TOP IRDS TO WATCH:
LEBER CONGENITAL AMAUROSIS

An update on management and approved and emerging treatments.

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Leber congenital amaurosis (LCA) comprises a heterogenous group of inherited retinal diseases (IRDs) characterized by severely reduced vison in the first few months of life. LCA has a prevalence of one in 50,000 to 100,000 people and is currently known to be caused by 29 different genes.[1,2] The diagnosis and treatment of LCA have come to prominence since the 2017 FDA approval of voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics) to treat LCA caused by mutations in the *RPE65* gene (Figure 1).[3]

CLINICAL FEATURES

LCA classically manifests before 6 months of age, and patients develop congenital nystagmus, poor pupillary light response, severely reduced vision, high hyperopia, and oculodigital reflex. Electroretinography is typically extinguished. However, there is significant functional variability; some patients have a visual acuity at light perception only, while others have more preserved vision, termed *severe early childhood-onset retinal dystrophy*. Some cases resemble retinitis pigmentosa with more preserved central vision.

Fundus examination is also variable and can be normal in early disease but commonly progresses with varying macular and peripheral atrophy and pigmentation. *CRB1*-related LCA can show extensive retinal dystrophy but with periarteriolar preservation of the retinal pigment epithelium, observed on both fundus imaging and autofluorescence (Figure 2). Other genes, including *RDH12*, can be associated with extensive retinal dystrophy and pigment clumping (Figure 3). OCT can be normal in early disease and demonstrate varying degrees of outer retinal degeneration.

LCA can be associated with renal disease, developmental delay, and Joubert syndrome, with underdevelopment of the cerebellar vermis identified by a "molar tooth" sign on brain MRI.[4]

AT A GLANCE

- Leber congenital amaurosis (LCA) has a prevalence of one in 50,000 to 100,000 people.
- LCA typically appears in early childhood, requiring the patient and family to consult a low vision specialist for evaluation and to learn about tools and adaptive technologies.
- In 2017, the FDA approved voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics) to treat LCA caused by mutations in *RPE65*.

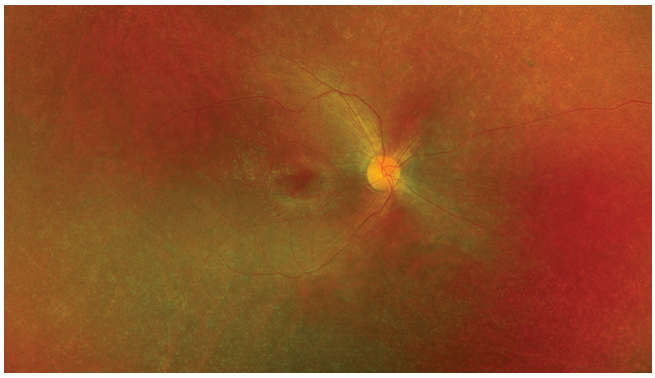

Figure 1. *RPE65*-associated LCA in the right eye of a 15-year-old girl presents with diffuse mild pigment mottling and multiple small white dots.

Supportive Care

LCA typically appears in early childhood, requiring the patient and family to consult a low vision specialist for evaluation and to learn about tools and adaptive technologies. For children, assistance from local education or other programs for sight impairment are suggested to provide early mobility and Braille training. Children with developmental delay may also require further generalized supportive care.

GENETICS

Genetic testing provides the definitive molecular diagnosis of LCA. Most cases are autosomal recessive, where individuals carry two abnormal copies of an LCA gene. The proteins expressed by these genes have varied functions, including visual cycle (*RPE65, RDH12, LRAT*), phototransduction (*AIPL1, GUCY2D, RD3*), signal transduction (*CABP4, KCNJ13*), protein folding (*CCT2*), ciliary transport (*CEP290, IQCB1, LCA5, RPGRIP1, SPATA7, TULP1, IFT140, CLUAP1*), photoreceptor morphogenesis (*CRB1, GDF6, PRPH2*), regulation of retinal differentiation (*CRX, OTX2*), NAD biosynthesis (*NMNAT1*), and nucleotide synthesis (*IMPDH1*).[5]

There are currently 25 genes associated with autosomal recessive LCA: *AIPL1, CABP4, CCT2, CEP290, CLUAP1, CRB1, CRX, DTHD1, GDF6, GUCY2D, IDH3A, IFT140, IQCB1, KCNJ13, LCA5, LRAT, NMNAT1, PRPH2, RD3, RDH12, RPE65, RPGRIP1, SPATA7, TULP1*, and *USP45*. Four genes (*CRX, IMPDH1, OTX2*, and *TUBB4B*) are associated with autosomal dominant transmission, where one abnormal copy of the gene is sufficient to cause disease.[5]

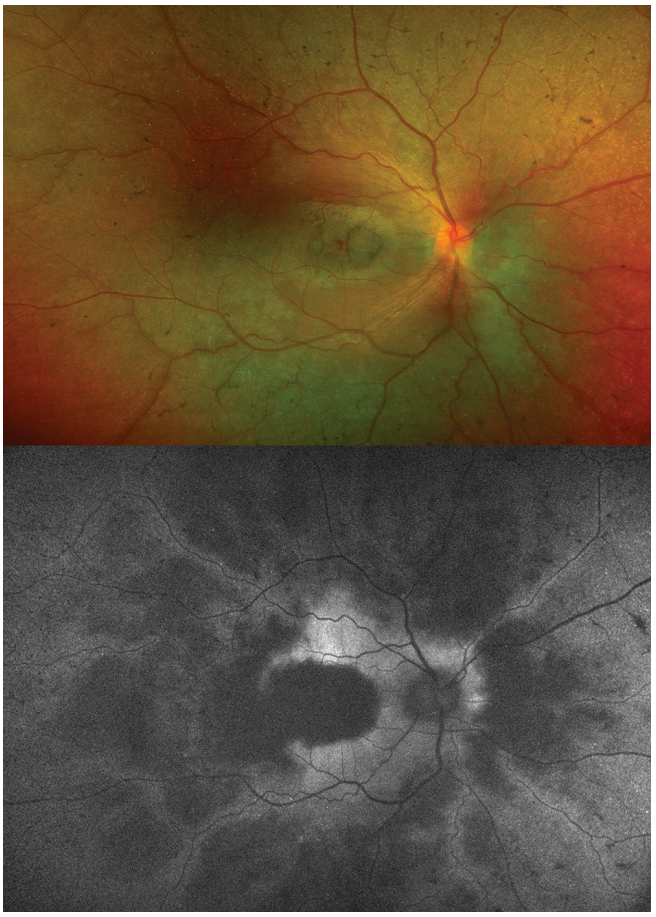

Figure 2. The fundus photograph (top) of the eye of a 10-year-old girl with *CRB1*-associated LCA presents with periarteriolar preservation of the retinal pigment epithelium. The fundus autofluorescence (bottom) shows loss of central macular autofluorescence.

The rationale for gene therapy is that replacing the abnormal gene with a functional copy will restore visual function in areas of preserved retinal structure. An ongoing trial of QR-110 (Sepofarsen, Splice Bio) uses antisense oligonucleotides targeting an intronic splice site in messenger RNA aiming to restore normal splicing. These approaches have been attempted for autosomal recessive LCA associated with better preserved retinal anatomy, including LCA associated with *RPE65, CEP290, GUCY2D, LCA5*, and *AIPL1*.

APPROVED THERAPY

Voretigene neparvovec-rzyl, the first gene therapy for a human IRD for *RPE65*-associated retinal dystrophy,[3] is a subretinal AAV2 vector expressing the *RPE65* gene in the retinal pigment epithelium to restore *RPE65* enzyme levels and help generate 11-cis-retinol protein from all-trans

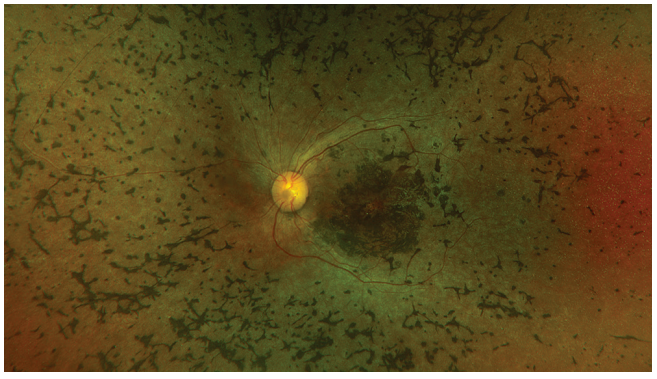

Figure 3. The fundus photograph of the left eye of a 29-year-old woman with *RDH12*-associated LCA demonstrates extensive pigment clumping throughout the fundus.

retinyl esters. The primary outcome of the phase 3 study was change in performance using a multiluminance mobility test (MLMT) that showed significantly improved scores at 1 year.[3] There was also significant improvement on full-field stimulus threshold (FST) testing and improvement in kinetic visual field testing. Four-year follow-up data confirmed the sustained benefit of the MLMT improvement. There were no reports of severe immune response.[6] However, development of chorioretinal atrophy in a subset of the treated patients has been reported after treatment.[7]

SELECT ONGOING AND EMERGING LCA TRIALS

EDIT-101 (Editas) is an AAV5-CRISPR-Cas9 construct that removes a splice site created in intron 26 of the *CEP290* gene. In the phase 1/2 study (NCT03872479), there was clinically meaningful improvement in visual acuity, FST testing, or mobility testing for nine (64%) of the treated participants.[8]

QR-110 is an RNA antisense oligonucleotide targeting the IVS26 mutation in the *CEP290* gene. Significant improvement in visual acuity and retinal sensitivity has been reported.[9] Although the phase 2/3 study did not meet the primary endpoint of improved visual acuity,[10] the company is pursuing a phase 3 trial (NCT06891443).

A phase 1/2 study of rAAV8.hRKp.AIPL1 (MeiraGTx) was conducted in the United Kingdom using an AAV8-AIPL1 construct delivered to the subretinal space in children with *AIPL1*-associated retinal dystrophy. Subjects had improvement in visual acuity and visual evoked potentials in the treated eye, with reduced function in the untreated eye.[11]

A phase 1/2 study (NCT03920007) is evaluating AAV5-GUCY2D (Atsena Therapeutics), which targets guanylate cyclase mutations to restore phototransduction. The 12-month data showed that some patients had improvement on the MLMT, and there was significant improvement on FST testing.[12]

A phase 1/2 dose-escalation study (NCT0561679) of AAV8-hLCA5 (OPGx-001, Opus Genetics) is investigating subretinal delivery in *LCA5*-associated retinal dystrophy. The LCA5 protein, lebercilin, is involved in the formation and function of the connecting cilia in photoreceptors, which is essential for protein transportation within the cell.[13]

Opus Genetics is also planning a phase 1/2 retinal gene therapy for *RDH12*-associated retinal dystrophy in 2025.[14]

TEST THE GENES

Although there are limited treatment options for LCA, we are approaching a paradigm shift where the causative gene can be identified in more than 75% of cases.[15] Additionally, there is an approved treatment for one form of LCA and ongoing clinical trials for other types of LCA. As a result, it is important for patients with suspected LCA to have genetic testing. This is ideally performed by IRD specialists who can manage patients and guide them to relevant clinical trials or treatments and low vision specialists at an early age. ■

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