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RPE65-Related Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy

Synonym: *RPE65*-Related LCA/EOSRD

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Summary

Clinical characteristics

RPE65-related Leber congenital amaurosis / early-onset severe retinal dystrophy (*RPE65*-LCA/EOSRD) is a severe inherited retinal degeneration (IRD) with a typical presentation between birth and age five years. While central vision varies, the hallmark of this disorder is the presence of severe visual impairment with a deceptively preserved retinal structure. Vision is relatively stable in the first decade of life, but begins to decline in adolescence. Most affected individuals are legally blind (visual acuity 20/200 and/or visual fields extending <20 degrees from fixation) by age 20 years. After age 20 years, visual acuity declines further and by the fourth decade all affected individuals are legally blind and many have complete loss of vision (i.e., no light perception). Milder disease phenotypes have been described in individuals with hypomorphic alleles.

Diagnosis/testing

The diagnosis of *RPE65*-LCA/EOSRD is established in a proband with suggestive findings and biallelic pathogenic variants in *RPE65* identified by molecular genetic testing.

Management

Treatment of manifestations: Individuals with any type of inherited retinal dystrophy are advised to eat a healthy balanced diet to reach the minimum Reference Daily Intake (RDI) for nutrients, as recommended by the USDA. Due to poor night vision, patients are advised to use a flashlight for illumination. Children with *RPE65*-LCA/EOSRD are usually of normal intellect but may experience learning difficulties and/or psychiatric/behavioral issues as a result of their visual impairment. Those with learning disabilities will benefit from referral to a developmental pediatrician for consideration of enrollment in a continuing program of care and support.

Subretinal gene augmentation, an FDA-approved therapy, compensates for loss-of-function *RPE65* variants (and hence improves vision) by providing the cells that use the protein product of *RPE65* with a functional copy of the

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gene using recombinant adeno-associated virus (AAV) vectors. Individuals age 12 months to 65 years with molecularly confirmed *RPE65*-LCA/EOSRD may be eligible for this therapy.

Surveillance: Follow up at regular intervals of ophthalmologic manifestations, developmental/educational needs, psychiatric/behavioral issues, and family support/resource needs.

*Agents/circumstances to av*oid: Although not typically seen in RPE65-IRDs, repeatedly poking and pressing on the eyes should be discouraged as it may cause damage to the cornea and/or retina.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of sibs of an individual with *RPE65*-LCA/EOSRD in order to identify those who may benefit from gene replacement therapy or other treatments.

Therapies under investigation: Clinical investigations of variations of the FDA-approved gene replacement therapy are underway. Oral retinoid supplementation is also being investigated as a possible therapy.

Genetic counseling

RPE65-LCA/EOSRD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *RPE65* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

RPE65-related LCA/EOSRD **should be suspected** in individuals with the following clinical, electroretinographic (ERG), and imaging findings.

Clinical findings

- Symptomatic onset between birth and age five years
- Roving eye movements or nystagmus
- Poor pupillary light responses in some
- Profound nyctalopia
- Oculodigital sign (i.e., poking, rubbing or pressing on the eye in order to stimulate phosphenes for visual perception). Once considered pathognomonic for LCA, the oculodigital sign is also found in other types of severe visual impairment and is not typically observed in *RPE65*-LCA.
- Central visual acuity decreased to the 20/100 range (which can be variably preserved if initial manifestations are between ages 1 and 5 years). Generally, central visual acuity is worse when onset is before age one year compared to onset between ages one and five years.
- Fundus examination that can be quite variable and can appear normal at presentation. Associated findings include RPE mottling, pigmentary retinopathy with attenuated vessels, optic nerve pallor, white spots at the level of the RPE, parafoveal RPE loss as a bull's eye maculopathy, and optic disc drusen (see Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview).

Full-field electroretinogram (ERG) findings. ERG is an electrophysiologic test that assesses the functional status of the photoreceptors and proximal neuronal layers of the retina. The ERG represents a composite response of millions of retinal cells. In *RPE65*-related LCA/EOSRD the ERG is barely detectable or severely abnormal [Jacobson et al 2009]. When onset of clinical manifestations is later (i.e., between ages 1 and 5 years), variable ERG findings can include residual activity on dark-adapted scotopic (rod) ERGs as well as light-adapted photopic (cone) ERGs.

Imaging findings

- **Fundus autofluorescence (FAF)** can detect autofluorescent material within the RPE and choroid (e.g., lipofuscin and melanin) that is indicative of retinal health. Severely diminished or absent short-wavelength (SW) fundus autofluorescence is observed as a consequence of the enzymatic blockade in the visual cycle. A relatively preserved central retinal structure by OCT and near infrared FAF in the presence of very abnormal or undetectable SW-FAF signals is nearly pathognomonic of this specific molecular subtype of LCA [Lorenz et al 2004]. SW-FAF can be performed on young children often without anesthesia.
- **Optical coherence tomography (OCT)** is a light-based imaging technology that uses tissue differences in optical interference to create cross-sectional high-resolution (micron scale) images to measure retinal thickness and to determine which outer layers of the retina are involved in retinal degeneration [Huang et al 1991, Huang et al 1998]. OCT findings in *RPE65*-LCA/EOSRD can be variable and can include a preserved central foveal region with thinning of the outer nuclear layer (ONL) that surrounds the fovea [Jacobson et al 2005, Jacobson et al 2007, Maeda et al 2009].

  Note: While two studies suggest that OCT in *RPE65*-LCA/EOSRD reveals an age-related decreased thickness in the foveal ONL layer [Jacobson et al 2007, Cideciyan et al 2013], a third study (which measured overall retinal thickness at the fovea) did not find a relationship between foveal ONL layer thickness and age [Chung et al 2019].

Establishing the Diagnosis

The diagnosis of *RPE65*-LCA/EOSRD is established in a proband with suggestive findings and biallelic pathogenic variants in *RPE65* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing). Note: Single-gene testing (sequence analysis of *RPE65,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because of the extensive genetic heterogeneity of LCA/EOSRD (see LCA/EOSRD Overview), individuals with the findings described in Suggestive Findings are likely to be diagnosed using multigene panel (see Option 1), whereas those in whom the diagnosis of *RPE65*-LCA/EOSRD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A comprehensive LCA/EOSRD multigene panel that includes *RPE65* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *RPE65*-LCA/EOSRD is not considered because an individual has atypical clinical findings, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *RPE65*-Related Leber Congenital Amaurosis / Early Onset Severe Retinal Dystrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
RPE65	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	1 deletion reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Morimura et al [1998], Thompson et al [2000], Astuti et al [2016], Chung et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. A deletion of exons 1-7 has been reported by Al-Gazali & Ali [2010] in a large family with six affected children.

Clinical Characteristics

Clinical Description

RPE65-related Leber congenital amaurosis/early-onset severe retinal dystrophy

(*RPE65*-LCA/EOSRD) is a severe degeneration of the retina with visual manifestations often appearing in the first year of life [Cideciyan 2010]. Visual function is generally poor (but in some instances central vision is variably preserved) and is often accompanied by nystagmus and sluggish or near-absent pupillary responses.

Visual impairment. Central vision can be variable, but the majority of affected individuals have severe visual impairment (mean visual acuity 20/126 measured in children ages 4-10 in largest case series) [Chung et al 2019]. While vision is relatively stable in the first decade of life, it begins to decline again starting in the teens. Fifty per cent of affected individuals are legally blind (visual acuity 20/200) by age 20 years. After age 20 years, vision loss is more rapidly progressive: all affected individuals are legally blind by the fourth decade and many have complete loss of vision (i.e., no light perception).

Other ophthalmic findings

- Late-stage findings can include keratoconus and cataract.
- Refractive error is common; most affected individuals are myopic [Chung et al 2019].

Systemic findings. In contrast to Leber congenital amaurosis of other genetic causes (see LCA/EOSRD Overview), systemic manifestations have not been reported in *RPE65*-LCA/EOSRD.

Genotype-Phenotype Correlations

Although numerous *RPE65* pathogenic variants have been identified, to date no clear genotype-phenotype correlations have been established [Chung et al 2019].

It has been suggested that the severity of *RPE65*-LCA/EOSRD is independent of the location or types of *RPE65* pathogenic variants [Katagiri et al 2016].

Nomenclature

Leber congenital amaurosis (LCA) and early-onset severe retinal degeneration (EOSRD) are clinical diagnoses that do not have well agreed-upon definitions; consequently, different designations may be variably applied to an affected individual. With nomenclature moving away from clinical descriptive terms to gene-based terms, *RPE65*-related LCA/EOSRD is considered the more appropriate term for these phenotypes.

Prevalence

It is estimated that between 1,000 and 2,000 individuals in the United States have *RPE65*-related inherited retinal dystrophy (*RPE65*-IRD), which includes *RPE65*-LCA/EOSRD and typical retinitis pigmentosa (RP type 20) [Lloyd et al 2019] (see Genetically Related Disorders).

RPE65-related IRD has been reported in individuals of European, Middle Eastern, North and South American, and Asian descent [Kabir et al 2013, Verma et al 2013, Ripamonti et al 2014, Katagiri et al 2016].

RPE65-LCA/EOSRD is thought to account for 5%-6% of LCA/EOSRD [Stone 2007, den Hollander et al 2008, Cideciyan 2010].

The incidence of LCA ranges from 2:100,000 to 3:100,000 [Koenekoop 2004] to 1:81,000 [Stone 2007].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *RPE65* are summarized in Table 2.

Table 2. *RPE65* Allelic Disorders

Gene	MOI	Disorder	Reference
RPE65	AR	Typical retinitis pigmentosa (RP type 20) [1]	Nonsyndromic Retinitis Pigmentosa Overview
	AD	Mild retinitis pigmentosa w/a phenotype resembling choroideremia	Jauregui et al [2018], Hull et al [2016]

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. RP type 20 is thought to account for up to 1%-2% of autosomal recessive RP; the estimated incidence of autosomal recessive RP is 1:3000 – 1:5000 (see Nonsyndromic Retinitis Pigmentosa Overview).

Differential Diagnosis

See Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of individuals diagnosed with *RPE65*-related Leber congenital amaurosis / early-onset severe retinal dystrophy (*RPE65*-LCA/EOSRD), the evaluations included in Table 3 (if

not performed as part of the evaluation that led to the diagnosis) are recommended, and their purpose summarized. Note that some evaluations may be indicated only in individuals considering subretinal gene supplementation therapy (see Treatment of Manifestations).

Table 3. Individuals with *RPE65*-LCA/EOSRD: Recommended Evaluations Following Initial Diagnosis

Evaluation		Purpose
Ophthal-mologic	**Best corrected visual acuity (BCVA)**	To determine visual acuity & provide a baseline for comparison of future assessments
	Refractive error	To prescribe corrective lenses
	Slit lamp examination	To document anterior segment findings such as cataract
	Indirect ophthalmoscopy	To document fundus findings
	Kinetic visual perimetry [1] (Goldmann perimetry)	To map out the entire visual field & provide a baseline
	Static visual perimetry [2]	To determine retinal sensitivity in any given location in the visual field & to provide a baseline
	Optical coherence tomography (OCT)	To assess the anatomic structure of the retina, which may identify patients more likely to benefit from *RPE65* gene replacement therapy
	Fundus photography	To document fundus findings & to provide a baseline
	Fundus autofluorescence (FAF)	To assess the presence of autofluorescent material in the retina which may serve as a marker for retinal health
	Full-field electroretinogram (ERG)	To assess residual activity of the rods (dark-adapted [i.e., scotopic] ERG) & cones (light-adapted [i.e., photopic] ERG)
	Full-field stimulus threshold (FST) test [3]	As a baseline in patients w/advanced inherited retinal disorders & to determine the level of rod & cone-mediated function for comparison w/future FST tests
	Multi-luminance mobility [4]	To assess functional vision by determining the minimum luminance at which the individual can complete a standard course successfully

Table 3. continued from previous page.

Evaluation		Purpose
Other	**Developmental assessment**	• Incl motor, adaptive, cognitive & speech/language evaluation. • Evaluate for early intervention/special education.
	Psychiatric/ Behavioral	Neuropsychiatric evaluation based on sensory loss present (i.e., blindness)
	Family support/ Resources	Assess: • Use of community vision services through Early Intervention or School District • Use of community or online resources such as Parent To Parent • Need for social work involvement for parental support and to connect families with local resources
	Consultation w/clinical geneticist/ genetic counselor	To include genetic counseling.

1. Kinetic visual field testing uses moving targets of various light sizes and intensities to map out the entire visual field, as well as the blind spot and any scotomas (decreased areas of vision). This type of testing is useful for mapping visual field sensitivity boundaries (www.ohsu.edu).
2. Static visual field testing systematically plots the field of vision using threshold testing with flashing light presentations of various intensities. This type of testing allows the determination of retinal sensitivity in any given location (www.ohsu.edu).
3. AAO Clinical Statement 2016
4. Chung et al [2018]

Treatment of Manifestations

For All Individuals with *RPE65*-LCA/EOSRD

Diet and micronutrients. Individuals with any type of inherited retinal dystrophy are advised to eat a healthy balanced diet to reach the minimum Reference Daily Intake (RDI) for nutrients, as recommended by the USDA (D Hoffman - Visions 2016). The RDI can include one to two servings of omega-3 fatty acid rich fish, as well as antioxidant- and lutein-rich foods such as dark green leafy vegetables. Docosahexaenoic acid (DHA) / eicosapentaenoic acid (EPA) supplements to 500 mg/day as well as lutein supplements to 10 mg/day can be considered if dietary intake is not sufficient.

Use of illumination devices. Due to poor night vision, patients are advised to use a flashlight for illumination.

Developmental Delay / Intellectual Disability Management Issues

Children with *RPE65*-LCA/EOSRD are usually of normal intellect, but may experience learning delays due to visual impairment. Those who have learning difficulties benefit from referral to a developmental pediatrician and enrollment in a continuing program of care and support.

Advice on learning / intellectual disability / educational issues will vary from country to country, or even region to region within a country, depending on support services available. Overarching principles should include the following:

- Involving child development and educational specialists at the earliest available opportunity, often with specialist teachers/schools for the visually impaired
- Early referral to low vision services to access low visual aids, especially with improving technologies, such as the refreshable Braille display

- As patients grow older, identifying further assistance including financial and/or employment (available in some countries through certification/registration processes)
- Registration with services to record population data on the causes and effects of visual impairment (available in some countries)

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability / educational issues in the United States.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, and speech, as well as infant mental health services, special educators and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, and social delay. The early intervention program typically assists with this transition. Developmental preschool is center-based; home-based services are provided as needed.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Social/Behavioral Concerns

Children who are legally blind may have difficulty integrating and socializing with peers in school. Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Subretinal Gene Supplementation Therapy

Rationale. *RPE65*-LCA/EOSRD subretinal gene supplementation therapy does not replace the native gene (which may still have some function), but provides a functional copy of the gene using recombinant adeno-associated virus (AAV) vectors to the cells that produce the *RPE65* protein product. In this way, the functional copy of the gene compensates for the loss-of-function *RPE65* pathogenic variants, increases the amount of the protein product, and improves vision. Using standard vitreoretinal surgical techniques, the AAV vectors are injected in each eye one time only subretinally (i.e., under the retina) in the foveal region (i.e., the cone-rich portion of the retina that mediates central vision).

Data supporting the utility of gene supplementation therapy

- **Phase I/II trials in humans.** Using subretinal injection of different recombinant AAV vectors containing *RPE65* cDNA, five Phase I/II trials [Bainbridge et al 2008, Hauswirth et al 2008, Maguire et al 2008, Weleber et al 2016, Le Meur et al 2018] and one Phase III trial [Russell et al 2017] showed improved retinal function of variable duration.
    - In one trial, visual sensitivity (determined with static perimetry) initially improved but then declined three to five years later, with evidence of continued retinal degeneration in the treated eye [Cideciyan et al 2013, Jacobson et al 2015b].
    - In another trial, static visual perimetry improved at year one post treatment, but then declined to baseline by years two to three post treatment [Bainbridge et al 2015].
    - In other Phase II trials the duration of more sustained visual improvement in children (as measured by best corrected visual acuity) was at three years post treatment [Testa et al 2013] and up to five years post treatment [Pennesi et al 2018].

  Of note, differences observed in the outcome of these trials may be due to differences in viral vectors and/or delivery protocols or the outcome measures used to assess change over time.

- **The Phase III trial** of subretinal administration of an AAV2/2 expressing wild-type *RPE65* vector reported benefit at one year post treatment, reaching its primary endpoint for efficacy with improved performance on a novel test of multi-luminance mobility [Russell et al 2017]. This test, a validated mobility course developed specifically for patients with retinal dystrophies to assess for functional vision, is graded by the minimum luminance at which the individual can complete the course successfully [Chung et al 2018]. Based on this endpoint, the FDA approved this product (voretingene neparvovec, Luxturna®, Spark Therapeutics, Inc) for the treatment of *RPE65*-LCA/EOSRD.

  For data on preclinical testing in animal models click here (pdf).

Availability of gene supplementation therapy. Currently the recombinant AAV vectors are only:

- Available from Spark Therapeutics;
- Administered through qualified *RPE65* Treatment Centers.

Requirements for consideration of subretinal gene supplementation therapy

- Age between 12 months and 65 years
- Presence of biallelic *RPE65* variants known to be pathogenic
- Ophthalmic evaluation that includes many of the evaluations in Table 3; especially OCT, as individuals with evidence of viable photoreceptors identified by this test may benefit from gene supplementation therapy.

Third-party payor issues regarding eligibility for payment of subretinal gene supplementation therapy

- Meeting eligibility requirements for treatment
- Prior authorization from the third party payer to approve coverage of this treatment
- Determination of the amount of the cost covered by the third party payor versus the amount covered by the patient / patient's family

Surveillance

Table 4. Recommended Surveillance for Individuals with *RPE65*-LCA/EOSRD

Evaluation		Purpose	Frequency
Ophthal-mologic	**Best corrected visual acuity**	To assess visual acuity	Yearly
	Refractive error	To assess changes in refractive error that would require change to corrective lenses	Yearly
	Slit lamp examination	To assess anterior segment changes such as cataract	Yearly
	Indirect ophthalmoscopy	To assess fundus findings, which may identify disease progression	Yearly
	Kinetic visual perimetry	To assess changes in the entire visual field	Yearly if possible
	Static visual perimetry	To assess changes in retinal sensitivity in any given location in the visual field	Yearly
	Optical coherence tomography (OCT)	To assess anatomic structure of the retina, which may identify disease progression	Yearly
	Fundus photography	To document fundus changes, which may identify disease progression	Yearly if possible
	Fundus autofluorescence	To document changes in native autofluorescent pigments to assess health of retina	Yearly if possible
	Full-field electroretinogram (ERG)	To assess residual activity of the rods (dark-adapted [scotopic] ERG) & cones (light-adapted [photopic] ERG)	Every 3-5 yrs
	Full field stimulus threshold	To quantify residual photoreceptor function	Every 3-5 yrs
Other	**Developmental/Educational assessment**	To assess developmental/educational needs	Yearly or as needed
	Psychiatric/Behavioral	To assess need for psychiatric or behavioral therapy	Yearly or as needed
	Family support/Resources	To assess need for additional family resources or other support groups	Yearly or as needed

Agents/Circumstances to Avoid

Children should be discouraged whenever possible from repeatedly poking and pressing on their eyes, which may cause damage to the cornea and/or retina.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of sibs of an individual with *RPE65*-LCA/EOSRD in order to identify those who would may benefit from gene replacement therapy or other treatments.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Clinical investigations of variations of the FDA-approved gene replacement therapy treatment for *RPE65*-LCA/EOSRD (i.e., subretinal injection of an AAV2 vector expressing full-length RPE65 protein) are underway. One is a Phase I/IIb clinical trial (NCT02781480) of an AAV2 vector with an AAV5 capsid (AAV2/5) with a codon-optimized RPE65 driven under an RPE-specific promoter (which has shown increased RPE65 expression compared to previous vectors in mice) [Georgiadis et al 2016].

Oral retinoid supplementation is being investigated as a possible replacement for the enzyme product of *RPE65*. The dramatic therapeutic efficacy of oral *9-cis* retinoid supplementation in *Rpe65*-deficient mice demonstrated proof of concept [Van Hooser et al 2000, Van Hooser et al 2002]. Of note, *9-cis* retinal was used instead of *11-cis* retinal, which is very unstable and, therefore, not suitable for pharmaceutical development; furthermore, *9-cis* retinal binds with iso-rhodopsin, which is also capable of phototransduction.

A Phase I clinical trial was conducted using oral supplementation of QLT091001 (synthetic *9-cis* retinal acetate) for one week in 14 patients with either *RPE65*- associated LCA (n=7) or *LRAT*-associated LCA (n=7) [Koenekoop et al 2014]. The drug was well tolerated and, in a majority of patients, visual acuity and Goldmann visual field testing were improved. In six of the 14 patients these improvements persisted for more than one year following a single one-week treatment.

In a Phase Ib follow-up multicenter trial, 18 patients with either *RPE65*-associated LCA (n=13) or *LRAT*-associated-LCA (n=5) received oral supplementation with QLT091001 for one week [Scholl et al 2015]. Results were consistent with the previous Phase I study: the majority of patients demonstrated visual improvement in the first two months. In addition, treatment responders had significantly longer photoreceptor outer segment lengths as measured by OCT compared to non-responders, suggesting that intact photoreceptor integrity may predict response to treatment. Note that acute, retina-wide improvements in rod-mediated function have been also documented in patients following this treatment [Jacobson et al 2015a]. Reversible side effects were frequent and included headache, fatigue, photophobia, photopsia, erythema, flushing, nausea and vomiting, elevations in triglyceride, LDL, cholesterol, AST and ALT levels, and reductions in HDL and thyroxine levels. Intracranial hypertension, a known class-effect of retinoids, was also reported.

A Phase III trial for this oral retinoid is being planned. In addition to potentially serving as a monotherapy for inherited retinal diseases with defects in the visual cycle, this oral retinoid could also be combined with gene therapy to provide a potentially synergistic effect.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

RPE65-related Leber congenital amaurosis / early-onset severe retinal dystrophy (LCA/EOSRD) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *RPE65* pathogenic variant).
- Heterozygotes (carriers) are not at risk of developing LCA/EOSRD.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are not at risk of developing LCA/EOSRD.

Offspring of a proband. The offspring of an individual with *RPE65*-LCA/EOSRD are obligate heterozygotes (carriers) for a pathogenic variant in *RPE65*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *RPE65* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *RPE65* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *RPE65* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Council of the Blind (ACB)**
  2200 Wilson Boulevard
  Suite 650
  Arlington VA 22201
  Phone: 800-424-8666 (toll-free); 202-467-5081

Fax: 202-467-5085
Email: info@acb.org
www.acb.org

- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org
- **Retina International**
  Ireland
  Phone: 353 1 961 9259
  Email: info@retina-International.org
  www.retina-international.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. RPE65-Related Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RPE65	1p31.3	Retinoid isomerohydrolase	RPE65 @ LOVD	RPE65	RPE65

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for RPE65-Related Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy (View All in OMIM)

180069	RETINOID ISOMEROHYDROLASE RPE65; RPE65
204100	LEBER CONGENITAL AMAUROSIS 2; LCA2

Molecular Pathogenesis

Normally, photoreceptors sense light through the isomerization of the visual chromophore *11-cis* retinal to *all-trans* retinal by photons of light. This chromophore binds rod and cone opsins to form rhodopsin and other visual pigments, and plays an essential part of photo transduction. *All trans*-retinal then needs to be converted back to *11-cis* retinal for continued phototransduction via a pathway called the visual cycle. *RPE65* is a key rate-limiting enzyme required for the regeneration of *11-cis* retinal from *all-trans*-retinal.

Therefore, without RPE65 function *11-cis* retinal cannot be regenerated from *11-trans* retinal, resulting in lack of phototransduction in photoreceptors as well as subsequent retinal degeneration, presumably due to accumulation of retinyl esters.

Mechanism of disease causation. All pathogenic variants are thought to be loss-of-function alleles, which result in either in complete loss of RPE65 function or significantly reduced RPE65 function.

***RPE65*-specific laboratory technical considerations.** Nearly all of the more than 200 reported pathogenic variants in *RPE65* are detected by sequence analysis. One large homozygous deletion encompassing exons 1-7 has been reported in a family with six children diagnosed with early-onset retinitis pigmentosa [Al-Gazali & Ali 2010].

Table 5. Notable *RPE65* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000329.2	c.1103A>G (c.T1156C)	p.Tyr368His	Founder variant in Dutch population [Yzer et al 2003, Astuti et al 2016]
	c.292_311del	p.Ile98HisfsTer26	Founder variants in Costa Rica [Glen et al 2019]
	c.242G>T	p.Arg81Ile	
	c.419G>A	p.Gly140Glu	
	c.1338G>T	p.Arg446Ser	
	c.11+5G>A	p.?	Common pathogenic variant [Astuti et al 2016, Chung et al 2019]
	c.271C>T	p.Arg91Trp	Common pathogenic variant in Saudi Arabia & Tunisia [Astuti et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

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Chapter Notes

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