GENEReviews

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Leber Congenital Amaurosis

[*LCA*]

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Summary

Disease characteristics. Leber congenital amaurosis (LCA), a severe dystrophy of the retina, typically becomes evident in the first year of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia, and keratoconus. Visual acuity is rarely better than 20/400. A characteristic finding is Franceschetti's oculo-digital sign, comprising eye poking, pressing, and rubbing. The appearance of the fundus is extremely variable. While the retina may initially appear normal, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. The electroretinogram (ERG) is characteristically "nondetectable" or severely subnormal.

Diagnosis/testing. The diagnosis of LCA is established by clinical findings. Eight genes are currently known to be associated with LCA: *CRX*, *CRB1*, *GUCY2D*, *AIPL1*, *RDH12*, *RPGRIP1*, *RPE65*, and *CEP290*. Together these genes are estimated to account for, depending on the survey, from one-third to one-half of all LCA. Three other disease loci for LCA have been reported. Molecular genetic testing of *CRX*, *CRB1*, *GUCY2D*, *AIPL1*, *RPGRIP1*, and *RPE65* is clinically available.

Management. Treatment of LCA is supportive. Surveillance includes periodic ophthalmic evaluation for assessment of vision and, in those with residual vision, assessment of the presence of amblyopia, glaucoma, or cataract.

Genetic counseling. Most often, LCA is inherited in an autosomal recessive manner. Rarely, LCA is inherited in an autosomal dominant manner as a result of mutations within the *CRX* gene. At conception, each sib of an individual with recessively inherited LCA 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. Carrier testing for at-risk family members is available on a clinical

basis once the mutations have been identified in the proband. Prenatal testing may be available through laboratories offering custom prenatal diagnosis. Although rare, the possibility of autosomal dominant inheritance resulting from a *de novo* mutation in *CRX* should be considered in and discussed with families of individuals with LCA and no family history of the disease.

Diagnosis

Clinical Diagnosis

The form of congenital or early-infantile blindness known as Leber congenital amaurosis (LCA) was first defined by Theodor Leber in 1869 and 1871 on the basis of clinical findings [Leber 1869, 1871]. While no universally agreed-upon diagnostic criteria are available, the following features are highly suggestive:

- **Blindness or severe visual impairment** presenting in infancy, frequently before age six months. Individuals with LCA usually do not achieve visual acuity better than 20/400 [Cremers et al 2002]
- **Extinguished or severely reduced scotopic and photopic electroretinogram (ERG).** Normal ERG responses rule out a diagnosis of LCA. Visual evoked responses are variable.
- **The oculo-digital sign,** characterized by poking, rubbing, and/or pressing of the eyes [Fazzi et al 2003]. The oculo-digital sign has been claimed to be virtually pathognomonic for LCA [Franceschetti & Dieterle 1954]; it can also be seen in other syndromic forms of severe vision impairment.
- **Family history** typically consistent with autosomal recessive inheritance

Individuals with Leber congenital amaurosis also frequently exhibit the following:

- **Sluggish or near-absent pupillary reactions** reflecting the severe retinal dysfunction
- **Nystagmus** that is pendular or roving and present in all positions of gaze
- **High hyperopia** (>5 diopters). Hyperopia is thought to result from impaired emmetropization (the ability of the eye to accomodate to visual stimuli) as a consequence of early-onset visual impairment.
- **Photophobia**
- **Keratoconus,** a noninflammatory, self-limiting axial ectasia of the central cornea. Keratoconus can significantly interfere with vision in normal individuals but usually does not become a vision-limiting factor in LCA.

Retinal findings. No retinal lesion is diagnostic. Although fundus abnormalities are frequently present later in life, infants with LCA typically show either a normal fundus appearance or only subtle retinal pigment epithelial (RPE) granularity and retinal vessel attenuation.

Of note, two specific retinal phenotypes can be observed:

- Preserved para-arteriolar retinal pigment epithelium (PPRPE) in individuals with *CRB1* mutations
- "Translucent RPE," white dots, and a peculiar star-shaped maculopathy in individuals with *RPE65* mutations

Later in life, some individuals develop a macular coloboma; while this finding has been reported to occur with mutations of *AIPL1* and *CRB1*, the correlation with LCA genotype has not yet been fully established.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Eight genes are now generally accepted to be associated with LCA (Table 1). Large studies of individuals with LCA report a combined molecular detection rate of 40%-50% in the *GUCY2D*, *RPE65*, *AIPL1*, *RPGRIP1*, *CRB1*, *CRX*, and *RDH12* genes, using a variety of molecular detection techniques. Based on early data, a recently identified eighth gene, *CEP290*, may account for a significant percentage of molecularly undiagnosed cases of LCA [den Hollender et al 2006].

Table 1. Genes known to be associated with LCA

Locus Name	Gene Symbol	% of LCA
LCA1	*GUCY2D*	6%-21%
LCA2	*RPE65*	3%-16%
LCA4	*AIPL1*	4%-8%
LCA6	*RPGRIP1*	~5%
LCA7	*CRB1*	5%-15%
LCA8	*CRX*	~3%
	RDH12	~4%
LCA10	*CEP290*	10%-20%?

Hanein et al 2004, Perrault et al 2004, Zernant et al 2005, den Hollender et al 2006, Yzer et al 2006

The following additional genes may be associated with an LCA-like phenotype:

- ***TULP1.*** An early-onset severe retinal degeneration with clinical and electrophysiologic similarities to LCA has been associated with a mutation in the *TULP1* gene encoding the tubby-like protein, the function of which is unknown [Banerjee et al 1998, Hagstrom et al 1998]. Until further mutations are established, it remains questionable whether this gene should be considered part of the LCA family [Lewis et al 1999].
- ***LRAT.*** An early-onset severe retinal degeneration with similarities to LCA has been reported with mutations in *LRAT*, the gene that encodes lecithin retinol acyltransferase [Thompson et al 2001]. It is likely that this gene accounts for only a very small portion of individuals with LCA.
- ***IMPDH1.*** Bowne et al (2006) described heterozygous, apparently *de novoIMPDH1* mutations in two unrelated individuals with a diagnosis of LCA. *IMPDH1* is a gene previously known to be associated with autosomal dominant retinitis pigmentosa. The clinical description of one of the individuals reported by Bowne et al (2006) fits the classic LCA phenotype; the other appears to have an early-onset retinal dystrophy better fitting the diagnosis of SECORD (see Differential

Diagnosis section). Additional studies must be undertaken to assess the prevalence of *IMPDH1* mutations in the LCA population.

Other loci. Three additional chromosomal loci may be associated with LCA:

- **LCA3** (14q24) [Stockton et al 1998]. Although *RDH12* lies 8 Mb from LCA3, it has conclusively been shown to be separate from the LCA3 locus. Thompson et al (2005) studied several individuals from different branches of the original large consanguineous LCA3 family, and no *RDH12* mutations, deletions, or rearrangements could be identified. Cosegregation with the *RDH12* gene was further excluded through the use of SNPs and microsatellite markers within and outside of the gene [Thompson et al 2005].
- **LCA5** (6q11-q13) [Dharmaraj, Li et al 2000; Mohamed et al 2003]
- **LCA9** (1p36) [Keen et al 2003]

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Carrier testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Molecular genetic testing: Clinical method

- **Sequence analysis** of all 80 exonic regions previously known to harbor at least one disease-causing mutation within *GUCY2D, RPE65, AIPL1, RPGRIP1, CRB1,* or *CRX* has been shown to identify mutations in fewer than 50% of individuals with LCA. When a single mutation is detected, the remainder of the gene in which that mutation was found is sequenced to look for novel mutations. For most of these genes, mutations range from missense and nonsense mutations to insertions, deletions, and splice-site disruptors.

Molecular genetic testing: Research. Molecular genetic testing for *RDH12* and *CEP290* is available on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Leber Congenital Amaurosis

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*GUCY2D* sequence variants	~50%	Clinical Testing
	RPE65 sequence variants		Clinical Testing
	AIPL1 sequence variants		Clinical Testing
	RPGRIP1 sequence variants		Clinical Testing
	CRB1 sequence variants		Clinical Testing
	CRX sequence variants		Clinical Testing
Direct DNA [1]	*RDH12* sequence variants	~4%	Research only
	CEP290 sequence variants	10%-20%	

1. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with this disorder.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

Hanein et al (2004) proposed a clinical flowchart using the presence or absence of photophobia, night blindness, hyperopia, macular/peripheral retinal abnormalities, and measurable acuity to help direct the order of genes selected for molecular studies.

Genetically Related (Allelic) Disorders

Different mutations within each of the LCA-associated genes are known to cause other retinal dystrophies, such as retinitis pigmentosa (RP) and cone-rod dystrophy. Sequence changes that cause LCA have therefore been considered to be at the severe end of the spectrum of retinal abnormalities and are presumed to render the protein product nonfunctional or absent.

- ***GUCY2D***mutations also cause autosomal dominant cone-rod dystrophy.
- ***RPE65.*** A proportion of mutations also cause retinitis pigmentosa [Marlhens et al 1997, Morimura et al 1998].
- ***AIPL1***mutations also cause cone-rod dystrophy and RP [Sohocki et al 2000].
- ***RPGRIP1.*** Homozygous mutations (R827L, A547S) of *RPGRIP1* are associated with autosomal recessive cone-rod dystrophy in four consanguineous Pakistani families [Hameed et al 2003].
- ***CRB1***The most common allele, C948Y, is found in the homozygous state only in individuals with LCA [den Hollander et al 2001, Lotery et al 2001]. Individuals with compound heterozygosity for the C948Y allele and a "milder" missense mutation on the other allele have retinitis pigmentosa (RP) [den Hollander et al 2001]. Less

deleterious mutations of *CRB1* cause RP, RP with Coats-like vasculopathy, and RP with preserved para-arteriolar RPE (PPRPE) [den Hollander et al 1999].

- ***CRX.*** Other mutations result in cone-rod dystrophy [Lotery et al 2000]. Heterozygous mutations of *CRX* have been associated with dominant LCA and dominant cone-rod dystrophy phenotypes. *De novo* dominant mutations of *CRX* have been recognized [Perrault et al 2003].
- ***RDH12.*** In their series of unrelated individuals with LCA, Perrault et al (2004) identified *RDH12* mutations only in individuals affected with "congenital severe yet progressive rod-cone dystrophy." In contrast, Janecke et al (2004) described three consanguineous Austrian kindreds with onset between age two and four years, severe retinal dystrophy affecting both rods and cones, and progression to legal blindness between 18 to 25 years. The ERG was "extinguished" at the first investigation, as early as age five years.
- ***CEP290***is a novel centrosomal protein that was first described in association with RD 16 in the mouse [Swaroop et al 1999]. Mutations of *CEP290* also cause Joubert syndrome [Sayer et al 2006], a complex genetic disorder characterized by early-onset retinal degeneration, juvenile nephronophthisis, cerebellar vermis aplasia, and mental retardation. The authors also screened unrelated families with isolated nephronophthisis and Senior-Loken syndrome, a related disorder comprising nephronophthisis and early-onset retinal degeneration. *CEP290* mutations were identified in one family with Senior-Loken syndrome but none of the families with isolated nephronophthisis [Sayer et al 2006]. Cremers et al (2002) have reported that *CEP290* accounts for a substantial percentage of individuals with LCA.

Clinical Description

Natural History

Leber congenital amaurosis (LCA) has retinal, ocular, and extraocular features and occasionally, systemic associations [Fazzi et al 2003].

Retina. The retina may appear normal initially; later, a variety of abnormalities may develop either in isolation or combination:

- "Macular coloboma": not a true coloboma, but reflecting discrete chorioretinal degeneration and atrophy centered about the fovea
- "Bone-spicule" intraretinal pigment migration
- Widespread subretinal flecks resembling retinitis punctata albescens
- "Marbled" fundus
- Discrete pigmented nummular lesions at the level of the retinal pigment epithelium (RPE)
- Optic disc abnormalities: swelling, drusen formation, and peripapillary neovascularization

Oculo-digital sign. The characteristic extraocular sign in LCA is Franceschetti's oculo-digital sign, comprising three components: eye poking, pressing, and rubbing. It is not known why this behavior occurs. The major sequela is enophthalmos, a physical defect in which the eye recedes into the orbit, presumably from atrophy of orbital fat. Keratoconus has been said to result from the repetitive trauma to the cornea, but others have suggested that this may be a feature of LCA itself.

Mental retardation/developmental delay. Rarely, LCA is seen in association with neurodevelopmental delay, mental retardation, and oculomotor apraxia-type behavior. However, many if not most of the historical reports date to earlier studies in which systemic phenocopies of LCA (see Differential Diagnosis) were not considered or ruled out. Still, some recent studies suggest that as many as 20% of children with LCA without associated anomalies develop mental retardation [Casteels et al 1996, Schuil et al 1998]. Whether these individuals represent undiagnosed systemic disorders or a genetic subtype of LCA is unknown. Prior to the identification of *CEP290*, none of the molecularly defined types of LCA was shown to be associated with mental retardation or neurodevelopmental degeneration. Whether mutations in *CEP290* can lead to early-onset retinal degeneration and mental retardation in the absence of the other systemic features of Joubert syndrome is unknown.

Visual impairment. Profound visual impairment is usually present from birth. One-third of individuals with LCA have no perception of light. The visual impairment is generally stable or very slowly progressive. Occasionally in the early stages, a mild degree of visual improvement is observed. This improvement has been attributed to development of the central visual pathways rather than retinal maturation [Fulton et al 1996]. Sustained improvements in acuity, visual field, and electrophysiologic measurements have been reported in one individual with a 529delG mutation in the *CRX* gene [Koenekoop, Loyer et al 2002]. Loss of visual acuity typically results from keratoconus, cataract, or evolving macular lesions.

Carriers. Carriers (heterozygotes) are usually asymptomatic; however, some heterozygotes for *GUCY2D* mutations have been shown to have mild cone dysfunction measured by decreased cone responses on electroretinogram [Koenekoop, Fishman et al 2002]. However, this is not associated with any findings on ophthalmologic examination and does not appear to interfere with vision.

Genotype-Phenotype Correlations

A number of genotype-phenotype correlations appear to be emerging.

GUCY2D. Mutations in *GUCY2D*, which encodes RetGC, have been associated with a congenital severe cone-rod dystrophy characterized by photophobia, high hyperopia, and poor but stable vision with no visual improvement [Perrault et al 1999, Lorenz et al 2000, Hanein et al 2004]. However, Perrault et al (2005) described a man with early-onset RP resulting from a homozygous 4-bp insertion in *GUCY2D*. The man has night blindness, peripheral vision loss, and preservation of central vision typical of RP. Unlike most null mutations described in *GUCY2D* to date, the 4-bp insertion is predicted to result in an elongation of the protein and residual protein function [Perrault et al 2005].

RPE65. Mutations in *RPE65* have been associated with night blindness, some transient improvement in vision, and eventual progressive visual loss [Perrault et al 1999; Dharmaraj, Silva et al 2000]. Lorenz found that four individuals with LCA and *RPE65* mutations had measurable visual acuity at age six to ten years, despite severe visual impairment from infancy and nystagmus in three of the four [Lorenz et al 2000]. Photophobia was not a feature and all individuals had preservation of measurable peripheral vision. Rod ERG responses were undetectable, whereas cone ERG responses were detectable in early childhood.

Paunescu et al (2005) presented detailed follow-up data on three adult siblings with LCA suggesting that photophobia and progressive visual loss occur with age. Using a genotyping microarray, Zernant et al (2005) found that only five of 69 individuals with LCA (7%) with detectable mutations had an *RPE65* genotype. The authors suggest that this detection rate — lower than previous studies would predict — suggests that allelic variation in *RPE65* may be more highly associated with early-onset severe retinal dystrophy than with classic LCA.

AIPL1. Dharmaraj et al (2004) studied 303 individuals with LCA and found that 26 probands (8.5% of their cohort) harbored homozygous or heterozygous mutations in *AIPL1*. Fifty-four percent of these individuals (14/26) had at least one allele with the W278X mutation. The authors described the phenotype of LCA in these individuals and compared them to those observed and reported with LCA from mutations of *GUCY2D, RPE65, CRX, CRB1,* and *RPGRIP1*. The phenotype of LCA in individuals with *AIPL1* mutations was found to be relatively severe, with maculopathy and marked bone-spicule pigmentary retinopathy in most and keratoconus and cataract in a large subset. The authors conclude that the visual loss associated with mutation of *AIPL1* is similar in severity to that observed with mutation of *GUCY2D*.

RPGRIP1. Hanein et al (2004) described the following features as characteristic of *RPGRIP1* mutations: early photophobia, hypermetropia less than +7 diopters, and visual acuity in the range of 20/400 to count fingers (CF). In follow-up of individuals with LCA, Galvin et al (2005) found that visual acuity in children with mutations in *RPGRIP* frequently progresses to light perception (LP) or no light perception (NLP) within the first decade of life.

CRB1. Night blindness is a constant feature of LCA resulting from *CRB1* mutations. Jacobson et al (2003) found thick unlaminated retinas by optical coherence tomography (OCT) in individuals with LCA and *CRB1* defects. Although some individuals with RP resulting from *CRB1* mutations have the fundus appearance of preserved para-arteriolar RPE (PPRPE), no individuals with LCA resulting from *CRB1* mutations have yet been reported to have PPRPE [den Hollander et al 2001].

CRX. Mutations of *CRX* have also been reported to be associated with stable vision [Dharmaraj, Silva et al 2000] or even some modest improvement [Koenekoop, Loyer et al 2002]. Single or double base-pair deletions of the gene account for only the dominant forms of LCA, as a result of either an inherited dominant mutation or a *de novo* mutational event [Sohocki et al 1998, Rivolta et al 2001, Tzekov et al 2001, Perrault et al 2003].

RDH12. In a further study of the individuals studied by Hanein et al (2004), Perrault et al (2004) identified 11 distinct mutations of the *RDH12* gene in 8/44 individuals with LCA characterized by congenital severe progressive rod-cone dystrophy. All eight with *RDH12* mutations had a clinical course similar to that of individuals with *RPE65* mutations: mild or absent hyperopia, transient improvement of visual acuity, and eventual macular atrophy with severe disease progression. Loss of visual acuity, however, occurred at an earlier age in those with *RDH12* mutations than in those with *RPE65* mutations. No *RDH12* mutations were observed in persons with LCA presenting with the congenital stationary cone-rod dystrophy form of the disease.

Keratoconus has been reported to occur in individuals with specific mutations in the *CRB1* and *AIPL1* genes.

Photophobia and nightblindness. Hanein et al (2004) performed molecular screening on 179 unrelated individuals with LCA and reported the genotype-phenotype correlations on 85 who were found to harbor mutations on one or both alleles in one of seven LCA genes. The frequencies of mutations in each gene were *GUCY2D*: 21.2% (38/179 families), *CRB1*: 10% (18/179), *RPE65*: 6.1% (11/179), *RPGRIP1*: 4.5% (8/179), *AIPL1*: 3.4% (6/179), *TULP1*: 1.7% (3/179), and *CRX*: 0.6% (1/179).

The authors found that the presence of photophobia or night blindness at age one and two years distinguished two groups:

- Those with photophobia comprised a cone-rod dystrophy class and were found to have mutations of *GUCY2D, AIPL1,* and *RPGRIP1*
- Those with night blindness comprised a rod-cone dystrophy class and were found to have mutations of *RPE65, CRB1, CRX,* and *TULP1*

Prevalence

The birth prevalence of LCA is two to three per 100,000 births. The condition is the most common cause of inherited blindness in childhood and constitutes more than 5% of all retinal dystrophies. LCA accounts for the cause of blindness in more than 20% of children attending schools for the blind.

LCA appears to be more prevalent when consanguinity is common [Sitorus et al 2003].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Leber congenital amaurosis (LCA) typically presents as an isolated ocular anomaly without systemic involvement. Occasionally, the same or similar retinal findings can be seen as part of a systemic disorder. Systemic abnormalities including renal anomalies, deafness, skeletal abnormalities, microcephaly, neurodevelopmental delay, mental retardation, or oculomotor apraxia should alert the clinician to consider syndromic disorders associated with early-onset retinal dystrophy. Systemic disorders to consider include the following:

Senior-Loken syndrome (MIM 266900) comprises juvenile nephronophthisis (medullary cystic renal disease) and early-onset retinal dystrophy.

Conorenal syndrome (MIM 266920) comprises cone-shaped digital epiphyses, cerebellar hypoplasia, and early-onset retinal dystrophy.

Joubert syndrome (MIM 243910) comprises nephronophthisis (a juvenile-onset cystic kidney disease), hypoplasia of the cerebellar vermis, early-onset retinal dystrophy, and either a) episodic hyperpnea and/or apnea or b) atypical eye movements or both a) and b).

Peroxisomal biogenesis disorders, Zellweger syndrome spectrum is a continuum of three phenotypes described before the biochemical and molecular bases of the disorders were known: Zellweger syndrome (ZS) (MIM 214100), neonatal adrenoleukodystrophy (NALD) (MIM 202370), and infantile Refsum disease (IRD) (MIM 266510). ZS is the most severe and IRD the least severe. Children with ZS have retinal dystrophy, sensorineural hearing loss, developmental delay with hypotonia, and liver dysfunction; they usually die during the first year of life. The clinical courses of NALD and IRD are variable. Retinal degeneration is associated with congenital, liver, and renal abnormalities.

Children with **infantileneuronal ceroid-lipofuscinosis** (Santavuori-Haltia disease) *(CLN1*, MIM 256730) are normal at birth but develop retinal vision impairment, loss of milestones, and progressive microcephaly by age six to 12 months. Virtual blindness ensues by age two years, seizures and progressive mental deterioration develop, and death generally occurs between age three and 11 years [Weleber 1998, Wisniewski 2006]. Affected children have characteristic electronegative electroretinograms early in the course of disease. The diagnosis can be established by assay of the enzyme defect of the protein gene product, palmitoyl-protein thioesterase 1 (PPT1), and/or identification of the causative mutations within the *PPT1* gene, *CLN1* [Wisniewski 2006].

In addition, an LCA-like retinal dystrophy has been documented in individuals with abetalipoproteinemia (MIM 200100), hyperthreoninemia (MIM 273770), and disorders of mitochondrial dysfunction (see Mitochondrial Disorders Overview). Common clinical features of mitochondrial disease include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus. The central nervous system findings are often fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity.

In a child presenting without systemic involvement, other inherited retinal dystrophies may be considered. Compared to LCA, early-onset retinitis pigmentosa (RP) has a later age of onset, better preservation of central visual acuity, and no nystagmus. The electroretinogram (ERG) is useful in distinguishing between LCA and RP: in the early stages of RP, the photopic component of the ERG typically shows some degree of sparing, while in LCA both the photopic and scotopic ERG are profoundly abnormal.

An intermediate category of retinal disease, presenting in early childhood with night blindness, variable degrees of central vision loss, and a severely abnormal but recordable ERG is now emerging. The authors favor the term "SECORD" (**s**evere **e**arly **c**hildhood **o**nset **r**etinal **d**ystrophy) to describe this entity, although terms such as early-onset severe retinal dystrophy (EOSRD) and early-onset severe RP have been variably used in the literature. SECORD is distinguished from LCA primarily by the age of onset and severity: the diagnosis of LCA should be reserved for infants presenting before age one year with nystagmus, severely impaired vision, and an unrecordable or nearly unrecordable ERG.

Other retinal dystrophies such as achromatopsia and congenital stationary night-blindness can be easily distinguished by characteristic patterns of electroretinographic abnormality.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Electroretinogram to confirm the diagnosis and to assess retinal function
- Clinical genetic assessment to evaluate for the presence of systemic abnormalities

Treatment of Manifestations

Because no cure for Leber congenital amaurosis exists, care is supportive. Parents should be referred to programs for the visually impaired child within their state or locality.

Affected individuals benefit from periodic ophthalmic evaluation to correct refractive error, assess the best low-vision aids, and optimize access to educational and work-related opportunities.

Prevention of Secondary Complications

Children should be discouraged from repeatedly poking and pressing on their eyes, although attempts to alter such behavior are not always successful.

Surveillance

Affected individuals should be periodically seen for assessment of vision, trials of correction for refractive error, and when residual vision is present, assessment of the presence of amblyopia, glaucoma, or cataract.

Rarely, vision appears to improve beyond expectations; in such cases, a repeat ERG is indicated.

Therapies Under Investigation

In a naturally-occurring Briard dog model of LCA resulting from mutations in *RPE65*, gene therapy utilizing AAV-mediated *RPE65* has been shown to restore visual function, an effect that has been documented to last for more than four years [Acland 2005]. More than 50 dogs have now been treated, with sustained success in 95% of treated eyes. A Phase I clinical treatment trial of AAV-mediated *RPE65* gene therapy in humans is in the development stages, and is expected to begin enrollment in 2007. Only individuals age 18 years or older in whom LCA resulting from mutations in *RPE65* has been molecularly confirmed will be eligible for the trial [Hauswirth 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Most often, Leber congenital amaurosis is inherited in an autosomal recessive manner. Rarely, mutations in *CRX* causing LCA are inherited in an autosomal dominant manner.

Risk to Family Members — Autosomal Recessive LCA

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with Leber congenital amaurosis are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Sibs of the proband's parents are at 50% risk of being carriers.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Risk to Family Members — Autosomal Dominant LCA

Parents of a proband

- Most children diagnosed as having autosomal dominant LCA have an affected parent.
- Occasionally a molecular diagnosis is made in the absence of family history. Such cases are the result of *de novo* mutations in the *CRX* gene [Freund et al 1997, Jacobson et al 1998, Sohocki et al 1998, Swaroop et al 1999, Rivolta et al 2001, Perrault et al 2003].

Sibs of a proband

- The risk to sibs depends upon the genetic status of the proband's parents.
- If one of the proband's parents is affected with LCA, the risk to sibs of inheriting the mutant allele is 50%.
- When neither parent of the proband is affected, the risk to sibs is negligible.

Offspring of a proband. Individuals with autosomal dominant LCA have a 50% chance of transmitting the mutant allele to each child.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of Leber congenital amaurosis are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Leber Congenital Amaurosis

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
LCA1	*GUCY2D*	17p13.1	Retinal guanylyl cyclase 1
LCA10	*CEP290*	12q21.32	Centrosomal protein Cep290
LCA2	*RPE65*	1p31	Retinal pigment epithelium-specific 65 kDa protein
LCA3	Unknown	14q24	Unknown
LCA4	*AIPL1*	17p13.1	Aryl-hydrocarbon interacting protein-like 1
LCA5	Unknown	6q11-q16	Unknown
LCA6	*RPGRIP1*	14q11	X-linked retinitis pigmentosa GTPase regulator-interacting protein 1
LCA7	*CRB1*	1q31-q32.1	Crumbs homolog
LCA8	*CRX*	19q13.3	Cone-rod homeobox protein
LCA9	Unknown	1p36	Unknown
	RDH12	14q23.3	Retinol dehydrogenase 12

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Leber Congenital Amaurosis

180069	RETINAL PIGMENT EPITHELIUM-SPECIFIC PROTEIN, 65-KD; RPE65
204000	LEBER CONGENITAL AMAUROSIS, TYPE I; LCA1
204100	LEBER CONGENITAL AMAUROSIS, TYPE II; LCA2
600179	GUANYLATE CYCLASE 2D, MEMBRANE; GUCY2D
602225	CONE-ROD HOMEOBOX-CONTAINING GENE; CRX
604210	CRUMBS, DROSOPHILA, HOMOLOG OF, 1; CRB1
604232	LEBER CONGENITAL AMAUROSIS, TYPE III
604392	ARYLHYDROCARBON-INTERACTING RECEPTOR PROTEIN-LIKE 1; AIPL1
604393	LEBER CONGENITAL AMAUROSIS, TYPE IV; LCA4
604537	LEBER CONGENITAL AMAUROSIS, TYPE V
605446	RETINITIS PIGMENTOSA GTPase REGULATOR-INTERACTING PROTEIN; RPGRIP1
608830	RETINOL DEHYDROGENASE 12; RDH12
610142	CENTROSOMAL PROTEIN, 290-KD; CEP290

Table C. Genomic Databases for Leber Congenital Amaurosis

Locus Name	Gene Symbol	Entrez Gene	HGMD
LCA1	*GUCY2D*	3000 (MIM No. 600179)	GUCY2D
LCA10	*CEP290*	80184 (MIM No. 610142)	
LCA2	*RPE65*	6121 (MIM No. 180069)	RPE65
LCA3	Unknown		
LCA4	*AIPL1*	23746 (MIM No. 604392)	AIPL1
LCA5	Unknown	167691 (MIM No. 604537)	
LCA6	*RPGRIP1*	57096 (MIM No. 605446)	RPGRIP1
LCA7	*CRB1*	23418 (MIM No. 604210)	CRB1
LCA8	*CRX*	1406 (MIM No. 602225)	CRX
LCA9	Unknown	619483 (MIM No. 608553)	
	RDH12	145226 (MIM No. 608830)	RDH12

For a description of the genomic databases listed, click here.

GUCY2D

Normal allelic variants: The GUCY2D gene has 20 exons.

Pathologic allelic variants: See Genomic Database table above.

Normal gene product: Retinal guanylyl cyclase 1 (retGC-1), a transmembrane protein located in the photoreceptor outer segments, is critical in the recovery process of the phototransduction cascade [Perrault et al 1996].

Abnormal gene product: Most mutations result in truncation of the protein and complete loss of function. Complete loss of function of retGC-1 catalytic activity from mutations in GUCY2D consistently results in LCA [Rozet et al 2001]. Pathologic study of the eyes of a 33-week aborted fetus disclosed cell loss of the outer nuclear layer, decreased immunolabeling of phototransduction proteins, and aberrant synaptic and inner retinal organization, suggesting that pathophysiologic events are well established prior to birth [Porto et al 2002]. Clinicopathologic correlation in an 11 1/2-year-old affected subject disclosed retention of substantial numbers of cones and rods in the macula and far periphery, portending well for therapeutic intervention at this age [Milam et al 2003].

RPE65

Normal allelic variants: The RPE65 gene has 14 exons.

Pathologic allelic variants: See Genomic Database table above.

Normal gene product: Retinal pigment epithelium-specific 65-kd protein forms a complex with LRAT to act as the isomerolhydrolase in the regeneration of the visual pigment, vitamin A [Redmond et al 2005].

Abnormal gene product: In the absence of the protein encoded for by RPE65, isomerisation of all-trans retinal to 11-cis retinal in the retinal pigment epithelium is inhibited.

AIPL1

Normal allelic variants: The AIPL1 gene has six exons.

Pathologic allelic variants: The majority of mutations result in a null genotype. The most frequent allele, W278X, probably represents a founder effect in the Pakistani population. See Genomic Database table above.

Normal gene product: The role of aryl-hydrocarbon interacting protein-like 1 (AIPL1) has yet to be defined, although it may act as a molecular chaperone. AIPL1 is expressed in adult retina only in rods, but expression coincides with both rod and cone photoreceptors during fetal development and AIPL1 may be essential for the normal development of both photoreceptor types [van der Spuy et al 2003].

Abnormal gene product: Certain mutations of AIPL1 (W278X, A197P, C239R), but not others (e.g., I206N, G262S, R302L, P376S), abolish an interaction with NEDD8 ultimate buster-1 (NUB1), which is an inducible protein that recruits ubiquitin-like proteins to the proteasome for degradation [Kanaya et al 2004]. The loss of the AIPL1 binding site that supports this interaction has been suggested to contribute to the pathogenesis of LCA in these cases [Kanaya et al 2004]. Clinicopathologic correlation of a 22-year-old subject with mutation of AIPL1 and LCA demonstrated almost total loss of photoreceptors, retinal gliosis, decreased ganglion cells, increased vacuolizations of the nerve fiber layer, and unusual vascular morphology [Heegaard et al 2003].

RPGRIP1

Normal allelic variants: The RPGRIP1 gene has 25 exons.

Pathologic allelic variants: See Genomic Database table above.

Normal gene product: Expression of X-linked retinitis pigmentosa GTPase regulator (RPGR)-interacting protein-1 is confined to the rod and cone retinal photoreceptor, where it localizes to the connecting cilium, is presumed to anchor RPGR in the photoreceptor cilium, and appears to be required for disk morphogenesis, putatively by regulating actin cytoskeleton dynamics [Zhao et al 2003].

Abnormal gene product: Most mutations result in truncation of the protein and complete loss of function.

CRB1

Normal allelic variants: The CRB1 gene has 12 exons.

Pathologic allelic variants: The most common allele, observed in 20% of individuals with LCA, is C948Y. See Genomic Database table above.

Normal gene product: *CRB1* encodes a protein (crumbs homolog) thought to play a role in determining and maintaining photoreceptor architecture.

CRX

Normal allelic variants: The CRX gene has three exons.

Pathologic allelic variants: See Genomic Database table above.

Normal gene product: Cone-rod homeobox protein is a transcription factor essential for the elongation of photoreceptor outer segments and the phototransduction cascade.

RDH12

Normal allelic variants: The RDH12 gene has seven exons.

Pathologic allelic variants: Mutations may be nonsense, missense, splice-site, or frameshift. The most frequent sequence variant is a frameshift deletion in exon 6, 806-810del5 [Perrault et al 2004]. See Genomic Database table above.

Normal gene product: Retinol dehydrogenase 12 (RDH12) is a photoreceptor-specific enzyme involved in all-trans- and cis-retinol transformations, critical for the mediation of vision. RDH12 may be the key enzyme in the formation of 11-cis-retinal from 11-cis-retinol during regeneration of the cone visual pigments [McBee et al 2001, Haeseleer et al 2002].

Abnormal gene product: Most *RDH12* mutations result in reduced expression and activity of the retinal dehydrogenase 12 enzyme, which disrupts the cycle of synthesis of the visual pigment chromophore, 11-*cis*-retinal, from 11-*trans*-retinal [Thompson et al 2005].

CEP290

Normal allelic variants: The *CEP290* gene has 55 exons.

Pathologic allelic variants: The most frequent sequence variant is c.2991 +1655A>G, an intronic donor splice site mutation that inserts a cryptic exon in the *CEP290* messenger RNA. To date, all individuals with LCA resulting from *CEP290* have had at least one c.2991 +1655A>G mutation identified [den Hollander et al 2006]. Heterozygous nonsense, frameshift, and splice-site mutations have been identified on the remaining allele.

Normal gene product: Centrosomal protein Cep290 (nephrocystin-6, NPHP6) is a centrosomal protein with probable ciliary function. The greatest concentration of NPHP6 occurs in the connecting cilium of mouse photoreceptor cells. NPHP6 putatively interacts with the protein retinitis pigmentosa GTPase regulator (RPGR), deficiency of which is the leading cause of X-linked retinitis pigmentosa (RP), and nephrocystin-5, which is mutated in nephronophthisis type 5. NPHP6 also interacts with and activates ATF4-mediated transcription [Sayer et al 2006].

Abnormal gene product: Although the common *CEP290*f splice site mutation leads to aberrant splicing, early studies indicate that this mutation allows low levels of the NPHP6 to remain intact. This level may be sufficient for normal cerebellar and renal function but insufficient for normal photoreceptor function [den Hollander et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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1155 15th Street NW Suite 1004
Washington DC 20005
Phone: 800-424-8666; 202-467-5081
Fax: 202-467-5085

Email: info@acb.org
www.acb.org

Foundation Fighting Blindness
11435 Cronhill Drive
Owings Mill MD 21117-2220
Phone: 888-394-3937 (toll-free); 800-683-5555 (toll-free TDD); 410-568-0150 (local)
Email: info@blindness.org
www.blindness.org

National Federation of the Blind (NFB)
1800 Johnson Street
Baltimore MD 21230
Phone: 410-659-9314
Fax: 410-685-5653
Email: nfb@nfb.org
www.nfb.org

Retina International
Ausstellungsstrasse 36
CH-8005 Zurich
Switzerland
Phone: 011-41-1-444-10-7
Fax: 011-41-1-444-10-7
Email: info@rpinternational.org
www.retina-international.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 12 October 2006 (me) Comprehensive update posted to live Web site

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- 7 July 2004 (me) Review posted to live Web site
- 30 December 2003 (rw, pf, kt) Original submission