Leber congenital amaurosis

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Abstract
Leber congenital amaurosis (LCA) is a retinal dystrophy and/or dysplasia of prenatal onset. About 10 to 20% of blind children are thought to suffer from LCA, which makes it one of the frequent causes of childhood blindness. It is thought to account for 5% of inherited retinal disease. Affected children fail to fix and follow due to little or no retinal sensitivity to visual stimuli. Electroretinography shows either no or very reduced retinal function. Fundus examination in the first months of life is frequently normal, but later chorioretinal atrophy with intraretinal pigment migration becomes apparent. In some patients, a macular puched-out lesion is present. Patients have nystagmus and frequently poke their eyes. LCA is inherited as an autosomal recessive trait in the large majority of patients, with only a limited number of cases with autosomal dominant inheritance described. LCA is genetically heterogeneous, and, to date, mutations have been identified in six different genes known to be associated with LCA: AIPL1, CRB1, CRX, GUCY2D, RPE65 and RPGRIP1. At least another three additional loci have been linked to the condition. Although therapy is not currently available, encouraging results have been obtained with gene therapy in a dog model for this disease.

Keywords
Leber congenital amaurosis, retinal dystrophy, childhood blindness, autosomal recessive inheritance, genes, genotype-phenotype correlations

Disease name /synonyms

- Leber congenital amaurosis (LCA)
- Genetic subtypes: LCA1, LCA2, LCA3, LCA4, LCA5, LCA6, LCA7, LCA8 & LCA9

Definition / Diagnostic criteria

LCA is a retinal dystrophy with:
- no or little sensitivity for visual stimuli from birth
- variable aspect of retina

- abolished or profoundly abnormal ERG
- autosomal recessive inheritance (rarely autosomal dominant)

Differential diagnosis

- All syndromes with an LCA-like retinal dystrophy and mental retardation
- *Senior-Loken syndrome*: early-onset retinal dystrophy + nephronophtisis (AR)
- *Saldino-Mainzer syndrome*: early-onset retinal dystrophy + nephronophtisis, cone-shapedepiphyses of the hand and cerebellar ataxia
- *Joubert syndrome*: early-onset retinal dystrophy + cerebellar vermis hypoplasia, oculomotoranomalies and neonatal respiratory problems (AR)
- *Alström syndrome*: early-onset retinal dystrophy + diabetes mellitus, cardiomyopathy, severesensorineural deafness, obesity (AR)

Etiology

LCA is inherited as an autosomal recessive trait, although infrequent accounts of dominant inheritance have been reported (Sorsby et al. 1960; Sohocki et al. 2000; Rivolta et al. 2001; Perrault et al. 2003).

To date, homozygous or compound heterozygous mutationsin six different retinal genes have been shown to cause LCA. The LCA genes currently known are (see also **Table 1**):

-Retinal guanylate cyclase (GUCY2D) (Perrault et al. 1996)

-Retinal pigment epithelium-specific 65kD protein (*RPE65*) (Marlhens et al. 1997)

-Cone-rod homeobox (*CRX*) (Freund et al. 1998; Jacobson et al. 1998; Silva et al. 2000; Sohocki et al. 2000; Tzekov et al. 2001)

-the Crumbs gene homolog of *CRB1* (den Hollander et al. 2001; Lotery et al. 2001)

-Retinitis pigmentosa GTPase regulator–interacting protein (*RPGRIP-1*) (Dryja et al. 2001; Gerber et al. 2001)

-*AIPL1*, encoding the aryl hydrocarbon receptor interacting protein-like 1 protein (Sohocki et al. 2000).

AIPL1, *CRX*, *GUCY2D,* *RPGRIP1* are expressed in the photoreceptor cells and *RPE65* in the retinal pigment epithelium.

The putative functions of the gene products are diverse and include the phototransduction cascade (*GUCY2D*), retinal embryonic development (*CRX*), photoreceptor cell and inner limiting membrane structure (*CRB1*), protein trafficking (*AIPL1*, *RPGRIP1*), and vitamin A regeneration metabolism (*RPE65*) (Cremers et al. 2002; Jacobson et al. 2003; Mehalow et al. 2003).

Evidence suggests that retinal dystrophy in LCA patients is already present prenatally (Porto et al. 2002). In patients with mutations in *CRB1* there is evidence to suggest that the retina is dysplastic (Jacobson et al. 2003).

At least another 3 loci have been linked to LCA (see **Table 1**).

Table 1: LCA genes

Disease	Gene	Chromosomal location	Frequency	References
LCA1 MIM 204000	*GUCY2D*	17p13.1	6%	(Camuzat et al. 1995; Camuzat et al. 1996; Perrault et al. 1996)
LCA2, MIM 204100	*RPE65*	1p31.2	7 to 16%	(Gu et al. 1997; Marlhens et al. 1997; Morimura et al. 1998)
LCA3 MIM 604232	unknown	14q24	One Saudi Arabian consanguinous family	(Stockton et al. 1998)
LCA4 MIM 604393	*AIPL1*	17p13.2	10%	(Hameed et al. 2000; Sohocki et al. 2000; Sohocki et al. 2000)
LCA5 MIM 604537	unknown	6q11-q16	limited number of consanguinous families	(Dharmaraj et al. 2000; Mohamed et al. 2003)
LCA6 MIM 605446	*RPGRIP1*	14q11.2	6%	(Dryja et al. 2001; Cremers et al. 2002)
LCA7 MIM 602225	*CRX*	19q13.32	3%	(Freund et al. 1998; Jacobson et al. 1998; Swaroop et al. 1999; Rivolta et al. 2001; Perrault et al. 2003)
LCA8 MIM 604210	*CRB1*	1q31.3	9 to 13%	(den Hollander et al. 2001; Lotery et al. 2001)
LCA9	unknown	1p36	Single family	(Keen et al. 2003)

Clinical description

General background

LCA was first described by Leber in 1869 (Leber, 1869) as a congenital type of retinitis pigmentosa (RP). LCA represents a clinically and genetically heterogeneous disorder with little or no sensitivity to visual stimuli from birth or shortly thereafter (Waardenburg 1961; Camuzat et al. 1996). Fundus examination is initially normal in the majority of cases, but chorioretinal atrophy, narrowing of the retinal vasculature, intraretinal pigment migration, white fundus flecks and rarely a macular punched out lesion (macular aplasia) may ensue (François 1968; Margolis et al. 1977; Mizuno et al. 1977; Noble et al. 1978; Heckenlively et al. 1988).

The absence of retinal sensitivity is confirmed by electroretinography (Franceschetti et al. 1954), which shows either an absent or severely diminished response. Roving eye movements in younger patients evolve to nystagmus. Sluggish pupillary responses are nearly invariably present. Additional symptoms and signs include keratoconus, cataracts and hyperopia (Wagner et al. 1985; Elder 1994; Stoiber et al. 2000). Enophthalmos is probably related to the progressive atrophy of retro-ocular adipose tissue secondary to frequent eye-poking (Franceschetti or oculo-digital sign). Whether the higher frequency of keratoconus can be explained by the same phenomenon and/or by genetic susceptibility, is still a matter of debate (Schroeder et al. 1987; Heher et al. 1992; Elder 1994; Stoiber et al. 2000).

Genotype-phenotype correlations

Currently, mutations in six different retinal genes have been shown to cause LCA and at least three other loci have been linked to the disease (see **Etiology** and **Table 1**). Evidence is emerging that more or less specific genotype-phenotype correlations may exist.

What follows is an overview of known correlations.

Retinal guanylate cyclase (GUCY2D)

The phenotype of LCA patients with mutations in *GUCY2D* is that of a severe cone-rod dystrophy with photophobia and hyperopia. Visual acuity ranges from light perception to counting fingers. Fundi are essentially normal at birth with signs of pigmentary retinopathy later in life. Keratoconus and atrophic maculopathy are infrequent (Perrault et al. 1999; Dharmaraj et al. 2000; Lotery et al. 2000). Some heterozygous carriers, parents of LCA patients with *GUCY2D* mutations, have recently been shown to have significant cone ERG abnormalities, with essentially normal rod ERGs (Koenekoop et al. 2002). This evidence suggests that cones may be affected earlier, and more severely in *GUCY2D*- related LCA patients. There is no improvement of retinal function over time.

Retinal pigment epithelium-specific 65kD protein (RPE65)

Contrary to those with mutations in *GUCY2D*, patients with *RPE65* defects have no photophobia and even may transiently acquire the ability to fix and follow large objects in a well-lit environment (Perrault et al. 1999; Dharmaraj et al. 2000; Lorenz et al. 2000). Patients have normal fundi at birth, and progressively develop pigmentary retinopathy. Their visual acuity ranges from 6/60 to 6/36. Night blindness is frequent. Associated refractive errors can be either hyperopia or myopia. Specific reports on the frequency of keratoconus and cataract in *RPE65*-related LCA patients are unavailable. Heterozygous carrier-parents of LCA patients with *RPE65* mutations have abnormal peripheral retinal function on dark-adapted perimetry (Felius et al. 2002). These findings further support the hypothesis that this type of LCA is likely to be of the rod-cone dystrophy type. Whether the autosomal recessive early-onset retinal dystrophy associated with mutations in *RPE65* is either a milder form of LCA, or a different clinical entity, remains the topic of debate (Marlhens et al. 1998; Lorenz et al. 2000; Thompson et al. 2000).

Cone-rod homeobox (CRX)

Visual acuities in LCA patients with *CRX* defects range from light perception to 20/300. The disease appears to be either autosomal recessive or due to novel autosomal dominant mutations. Both high myopic and high hypermetropic refractive errors have been reported (Jacobson et al. 1998; Swaroop et al. 1999; Silva et al. 2000; Rivolta et al. 2001; Rivolta et al. 2001; Koenekoop et al. 2002).

the Crumbs gene homolog of CRB1

The phenotype of LCA patients with *CRB-1* is variable with visual acuities ranging from light perception to 20/80. Refractive errors range from high myopia to high hyperopia. Fundoscopy shows variable retinal phenotypes with nummular pigment clumping and white dots in a large subset of patients. Macular aplasia and preservation of the para-arteriolar pigment epithelium can be present.

Keratoconus is seen in a small subset of patients (Lotery et al. 2001).

Retinitis pigmentosa GTPase regulator–interacting protein (RPGRIP-1)
The *RPGRIP-1*-related LCA phenotype is that of classical severe LCA, with hyperopia in the limited number of patients that have been described clinically (Dryja et al. 2001).

AIPL1, encoding the aryl hydrocarbon receptor interacting protein-like 1 protein
LCA in this subset of patients is severe and is associated with a high frequency of macular aplasia and keratoconus as part of the phenotype. Visual acuity is in the range of light perception to 20/400 and patients can be hyperopic and myopic. Pigmentary retinopathy is frequent in the later stages (Damji et al. 2001).

LCA5, due to mutations in an unknown gene on 6q11-q16
Only two families with this subtype of LCA have been described. The original family is an inbred American kindred of the Old Order River Brethren, descendants from Swiss immigrants (Dharmaraj et al. 2000). A second consanguinous family of Pakistani origin was only recently described (Mohamed et al. 2003). Patients have visual acuities ranging from perception of light to 20/200 (Dharmaraj et al. 2000; Mohamed et al. 2003). Although patients have normal fundi, mild macular changes may evolve to more pronounced macular atrophy and staphyloma (Mohamed et al. 2003). Pigmentary retinopathy develops in the later stages of the disease. Neither keratoconus nor cataract have been described.

Diagnostic methods
The diagnosis of LCA is based on a clinical history of failure to develop reactions to visual stimuli, roving eye movements or nystagmus, sluggish pupillary responses and a normal, or less frequently an abnormal fundus on dilated fundoscopy. Absent or near absent responses on full-field flash electroretinography are essential for the diagnosis.

Epidemiology
About 10 to 20% of children in institutions for the blinds are thought to suffer from LCA (Alström et al. 1957; Phillips et al. 1987). The condition is estimated to account for 5% of inherited retinal disease (Mohamed et al. 2003). Currently, about 50% of patients are genetically accounted for by mutations in one of the known genes (Cremers et al. 2002).

Genetic counseling
LCA is traditionally inherited as an autosomal recessive (AR) trait, while only a limited number of cases with autosomal dominant (AD) inheritance have been described (Sorsby et al. 1960; Sohocki et al. 2000; Rivolta et al. 2001; Perrault et al. 2003).
The AR inheritance implies a 1 out of 4 recurrence risk for future offspring of parents. As carrier frequencies are quite low, the recurrence risk for offspring of patients is also low provided there is no consanguinity between them and their partner.
As several of the mutations in *CRX* are dominant and occur *de novo*, the recurrence risk for parents of these children is obviously lower than 25%. The recurrence risk for children of affected patients however would be 50%.

Prenatal diagnosis
LCA is a condition with considerable genetic heterogeneity (Waardenburg et al. 1963). Consequently, prenatal diagnosis is only possible when a clear link has been established between mutations identified on both alleles of one of the LCA genes, and LCA in (an) affected child(ren) in a family.
Demands for prenatal diagnosis will undoubtedly increase with novel high-throughput systems made available to molecular genetic labs specialising in LCA genotypes around the world.

Management including treatment
No effective treatment is currently available. However, successful gene replacement therapy in a Swedish Briard-Beagle dog model for *RPE65*-related LCA suggests that such treatment may become possible in humans in the foreseeable future, especially now that sustained rescue of photoreceptor and RPE cells has been shown (Acland et al. 2001; Narfstrom et al. 2003). Nevertheless, the degree of retinal degeneration in a foetus with LCA due to *RPE65* mutations aborted late in pregnancy, suggests that gene replacement therapy is needed early in life, and may be even prenatally (Porto et al. 2002). This may also be true for patients with mutations in *CRB1*, in whom the dysplastic nature of the retina (Jacobson et al. 2003) suggests a need for early treatment. In cases associated with mutations in *GUCY1D*, the presence of significant numbers of photoreceptors at an older age may allow for efficient treatment to be instigated later (Milam et al. 2003).

Unresolved questions

Currently only 50% of LCA patients are genetically accounted for. This suggests that many more genes remain to be discovered.

As the products of the six genes in which mutations are currently known to cause LCA have very different functions, many questions remain as to the functions of the other unidentified genes . Questions about when and how to effectively treat affected young children once gene therapy becomes available in humans, cannot be answered easily. In the meantime, the vast but important task of genotyping and phenotyping all patients lies ahead.

Evidence suggests that several of the genetic LCA subtypes have prenatal quality loss of the retina. Therefore these LCA subtypes may require therapeutic strategies that can be applied before birth.

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