 letters (p=0.006) and the mean log contrast sensitivity was 0.33 log (p=0.003). There was also improved color vision, with a reduction of chromatic discrimination threshold by 5.3/1000th^2 L*u*v (p=0.04). Four patients had an increased critical fusion frequency by ≥5 Hz. This reflects a new gain of cone function of the retina. Subjectively, validated visual functional questionnaire demonstrated improvements in six of 25 items in terms of the ability to identify letters and numbers, and color vision.

In nine patients with *CNGA3*-mutated achromatopsia who received three doses of subretinal injection of AAV8. CNGA3 in the worse eye,[32] at 3 years BCVA of the treated eye improved by 4.6 letters (p=0.001), with a mean improvement of 0.23 log in contrast sensitivity (p=0.019). The color contrast sensitivity improved in the first 2 years but not beyond. Microperimetry did not show significant improvement over time. However, A3-PRO, a questionnaire to assess the quality of life, revealed that patients had improved ability in fixating, recognizing letters or numbers, and photoaversion.

AAV2.GL and AAV2.NN

In a model of achromatopsia using *CNGA3*-knockout mice that received intravitreal injection of AAV2.GL and AAV2.NN (both vectors achieved widespread panretinal transduction in the mice, dogs, and non-human primates. Both could transduce human photoreceptors using human retina *ex vivo* culture),[33] photopic ERG showed restored single-flash responses and cone-mediated flicker. B-wave amplitude was higher for 1, 3, and 10 cf.s/m^2 (p<0.001 for all). Cnga3 was stained proximally and distally to the site of vector injection and cones. This shows that gene therapy effectively promotes *CNGA3* distribution and localization.

AAV-hCNGB3

50% cases of achromatopsia were due to the mutation of the cyclic nucleotide gated channel beta subunit (*CNGB3*) gene. In *CNGB3* deficient mice subjected to subretinal injection of AAV-hCNGB3 vectors containing a 1.7-kb L-opsin promotor (PR1.7),[34] vectors containing PR1.7 promotors showed a high expression of green fluorescence protein, a marker for cone cells, in short, medium, and long cone types, compared with those without promotors. mRNA level of green florescence protein increased with the induction of vector with PR1.7 promotor. This reflects the role of PR1.7 promotor in upregulating cones survival upon gene therapy. After 3 months of injection, transgenic mice revealed a significant improvement in photopic b-wave amplitude in ERG (p=0.028). This suggests that the AAV-hCNGB3 may be a treatment option in patients with *CNGB3*-induced achromatopsia.

Generalized retinal dystrophies

Leber congenital amaurosis

LCA is a heterogeneous and progressive rod-cone dystrophy caused by mutation of 13 genes. It is a less common and more severe RP subtype, with genetic overlap with RP, but presents with earlier onset and faster progression.[15] LCA type 2 mainly involves *RPE65* mutation, a gene that encodes for 11-*cis*-retinol required for RPE activity. Patients often present with weakly reactive pupils, poor visual acuity, nystagmus, and eventually vision loss.

Table 4. Gene therapies for Leber congenital amaurosis

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2-hRPE65v2					
Maguire et al, 2009[35]	Italy	*RPE65*	12 patients with *RPE65*-associated LCA were given single subretinal injection of AAV2-hRPE65v2 for up to 2 years.	BCVA, dark adaptometry, pupillometry, ERG.	7 patients showed substantial and stable improvement in visual acuity, with all patients having improvement in visual field and pupillary responses. A large interocular difference in full-field sensitivity was found in 5 patients.
Ripamonti et al, 2015[36]	United Kingdom	*RPE65*	8 subjects with *RPE65* mutation received rAAV vector expressing human *RPE65*.	Dark-adapted spectral sensitivities, cone plateau spectral sensitivities.	Improved rod function was found in 2 patients and improved rod sensitivity in 1 patient. Cone sensitivity was found to be improved in 1 patient.
rAAV2/5-hGRK1p.hRDH12					
Feathers et al, 2019[38]	United States	*RDH12*	*Rdh12*$^{-/-}$ mice received unilateral subretinal rAAV2/5-hGRK1p.hRDH12 vector.	Immunostaining, immunoblotting, electroretinogram.	Treated eyes showed stable expression of RDH12 in photoreceptor inner segments. Retinal reductase activity was restored after vector injection. No significant difference in ERG magnitude was found between non-injected and injected eyes. RDH12 expression was found to protect against light damage.

Injection of AAV-carrying genes that affect LCA including AAV2-hRPE65v2 or rAAV2/5-hGRK1p.hRDH12 has been reported to enhance photoreceptor responses in human and animal studies (**Table 4**).

AAV2-hRPE65v2

A lack of *RPE65* leads to insufficient 11-*cis*-retinol and inability of rods to respond to light. In a phase 1 trial of 12 patients with *RPE65*-associated LCA who received subretinal AAV2-hRPE65v2 in the worse-seeing eye and were followed up for 2 years,[35] all patients had better vision in a dim environment at 2 weeks (with children having higher BCVA at baseline). All patients had improvement in visual field. Younger patients had improvement in full-field sensitivity to white light, with a gain of several log units of sensitivity. An 8-year-old patient even had a light sensitivity similar to age-matched normal-sighted controls. Pupillometry showed ≥2 log unit increase in pupillary light response. Full-field ERG photopic responses occurred in a part of the injected retina on day 30 and then in several other parts on day 60 and day 90. This indicates the clinical benefit of subretinal gene therapy in preventing retinal degeneration.

In a phase 2 trial of eight young adults and children with *RPE65* mutation who received subretinal injection of rAAV2/2. hRPE65p.hRPE65,[36] two patients showed improvement in rod functions in dark-adapted spectral sensitivities at year 3. Both showed substantial improvement in sensitivity at month 2 or 4, which remained constant until month 12 at all wavelengths. The spectral sensitivity showed a M-cone shape during the cone plateau; there was a switch from rod-mediated vision to cone-mediated after bleaching. Nevertheless, dark-adapted sensitivity in the remaining six patients remained cone-like, without much improvement or declination.

rAAV2/5-hGRK1p.hRDH12

Retinal dehydrogenase 12 (RDH12) is an enzyme that reduces 11-*cis* retinaldehyde and all-trans retinaldehyde for the visual cycle and detoxification of lipid peroxidation.[37] Its mutation has been linked to LCA and autosomal dominant RP. In an *in vivo* study of *Rdh12*-knockout mice with subretinal injection of different doses of rAAV2/5-hGRK1p.hRDH12 (an AAV vector containing *RDH12* cDNA),[38] there was an increased average initial rate of all-*trans* retinol formation of 0.046 pmol min^{-1} μg protein^{-1} in treated mice, compared with 0.013 pmol min^{-1} μg protein-1 ($p<0.01$) in controls. This reflects the ability of gene therapy to restore retinal reductase activity. Moreover, *Rdh12*-knockout mice were bred onto albino mice to produce Rpe65-Leu450 knockout species. ERG under scotopic condition revealed improvement in rod b-wave, rod-cone a-wave, and rod-cone b-wave ($p<0.001$) in treated eye of *Rdh12*-knockout mice after 1 week, compared with controls. This reflects that *RDH12* gene therapy may protect patients with LCA against light damage.

Choroideremia

Choroideremia is an X-linked recessive disorder that leads to loss of night vision and gradually peripheral vision loss. It is commonly caused by the mutation of *CHM*, a gene that encodes ras-associated binding escort protein 1 (REP1). Subsequently, degeneration of photoreceptors and RPE, neuronal cell death, and retinal remodeling occur.[39] Injection of AAV-carrying genes that affect choroideremia including AAV2-REP1 has been reported to achieve variable results in terms of visual acuity and retinal sensitivity in clinical trials (**Table 5**).

AAV2-REP1

In a phase 1 trial of six patients with choroideremia who received subfoveal injection of rAAV2.REP1 (a recombinant

Table 5. Gene therapies for choroideremia

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2. REP1					
Dimopoulos et al, 2018[40]	Canada	*CHM*	6 patients confirmed with choroideremia received single subfoveal injection of rAAV2. REP1 and were followed up for 2 years.	BCVA, microperimetry, fundus autofluorescence.	5 patients did not experience significant visual acuity gain over 2 years. Microperimetry sensitivity or area of preserved RPE did not reveal changes after vector administration compared to untreated eyes.
Fischer et al, 2019[41]	Germany	*CHM*	6 patients with diagnosed choroideremia received single AAV2-REP1 subretinal injection and were followed up for 24 months.	BCVA, microperimetry, fundus autofluorescence.	Treated eyes gained a mean of 4.7 and 3.7 letters at months 3 and 24 respectively, with a mean difference of 3.7 letters compared to the fellow eye. Retinal sensitivity in the treated eyes showed an increase of 10.3. 5 patients had improvement in peak retinal sensitivity and/ or gaze fixation area.
Lam et al, 2019[42]	United States	*CHM*	6 patients with choroideremia received subfoveal injection of AAV2-REP1 in the worse-sighted eye and were followed up for 24 months.	BCVA, microperimetry, contrast sensitivity, color vision.	BCVA changes in letter scores ranged from -1 to +10 letters from baseline in the treated eye while that ranged from -2 to +4 letters in untreated eyes. No microperimetric changes, contrast sensitivity and color vision were detected at month 24 compared to baseline.
Fischer et al, 2020[43]	Germany	*CHM*	6 patients with chorioderemia had subretinal injection of AAV2-REP1 followed up for 12 months.	BCVA, microperimetry, fundus autofluorescence.	5 patients had improved BCVA yet 1 patient lost 14 letters at month 12. 5 patients had improved mean retinal sensitivity of 2.3 dB and peak retinal sensitivity of 2.8 dB. Gaze fixation area was improved to -36.1 deg^2.
MacLaren et al, 2014[44]	United Kingdom	*CHM*	6 patients with choroideremia were administrated with subfoveal AAV.REP1 and followed up for 6 months.	BCVA, microperimetry, retinal sensitivity tests.	There was a mean gain of VA by 3.8 letters in treated eyes. Maximal sensitivity increased from 23.0 to 25.3 dB after gene therapy. Increased retinal sensitivity by 1.7 was found over 6 months.
Xue et al, 2018[45]	United Kingdom	*CHM*	14 patients with CHM gene mutation had unilateral subretinal injection of AAV2. REP1 vector and followed up for 2 years.	BCVA, microperimetry, fundus autofluorescence	Mean visual acuity improved by 4.5 letters while untreated eyes declined by -1.5 letters. However, there was a slight decline of mean retinal sensitivity of treated eyes from 4.0 to 3.3 dB at 2 years. Area of retinal autofluorescence was similar between groups.

vector with REP1 expression and prenylation activity against ras-associated binding substrate),[40] at 2 years five patients did not have significant BCVA gain and only one patient had an improvement of >15 letters. Treated eyes demonstrated linear decline of area of fundus autofluorescence (correlating to area of surviving photoreceptors) with time ranging from -0.012 to -0.046 mm^2/month. The rate of decline in treated and untreated eyes was similar (p=0.062). Spectral domain optical coherence tomography in four patients showed a more prominent central foveal thickness loss in the treated eye than in the untreated eye. Microperimetry showed no improvement in mean sensitivity in the treated eyes.

In a phase 2 study of six patients with choroideremia who received AAV2-REP1 therapy,[41] at year 2 the mean BCVA was 20/50 in the treated eyes and 20/40 in the untreated eyes; the difference was 3.7 letters and not significant (p=0.43). Retinal sensitivity was similar in treated and untreated eyes (p=0.74), although five of six treated eyes showed improvement in mean retinal sensitivity and peak retinal sensitivity.

In a phase 2 trial of six patients with choroideremia who received subretinal injection of AAV2-REP1,[42] subjective visual observation in the treated eye suggested mainly vision 'clearer' or 'shaper', followed by 'mild shade'. At year 2, the change in letter scores varied from -1 to +10 letters in the treated eye and from -2 to +4 letters in the untreated eye. In two patients, BCVA in the treated eye showed improvement of 5 and 10 letters. However, there was no change in visual field, contrast sensitivity and color vision, and area of foveal autofluorescence. Similarly, in a phase 2 trial of six patients with choroideremia who received subretinal AAV2-REP1,[43] at year 1 four patients experienced minimal BCVA changes ranging from -4 to +1 letters, with one patient gaining 17 letters. Microperimetry in the treated eye showed increased mean retinal sensitivity of 2.3 dB, peak retinal sensitivity of 2.8 dB, and gaze fixation area of -36.1 deg^2. The fundus autofluorescence area showed a mean annual decline of 16%, whereas the ellipsoid zone showed a decrease of 14% at year 2.

In a phase 1 and 2 trial of six patients treated with subfoveal

injection of AAV.REP1 for choroideremia,[44] there was a mean gain of 3.8 letters in visual acuity at month 6. Two patients with a reduced visual acuity at baseline gained 21 or 11 letters. In the treated eye, dark-adapted microperimetry showed that the point of maximal sensitivity increased by 2.3 dB and the mean retinal sensitivity increased by 2.5 dB. The mean retinal sensitivity increase was correlated with the dose injected per unit area (r=0.82, p=0.04). In a study of 14 patients with choroideremia who had subretinal AAV2.REP1 vector injection,[45] at 2 years there was a median improvement of BCVA of 4.5 letters in treated eyes and a decline of 1.5 letters in untreated eyes (p=0.04). The mean retinal sensitivity declined from 4.0 dB to 3.3 dB at 2 years (p=0.07). However, measurement of fundus autofluorescence area showed no significant difference between treated and untreated eyes.

Among all gene therapies, voretigene neparvovec-rzyl (Luxturna) is the only approved treatment for inherited retinal dystrophies.[46] It targets patients with biallelic *RPE65* mutation–associated retinal dystrophy (including LCA and RP) and those with sufficient viable retinal cells. Voretigene neparvovec-rzyl is injected beneath the retina to allow a new and functional gene copy to pass into the RPE. It is approved for patients aged ≥1 year. Genetic testing on both *RPE65* gene is important in confirming the diagnosis of LCA or RP at an early stage before commencing injection therapy. Subretinal delivery of AAVs requires pars plana vitrectomy, which increases risks of retinal detachment, cataract, endophthalmitis, and even blindness.[47] Voretigene neparvovec-rzyl injection costs US$425 000 per eye and thus imposes huge financial burden on patients.

Application of gene therapy in Chinese patients with inherited RD

There is a lack of clinical trials of gene therapy for retinal diseases in the Chinese population. In China, gene therapeutics for hematological and immunological disorders such as hemophilia, thalassemia, severe combined immune deficiency, and chronic granulomatous disease have been reported.[48] Gene therapy for Chinese patients with RD may be similar to that for Western populations if the genes identified are compatible with those identified in previous trials. The genetic pattern of RD in Chinese eyes is summarized in **Table 6**.

In the Chinese population, most inherited RD is autosomal recessive secondary to *USH2A* mutation, leading to non-syndromic RP. *RHO* and *RGRP* are common genes causing autosomal dominant and X-linked RD, respectively.[49] In Shanghai patients with RP, the commonest gene mutation for rod-dominant diseases was *USH2A* (18%), *CYP4V2* (15%), *RYS* (7%), *RPGR* (4%), *RHO* (4%), and *RP1* (4%).[50] In the Zhongshan population, the most frequently involved gene were *USH2A* (9%), *RHO* (6%), and *RPGR* (4%).[51] Similarly, in Shenyang patients, *USH2A* was the most commonly mutated gene (40%), followed by *RP1* (16%) and *EYS* (9%).[52] This may indicate the use of AAV8.coRPGR in RD patients to improve visual acuity and visual field. *LRIT3* and *NYX* mutations were found in Zhongshan and Guangdong patients with CSNB, respectively.[53,54] This suggests the role of AAV2-7m8-Lrit3 and AAV2(quadY-F+T-V)-Ple155 in restoring ON-BC functions and localizing TRPM1 in Chinese patients. Cone dystrophies in

Table 6. Genes involved in Chinese patients with inherited retinal dystrophies

Study	City	Group and sample size	Genes involved
Wang et al, 2018[49]	Beijing	319 patients with inherited RD.	*RHO* is the commonest disease-causing gene for autosomal dominant RD. *USH2A* is the commonest disease-causing gene for autosomal recessive RD. *RPGR* is the most common X-linked RP causing gene.
Gao et al, 2019[50]	Fudan	1243 patients with clinically suspected RP.	The commonest gene mutation was *USH2A* (18%), *CYP4V2* (15%), *RYS* (7%), *RPGR*, *RHO*, and *RP1* (each 4%).
Xu et al, 2014[51]	Zhongshan	157 patient with RP.	The most frequently harboured mutations were *USH2A* (9%), *RHO* (6%) and *RPGR* (4%).
Sun et al, 2020[52]	Shenyang	87 patients with RP.	Commonest mutation of RP were *USH2A* (40%), *RP1* (16%), *EYS* (9%), *AGBL5* (4%), *RHO* (4%).
Dan et al, 2017[53]	Zhongshan	8 patients with CSNB.	*LRIT3* gene mutation was found but not *CABP4* and *GRP179*.
Xiao et al, 2006[54]	Guangdong	2 families with CSNB1.	*NYX* mutation was discovered, with sequence analysis showing c.281G>C and c.302T>C.
Li et al, 2014[57]	Zhongshan	138 patients with cone dystrophies and 129 patients with LCA.	*CNGA3* mutation was found in 46 patients with cone dystrophies, with 18 patients with achromatopsia and 28 patients with cone-rod dystrophies.
Xu et al, 2020[55]	Beijing	91 patients with LCA and 57 patients with early onset severe retinal dystrophies.	In LCA patients *AIPL1* (11.0%), *RPGRIP1* (8.8%), *CEP290*, *GUCY2D* and *RPE65* (each 7.7%) were involved. In EOSRD patients, *RPGR* (12.3%), *CRB1* (10.5%), *RPE65* (10.5%), *RDH12* (7.0%), *RP2* (5.3) were involved.
Han et al, 2020[56]	Beijing	48 patients with choroideremia.	*CHM* gene mutation was shown, with 11 splicing sequence variants, 8 non-sense sequence variants, and 4 copy number variants.

Zhongshan populations were due to the mutation of *CNGA3*, which suggests the use of AAV8.CNGA3 to improve BCVA and contrast sensitivity in Chinese patients. Regarding generalized retinal dystrophies, LCA mutation was mostly attributed to *AIPL1* (11.0%), followed by *RPGRIP1* (8.8%), *CEP290*, *GUCY2D* (7.7%), and *RPE65* (7.7%).[55] In patients with early-onset severe retinal dystrophy, *RPGR* (12.3%), *CRB1* (10.5%), *RPE65* (10.5), *RDH12* (7.0%), *RP2* (5.3%) were involved. Thus, *RPE65* and *RDH12* gene therapy may be useful in Chinese LCA patients. In Beijing patients with choroideremia secondary to *CHM* mutation, AAV.REP1 vector administration may confer beneficial visual effects.[56]

Conclusion

Gene therapies using AAVs to encode a specific gene that is mutated in RDs are emerging. Clinical and animal studies have shown that gene therapy confers beneficial visual effects in patients with RP, CSNB, achromatopsia, LCA, or choroideremia. In studies involving Western populations, the genes found to be affected are mostly similar to those in the Chinese population. This gives rise to the potential use of gene augmentation in Chinese patients with inherited RD. A thorough understanding of the emerging gene therapy of different RD subtypes may allow more personalized management.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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