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Retinal Dehydrogenase 12 (*RDH12*) Mutations in Leber Congenital Amaurosis

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Leber congenital amaurosis (LCA), the most early-onset and severe form of all inherited retinal dystrophies, is responsible for congenital blindness. Ten LCA genes have been mapped, and seven of these have been identified. Because some of these genes are involved in the visual cycle, we regarded the retinal pigment epithelium and photoreceptor-specific retinal dehydrogenase (*RDH*) genes as candidate genes in LCA. Studying a series of 110 unrelated patients with LCA, we found mutations in the photoreceptor-specific *RDH12* gene in a significant subset of patients (4.1%). Interestingly, all patients harboring RDH12 mutations had a severe yet progressive rod-cone dystrophy with severe macular atrophy but no or mild hyperopia.

Introduction

Leber congenital amaurosis (LCA), the most early-onset and severe form of all inherited retinal dystrophies, is responsible for congenital blindness. On the basis of the course of the disease, two clinical subtypes have been recognized in LCA: a severe, congenital stationary cone-rod dystrophy and a severe yet progressive rod-cone dystrophy. This latter phenotype may represent the upper extreme of the spectrum of retinitis pigmentosa (RP) (Perrault et al. 1999; Hanein et al. 2004). A total of 10 LCA genes have been mapped, and 7 of them have been identified—namely,

1. the retinal-specific guanylate cyclase gene (*GUCY2D,* or "*retGC1*" [MIM 600179]) at the *LCA1* locus (17p13.1) (Perrault et al. 1996),
2. the gene encoding the 65-kDa protein specific to the retinal pigment epithelium (RPE) (*RPE65* [MIM 180069]) at the *LCA2* locus (1p31) (Marlhens et al. 1997; Perrault et al. 1999),
3. the cone-rod homeobox-containing gene (*CRX* [MIM 60225]) at 19q13.3 (Freund et al. 1998; Swaroop et al. 1999),
4. the gene encoding arylhydrocarbon receptor interacting protein-like 1 (*AIPL1* [MIM 604392]) at the *LCA4* locus (17p13.1) (Sohocki et al. 2000),
5. the gene encoding retinitis pigmentosa GTPase regulator-interacting protein 1 (*RPGRIP1* [MIM 605446]) at the *LCA6* locus (14q11) (Dryja et al. 2001; Gerber et al. 2001),
6. the human homologue of the *Drosophila melanogaster* gene encoding the crumbs protein (*CRB1* [MIM 604210]), at 1q31 (den Hollander et al. 2001; Lotery et al. 2001; Gerber et al. 2002), and
7. the gene encoding tubby-like protein 1 (*TULP1* [MIM 602280]) at 6q21.3 (North et al. 1997; Hanein et al. 2004).

On the other hand, the disease-causing genes remain unknown in LCA3 (MIM 604232), linked to 14q24 (Stockton et al. 1998); LCA5 (MIM 604537), linked to 6q11-16 (Dharmaraj et al. 2000); and LCA9, linked to 1p36 (Keen et al. 2003).

Identification of *RPE65* and lecithin retinol acyltransferase (*LRAT*) as disease-causing genes in LCA and childhood-onset retinal dystrophy (CSRD) prompted us to consider proteins of the visual cycle as candidate genes in LCA (Gu et al. 1997; Thompson et al. 2001). For this reason, genes encoding the RPE-specific RDH10 and RDH11 proteins and the photoreceptor-specific genes *RDH8* and *RDH12–RDH14* were regarded as strong candidates, especially since *RDH11* and *RDH12* map close to LCA3 on 14q23.3 (Stockton et al. 1998). Here we report on photoreceptor-specific *RDH12* gene mutations in a significant subset of patients with LCA. Interestingly, all patients with LCA carrying *RDH12* mutations had severe, congenital (yet progressive) rod-cone dystrophy, delineating the first genotype-phenotype correlation in this subtype of LCA.

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Material and Methods

Patients

Minimum inclusion criteria for LCA were (1) severe impairment of visual function, detected at birth or during the first months of life, with pendular nystagmus, roving eye movements, eye poking, inability to follow light or objects, and normal fundus; (2) extinguished electroretinogram responses; and (3) exclusion of ophthalmological or systemic diseases sharing features with LCA. Detailed clinical data were required for each patient—namely, (1) age at and mode of onset; (2) light behavior since birth; (3) natural history of the visual impairment since the first months of life, including the subjective impressions of the parents; (4) refraction data; (5) ophthalmologic findings (anterior chamber and fundus); (6) visual acuity (when measurable); and (7) electrophysiology recordings. The course of the disease was determined by interviewing the patients or their parents, and a pedigree was established.

Our series of 179 unrelated patients with LCA has been previously divided into two groups on the basis of the clinical course of the disease (Hanein et al. 2004). In group A, we have included the patients with congenital stationary cone-rod dystrophy, and group B includes the patients with severe yet progressive rod-cone dystrophy. We have previously shown that no mutation is found in 59/179 patients belonging to group A and 35/179 patients belonging to group B (Hanein et al. 2004). These individuals, as well as 16 other unrelated patients with LCA in whom no mutation has been found (group A, $n = 7$; group B, $n = 9$), were included in the present study (group A, $n = 66$; group B, $n = 44$; total, $n = 110$).

Genomic DNA was extracted from whole blood or immortalized lymphoblast cell lines of patients, through use of standard methods. When a mutation was identified, parents and other family members were examined, when available. Genomic DNA of 196 unrelated healthy individuals of French ancestry were used as controls.

Mutational Screening

The study of the *LRAT* and *RDH* genes was performed on genomic DNA through use of primers designed to flank the splice junctions of each coding exon (table 1). After standard PCR amplification (conditions available on request), products were screened for mutations through use of denaturing high-performance liquid chromatography (DHPLC). Heteroduplex formation was induced by heat denaturation of PCR products at 94°C for 10 min, followed by gradual reannealing from 94°C to 25°C over 30 min. DHPLC analysis was performed with the WAVE DNA fragment analysis system (Transgenomic). PCR products were eluted at a flow rate of 0.9 ml/min with a linear acetonitrile gradient. The values of the buffer gradients (buffer A: 0.1 M triethylammonium acetate; buffer B: 0.1 M triethylammonium acetate/25% acetonitrile), start and end points of the gradient, and melting temperature predictions were determined by WAVEMAKER software (Transgenomic). Optimal run temperatures were empirically determined. Mobile-phase temperatures were assessed, within a 5°C window above and below the suggested run temperature, on the basis of the melting profile.

PCR fragments displaying DHPLC abnormal profiles were further sequenced using the Big Dye Terminator Cycle Sequencing Kit v2 (ABI Prism, Applied Biosystems) on a 3100 automated sequencer.

Mutation Nomenclature

The adenine (A) of the start codon (ATG) of the *RDH* cDNA was assigned as nucleotide 1 (GenBank accession numbers: *RDH8,* NM_015725; *RDH10,* BC067131; *RDH11,* BC011727; *RDH12,* BC025724; *RDH13,* BC009881; and *RDH14,* BC009830).

Results

No *RDH12* mutations were found in patients with LCA presenting with congenital stationary cone-rod dystrophy (group A), but homozygosity or compound heterozygosity for 11 distinct *RDH12* mutations were found in 8/44 patients with LCA who were affected with the congenital severe yet progressive rod-cone dystrophy form of the disease (group B; fig. 1). Mutations included two nonsense mutations, one splice-site mutation, seven missense mutations, and one frameshift deletion (table 2). The frameshift deletion, a 5-bp deletion in *RDH12* exon 6, was found in four of eight unrelated families of French ancestry.

The seven missense mutations involved amino acids highly conserved in the mouse ortholog and in the genes *RDH8* and *RDH10–RDH14* (fig. 2). Two of them involved the histidine at position 151. In one, the mutation changed the positively charged histidine into a negatively charged amino acid (p.His151Asn in fig. 2); in the second, the histidine was changed into an uncharged amino acid (p.His151Asp in fig. 2). The mutations segregated with the disease and were absent in 196 ethnically matched control individuals (392 chromosomes).

None of the 110 patients with LCA was found to carry *LRAT, RDH8, RDH10, RDH11, RDH13,* or *RDH14* gene mutations. Only some silent changes and benign variants were identified (table 3).

Although a congenital nystagmus related to profound visual impairment was constantly present in all patients with LCA, it appeared retrospectively that the clinical course of LCA in patients carrying *RDH12* mutations

Table 1

Sequences of Forward and Reverse Primers Used for the Mutation Screening of the *LRAT, RDH8,* and *RDH10–RDH14* Genes

Gene and Exon Number	Primer Sequence (5′→3′)	
	Forward	Reverse
LRAT (3 exons, 2 coding exons):		
2.1	ACCTCTCCAAGACGCCCT	TGCTGGCCACTTTGACAATA
2.2	GGTGGTCTCCAACAAGCGTC	GGGAAGAGAAAAGGTCAGGG
3	TCTTCTTGGGTTTAGCCACC	TTTACATACAGAATACACAC
RDH8 (6 exons):		
1	GGATGAATGGTCAGAGTCAG	TAGGGGAGACAGTGCTGG
2	AACGCAAGATCACAGACACG	TGAGGGTCTATACTCAGACC
3	GGGAGTGTCTAGAAGTAATG	GGGGAGGATCAGACACTG
4	ACCCTGGAACCCACAAAGCC	CCCCTTTCGATGCCACCTCC
5	GGACAAAATAGGTCAGGGAG	CAACATACCTGAGCCACGTC
6	GTGGCTCAGGTATGTTGC	CATCCTTTGAATTAGATGTGG
RDH10 (6 exons):		
1	CCCGATTGCCGGGCTCGG	GGCGCGGGGTGGAAAGAGG
2	ATGTGACTCACTTTCTGCAC	TCCCAACCTTCTCATTAAGG
3	GTTTTGTGATCCTGGACTGG	TCTGGTGTACTTATCACAGG
4	TTAGTTTGGTTGGAGATAGG	CAGTTCCACATATTCTCC
5	GTACCCAAAATCCCATCACTC	TAAGACATCGGGCAGGCATG
6	CCATGCCTGCCCGATGTC	TGCTGATGTGCACTGGACTG
RDH11 (7 exons):		
1	AAGCCATAGTCGGCGAGCAA	CCGCAACAAGAATTCTCAAG
2	GAACCTACTGGCTGAGACAG	GAATCATCATTACTGTGAGG
3	TAGATTTATAATGCCAGCTC	GTTGAATCTGCCATGTTGAC
4	AAGATGTAATAGCCTTGGCT	CAAGAAGCCTCAATCTGACC
5	CACGACTCCTGTCATTCCTA	TGTGGCTTTTACCTGCCTCT
6	TTGGGCTATTCTGCAAAATC	CCAAATTATCTCCTTTGAGC
7	TGGCAGATGGCAGACTTCAT	GACGAATCTGGCAGTACACT
RDH12 (7 exons):		
1	CAGGAACCTGAGCCAGAGC	TTTCTCCTCTGTCAGCCTCC
2	CGTATCTTAGTGTGAGCTCG	GAATTTCTAGTCAGAGCCCC
3	CCAGTCCCAAGCTCACTTAC	AGGGTGGAGCAGCCACTC
4	ATTATGCAGGTCTGTTACAG	CTCCACATTTACACAGTGTC
5	TCCTCTTGGCTCCCACATGC	CCCAAGTTGCTGTGGACCTC
6	TGTGTATTTTGCTGCAGGAG	GATGAACAGCCCAGCGAG
7	GGGACCATAAAGATTTCCAG	GATCAGAGCAGGCAGGATTC
RDH13 (8 exons, 5 coding exons):		
4	GGTCAGTACCCAGGAGTGG	CACTTCTCAGAGCCTGGCC
5	GCTGGTGCATCAGGCTGG	CACTTTGGGAGGACGACG
6	GTGCTGGGATTTTAGGTGTG	CTCTAGGCTCAGAGTAAAGC
7	CTCCCAGGTGAGGCTGGAC	GGCTGAGAAAGCAGGGGTGG
8	GCGAGTGTGGACTAAATGGCC	GCTGTCCTCGGTCTGGAG
RDH14 (2 exons):		
1.1	GTTCCGGTAAGGCGGCGG	ACCCGCCGCCTCCTCGGC
1.2	CTACTGCGCCTGGGAGCG	TCCCTCGCGGCTCAGCCCCA
2.1	GTGTTCTTAATAATTCTGCC	ACAATACCAGGATGCAACAC
2.2	GCTTTTGTTATAGCCGGAGC	CACAGATATAACTGATATGCAG

was initially similar to that of patients with LCA harboring *RPE65* mutations—namely, mild or no hyperopia (or even mild myopia), as well as pigmentary deposits in the peripheral retina followed by a transient improvement of visual acuity (VA) that could reach 1/10 to 2/10 (or more), prompting one to even question the diagnosis of LCA. In patients with *RPE65* mutations, this transient improvement could last for >15 years, whereas it lasted <10 years in the eight patients with *RDH12* mutations (and <5 years in two of eight families). Finally, this severe and rapid progression of the disease was consistently associated with development of a large and severe macular atrophy in patients carrying *RDH12* mutations.

Discussion

The rod and cone photoreceptor cells of the retina utilize a unique photosensitive vitamin A analog (11-*cis* retinal) to absorb photons and initiate the process of phototrans-

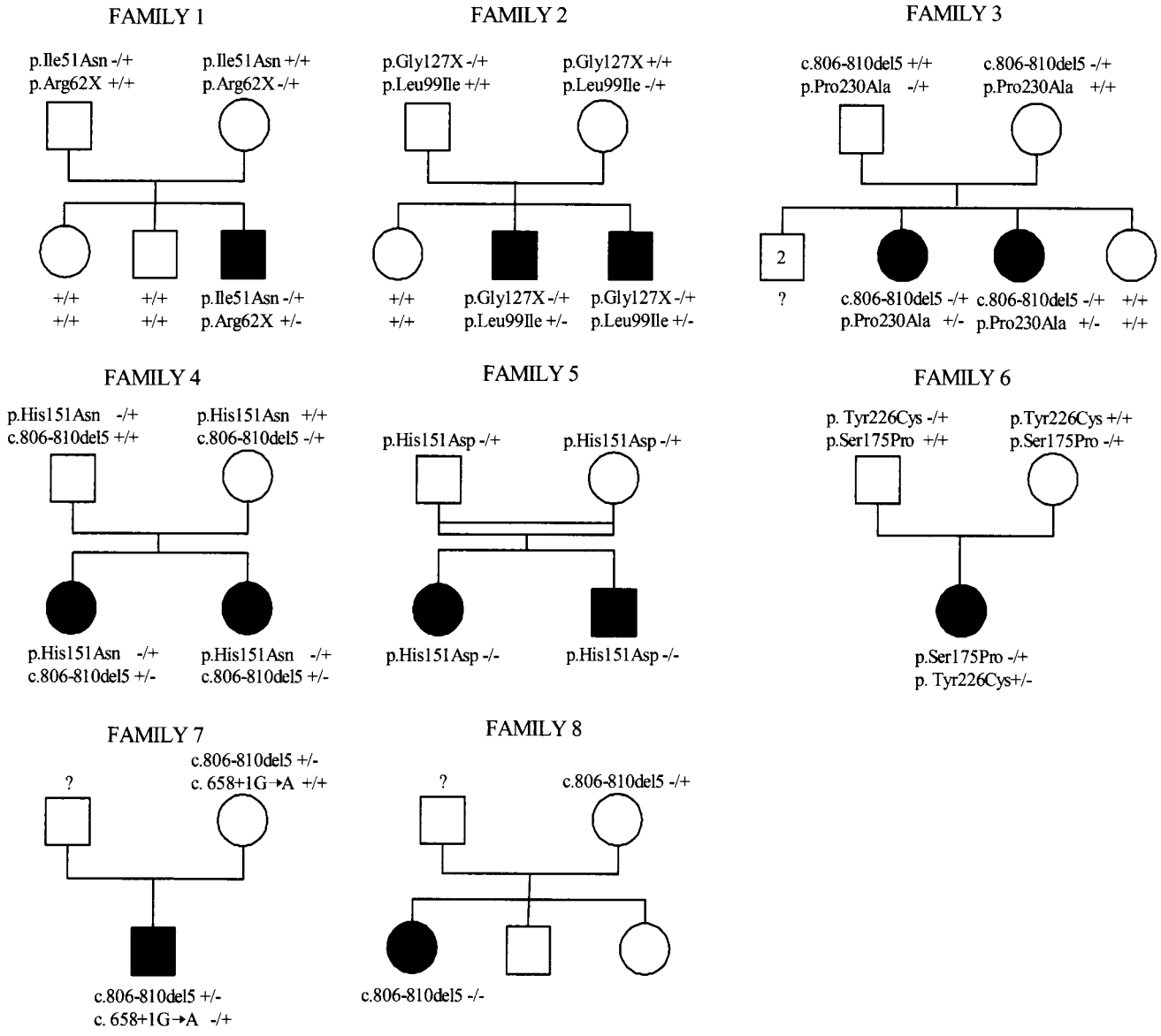

Figure 1 Pedigrees and segregation analysis of *RDH12* disease-causing mutations in eight families with LCA

duction. Dietary vitamin A (all-*trans* retinal) is converted into the 11-*cis* retinal photoactive chromophore in the RPE, whereas the reception of photons occurs in the outer segments of photoreceptors. The cycling of retinoid analogs between these two cell types is defined as the "visual cycle." Mutations in genes encoding several proteins involved in this process have been shown to cause autosomal recessive retinal dystrophies—namely, (1) retinaldehyde-binding protein 1 (RLBP1) in RP and *retinitis punctata albescens;* (2) the fourth member of the A subfamily of the ATP-binding cassette superfamily (ABCA4) in Stargardt disease, *fundus flavimaculatus,* RP, and cone-rod dystrophy (CRD); (3) 11-*cis* retinol dehydrogenase (RDH5) in *fundus albipunctatus;* (4) LRAT in early-onset severe RP; and (5) RPE65 in early-onset severe RP and in the congenital severe yet progressive rod-cone dystrophy form of LCA (Hanein et al. 2004; for review, see Haeseleer et al. 2002; Kuksa et al. 2003; Thompson and Gal 2003).

Because a gene encoding a protein of the visual cycle, RPE65, accounts for ~6% of patients with LCA in our series (Hanein et al. 2004), we hypothesized that a fraction of hitherto unexplained LCA cases could be ascribed to genes encoding other proteins of the visual cycle. Here, we report on nonsense or missense mutations and frameshift deletions of the photoreceptor-

Table 2

***RDH12* Mutations, Silent Polymorphisms, and Benign Variants Identified in Patients Affected with LCA**

Type of Change, Family, and Allele Number	Exon	Base Change	Predicted Amino Acid Change
Mutations:			
Family 1:			
1	2	c.184C→T	p.Arg62X
2	2	c.152T→A	p.Ile51Asn
Family 2:			
1	4	c.379G→T	p.Gly127X
2	3	c.295C→A	p.Leu99Ile
Family 3:			
1	6	c.806-810delCCCTG	p.Ala269fsX270
2	6	c.687C→G	p.Pro230Ala
Family 4:			
1	6	c.806-810delCCCTG	p.Ala269fsX270
2	5	c.451C→A	p.His151Asn
Family 5:			
1	5	c.451C→G	p.His151Asp
2	5	c. 451C→G	p.His151Asp
Family 6:			
1	5	c.523T→C	p.Ser175Pro
2	6	c.677A→G	p.Tyr226Cys
Family 7:			
1	6	c.806-810delCCCTG	p.Ala269fsX270
2	5	c. 658+1G→A	Aberrant splicing
Family 8:			
1	6	c.806-810delCCCTG	p.Ala269fsX270
2	6	c.806-810delCCCTG	p.Ala269fsX270
Silent polymorphisms:			
Family 1	5	c.482A→G	p.Gln161Arg
Family 2	Intron 3	187+60G→A	…
Family 3	Intron 3	187+54A→T	…
Family 4	Intron 3	188−14insT	…
Family 5	Intron 5	448+24A→G	…
Family 6	Intron 6	659−25T→A	…

specific *RDH12* gene in 8/44 patients with LCA affected with the congenital severe yet progressive rod-cone dystrophy form of LCA (group B).

Most interestingly, the course of the disease differed from that in patients harboring mutations in other LCA genes. Indeed, unlike *RPE65* or *TULP1* mutations, *RDH12* mutations caused a severe macular atrophy leading to a severe visual loss before the end of the 2nd decade of life. Moreover, unlike patients with CRB1, they displayed mild or no hyperopia (Hanein et al. 2004). Interestingly, no mutation was found in patients with LCA who were affected with the congenital severe stationary cone-rod dystrophy form of the disease (group A).

The *RDH12* gene maps to chromosome 14q23, 8 Mb from the LCA3 locus (Stockton et al. 1998; University of California Santa Cruz Genome Bioinformatics Web site). One cannot exclude, therefore, *RDH12* as the disease gene in the large consanguineous family of Arabian origin that defined the LCA3 locus. Indeed, several examples of gene location reassignment have recently been reported (e.g., *RP15* [MIM 300029]), and clinical findings reported in the LCA3 family are similar to those in patients with *RDH12* mutations: both displayed moderate hypermetropia with fundus evidence of diffuse bone spicule clumps in the mid and far retina and macular atrophy (VA was poor but could be evaluated as <2/500 [Stockton et al. 1998]).

Unlike *RPE65*, *RDH12* is specifically expressed in photoreceptor cells (Haeseleer et al. 2002). It has recently been suggested that *RDH12* might play a pivotal role in the formation of 11-*cis* retinal from 11-*cis* retinol, during regeneration of cone visual pigments (Haeseleer et al. 2002). The involvement of *RDH12* in a dynamic process (the regeneration of retinal) could account for the progressive nature of the disease, which contrasts with the congenital severe stationary cone-rod dystrophy form of LCA ascribed to the *GUCY2D*, *AIPL1*, or *RPGRIP1* genes (group A). In addition, the

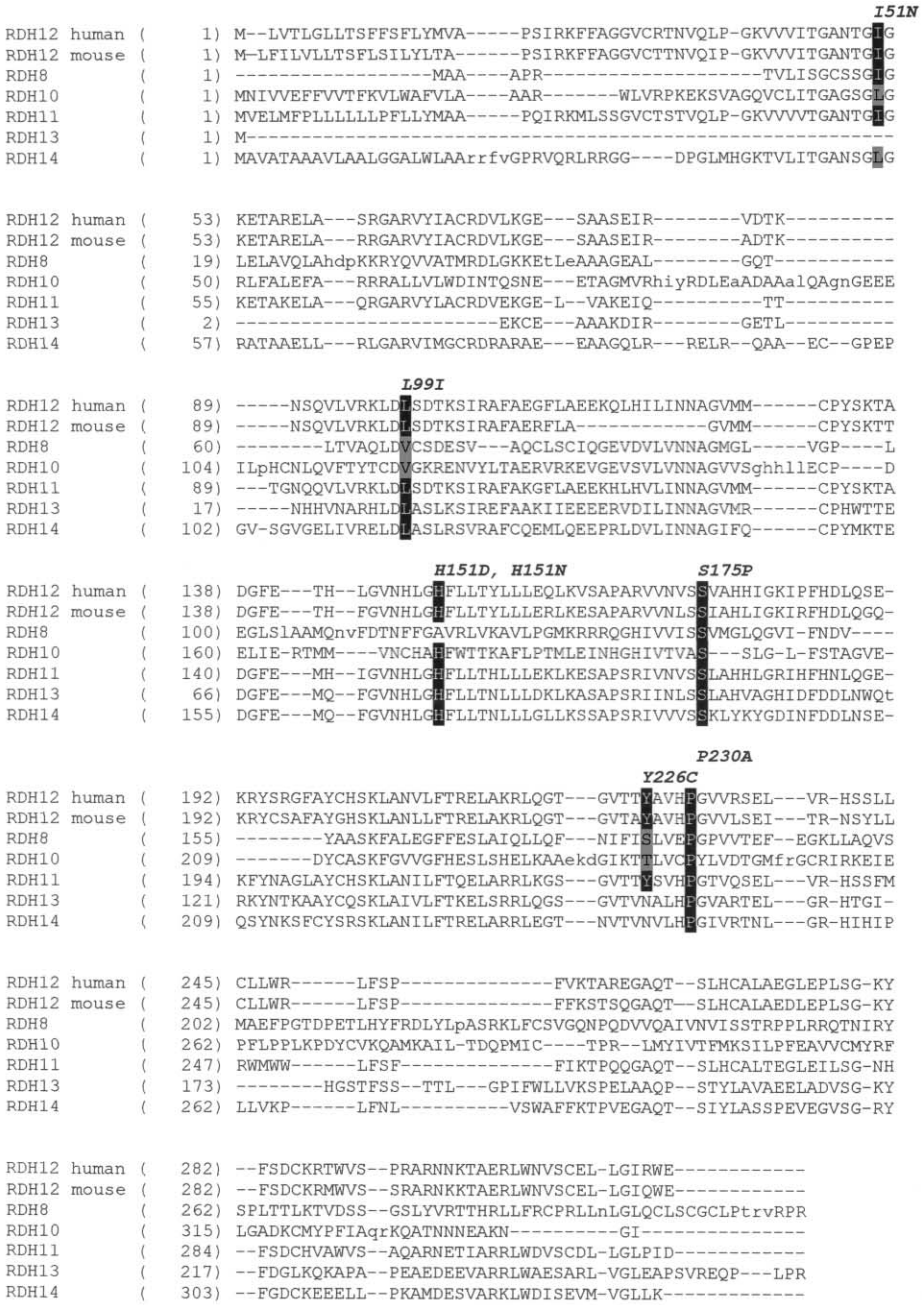

Figure 2 Amino acid sequences of human and mouse *RDH12* and of human *RDH8, RDH10, RDH11, RDH13,* and *RDH14*, deduced from cDNA sequences (GenBank accession numbers BC025724, BC016204, NM_015725, BC067131, BC011727, BC009881, and BC009830, respectively) and conservation of amino acids mutated in patients with LCA.

Table 3

Silent Polymorphisms and Benign Variants Identified in *LRAT, RDH8,RDH10, RDH11, RDH13,* and *RDH14*

Gene and Family Number	Exon	Base Change	Predicted Amino Acid Change	Frequency (%)
LRAT:				
1	2	c.525T→G	p.Ser175Pro	3
RDH8:				
1	2	c.237T→C	p.Cys79Cys	1
2	3	c.408C→G	p.His136Gln	35
RDH10:				
1	1	c.1−33G→A	None	1
RDH11:				
1	5	c.628A→G	p.Ile210Val	1
RDH13:				
1	4	c.63C→T	p.Asn21Asn	1
2[a]	4	c.63C→A	p.Asn21Lys	
2[a]	4	c.64G→A	p.Ala22Asn	11
2[a]	Intron 5	c.127+42C→T		
3	6	c.427C→T	p.Leu143Leu	2
4	8	c.651C→G	p.Phe217Leu	3
5	8	c.771C→A	p.Pro257Pro	2
RDH14:				
1	2	c.855T→C	p.Thr285Thr	8
2	2	c.838G→A	p.Val280Ile	1

[a] Three nucleotide changes were found on the same *RDH13* allele; the frequency value (11%) is for all three combined.

role of RDH12 in cones might explain why loss of visual acuity is the most progressive feature of the disease.

In conclusion, the congenital severe yet progressive rod-cone dystrophy form of LCA results from an impairment of the visual cycle in 10.5% of cases. To date, the treatment of animal models lacking *RPE65* has been the subject of intense interest. Promising results have already been reported through use of either gene replacement (for review, see Bennett 2004) or pharmaceutical delivery of 9-*cis* retinal, a functional analog of 11-*cis* retinal (Van Hooser et al. 2000, 2002). Although photoreceptor cells appear to be less accessible than RPE cells to therapeutic intervention, one can expect that 11-*cis* retinal to the retina would rescue the enzyme deficiency in future *RDH12*-deficient animal models.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *RDH8* [accession number NM_015725], *RDH10* [accession number BC067131], *RDH11* [accession number BC011727], *RDH12* [accession number BC025724], *RDH13* [accession number BC009881], *RDH14* [accession number BC009830], and mouse *RDH12* [accession number BC016204])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *GUCY2D, RPE65, CRX, AIPL1, RPGRIP1, CRB1, TULP1, LCA3, LCA5,* and *RP15*)

University of California Santa Cruz Genome Bioinformatics, http://genome.ucsc.edu/ (for the working draft of the human genome)

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