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Identification of a novel C-terminal extension mutation in *EPHA2* in a family affected with congenital cataract

Linda M. Reis,[1] Rebecca C. Tyler,[1] Elena V. Semina[1,2]

[1]Department of Pediatrics and Children's Research Institute, Medical College of Wisconsin, Milwaukee, WI; [2]Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI

Purpose: Congenital cataracts occur in 3–4 per 10,000 live births and account for 5% to 20% of pediatric blindness worldwide. With more than 37 genes known to be associated with isolated congenital cataract, whole exome sequencing (WES) was recently introduced as an efficient method for screening all known factors.
Methods: Whole exome analysis in two members of a four-generation pedigree affected with dominant congenital cataract and glaucoma was performed by WES; co-segregation analysis of identified variants in all pedigree members was completed by Sanger sequencing.
Results: Analysis of the WES data identified a novel pathogenic variant in *EPHA2*, c.2925dupC, p.(Ile976Hisfs*37), that demonstrated complete cosegregation with the phenotype in the pedigree. The mutation occurs in the final amino acid before the stop codon of the normal EPHA2 protein and is predicted to produce a mutant protein with an erroneous C-terminal extension of 35 amino acids. Nine other families have been previously reported with dominant congenital/juvenile cataracts and mutations in *EPHA2*. Two additional likely loss-of-function variants in genes known to cause dominant congenital cataract were considered and excluded based on control data and cosegregation analysis: a nonsense variant in *CYRBB3*, c.547G>T, p.(Glu183*), and a splicing variant in *CRYBA2*, c.446+1G>A.
Conclusions: Identification of a novel pathogenic *EPHA2* allele further implicates this gene in congenital cataract. This is only the second *EPHA2* mutation that specifically affects the most C-terminal PSD95/Dlg/ZO1 (PDZ)-binding motif and the third pathogenic allele associated with an erroneous C-terminal extension beyond the normal stop codon.

Congenital cataracts occur in 3–4 per 10,000 live births in the United States and account for 5% to 20% of blindness in children worldwide [1]. Congenital cataract can occur as an isolated condition or in association with syndromic anomalies; approximately 10% to 25% are thought to be due to genetic causes [2]. With more than 37 genes known to be associated with nonsyndromic cataract, whole exome sequencing (WES) was recently introduced as an efficient method for screening all known genes, as well as providing the opportunity for novel gene identification [3]. Although this approach offers the advantage of a comprehensive exome and genome examination to identify causative mutations, interpretation of the large volume of identified variants may be complicated, especially for novel changes [4-6].

Autosomal dominant is the most common inheritance pattern for familial nonsyndromic cataracts; however, autosomal recessive and X-linked inheritance has also been reported [7,8]. Interestingly, eight cataract genes have been linked to dominant and recessive patterns of inheritance: *CRYAB* (OMIM 123590), *CRYAA* (OMIM 123580), *CRYBB1* (OMIM 600929), *CRYBB3* (OMIM 123630), *GJA8* (OMIM 600897), *SIL1* (OMIM 608005), *HSF4* (OMIM 602438), and *EPHA2* (OMIM 176946) [3,7,9]. Although some genes, such as *CRYBB1*, show a clear distinction between the two types of alleles with dominant alleles likely having a dominant negative effect (missense, late truncating) and recessive alleles likely resulting in null alleles (early truncating and initiation codon mutations) [10-12], for many genes, such as *CRYBB3*, there is no obvious distinction between the two types of alleles [3].

The EPHA2 protein belongs to the ephrin receptor group of the protein-tyrosine kinase family, which is important in cell–cell interactions, including effects on neuronal cell migration, cell proliferation, survival, differentiation, and secretion [13,14]. Ephrin receptors are type-I transmembrane proteins; their primary ligand, ephrin, is also membrane bound, and the complex is unique in its ability to generate bidirectional signals into both cells [13,14]. The ephrin receptors and ephrin ligands are divided into two groups, A and B; crossover binding between classes can occur [13,15]. The EphA2 protein contains an extracellular domain and an intracellular domain. The extracellular domain is divided into an N-terminal ligand binding domain, a cysteine-rich domain, and two fibronectin type III repeats; the intracellular domain consists of the juxtamembrane region, a tyrosine kinase

Correspondence to: Elena V. Semina, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509, Phone: (414) 955-4996; FAX: (414) 955-6329; email: esemina@mcw.edu

domain, a sterile-α-motif (SAM) domain, and a PSD95/Dlg/ZO1 (PDZ)-binding motif [14].

EPHA2 expression has been shown in the lens of wild-type mice, with highest expression in the cortical lens fiber cells [16]. Mutations in *EPHA2* have been associated with autosomal dominant congenital/juvenile cataract and autosomal recessive congenital cataract. In dominant families, a frameshift mutation and a splicing mutation were associated with congenital cataract (four families) while the age of diagnosis in families with missense mutations ranged from birth to 15 years of age (four families) [17-20]. An additional rare heterozygous missense variant was seen in a family with onset at 17 and 20 years of age as well as two controls with age-related cataracts [20]. In recessive families, homozygous missense mutations were associated with congenital cataracts (two families) [9,21]. In addition, several polymorphisms in *EPHA2* have been associated with increased risk for age-related cataracts [16,17,22-24]. We present the identification of a novel *EPHA2* pathogenic allele along with two rare variants in other known cataract genes through WES in a single family with dominant congenital cataract with or without glaucoma.

METHODS

Human subjects: Thirteen members of a Caucasian family affected with congenital cataract with or without glaucoma in three generations (3 affected and 10 unaffected, 6 males and 7 females; Figure 1A) were recruited for the study through referral to the study coordinator; all individuals were healthy other than the ocular diagnoses. Blood samples were collected in EDTA tubes and DNA extraction was performed via standard protocols using Qiagen Puregene products (Valencia, CA). This study adhered to the tenets of the Declaration of Helsinki and the ARVO statement on human subjects and was approved by the Institutional Review Board at the Children's Hospital of Wisconsin with written informed consent obtained from every subject or their legal representative (minors).

Whole exome sequencing and analysis: WES was completed through Perkin Elmer (Branford, CT) using Agilent Sure Select v4 (proband) or v4 with untranslated region (UTR; daughter; Santa Clara, CA) for exome capture and the Illumina HiSeq 2000 system (San Diego, CA) for sequencing; variants in 37 known cataract genes were reviewed as previously described using the Geospiza GeneSifter Analysis program hosted through Perkin Elmer Bioinformatics using the GATK V2.10 pipeline [3]. Variants of interest were investigated for their presence or absence in the NCBI Single Nucleotide Polymorphism Database (dbSNP), 1000 Genomes project (1 kg), and frequency in the Exome Variant Server (EVS).

Sanger sequencing: Variants of interest were confirmed with independent Sanger sequencing reactions, and family members were tested for cosegregation using gene-specific primers and PCR conditions as specified in Table 1 with betaine solution (Sigma Aldrich, St. Louis, MO) or FailSafe Mix (Epicenter Biotechnologies, Madison, WI) added to some reactions according to the manufacturer protocols and as described in Table 1. PCR products were sequenced in both directions using the ABI 3730XL sequencer and protocols (Applied Biosystems/Life Technologies, Carlsbad, CA). Sequences were reviewed manually and using Mutation Surveyor (SoftGenetics, State College, PA).

RESULTS

Clinical features: The proband (II:2) was diagnosed with bilateral congenital cataract with cataract extraction in infancy; at age 6 she lost vision in one eye due to undetected aphakic glaucoma. Her daughter (III:4) had bilateral congenital zonular cataracts with cataract extraction at 7 and 11 weeks of age; reextraction was required at 1.5 and 2 years of age. She subsequently developed aphakic glaucoma at age 8 with intraocular pressure in the 40–50 mmHg range. She has been treated with eye drops, shunts, laser surgery, and corneal transplant. The proband's granddaughter (IV:2) had cataracts diagnosed at 10 days of age with cataract extraction at 3 and 4 weeks of age; she is currently 7 years old and shows no signs of glaucoma. All three affected family members are aphakic and use contact lenses or glasses to correct vision.

Whole exome sequencing results: WES was performed in the proband and her daughter. The average mean read depth for the whole exome was 78.5X and 75X with 85.6% and 90.9% of bases with a read depth >10X in the proband and her daughter, respectively. Similar to the previous report, the 37 known cataract genes showed good coverage with the exception of *MAF* (OMIM 177075), *FOXE3* (OMIM 601094), and *PITX3* (OMIM 602669), which were screened with Sanger sequencing [3]. Review of the 37 known cataract genes in the proband identified a novel frameshift variant in the ephrin receptor (*EPHA2*) gene (Figure 1) and two rare variants in the beta-B3 crystallin (*CYRBB3*) and beta-A2 crystallin (*CRYBA2*) genes (Figure 2).

Variant analysis: The novel frameshift variant in *EPHA2*, c.2925dupC, p.(Ile976Hisfs*37), occurs in the final amino acid before the stop codon of the normal EPHA2 protein and is predicted to produce a mutant protein with an erroneous C-terminal extension of 35 amino acids. This variant was not seen in 8,600 European American alleles or 4,406

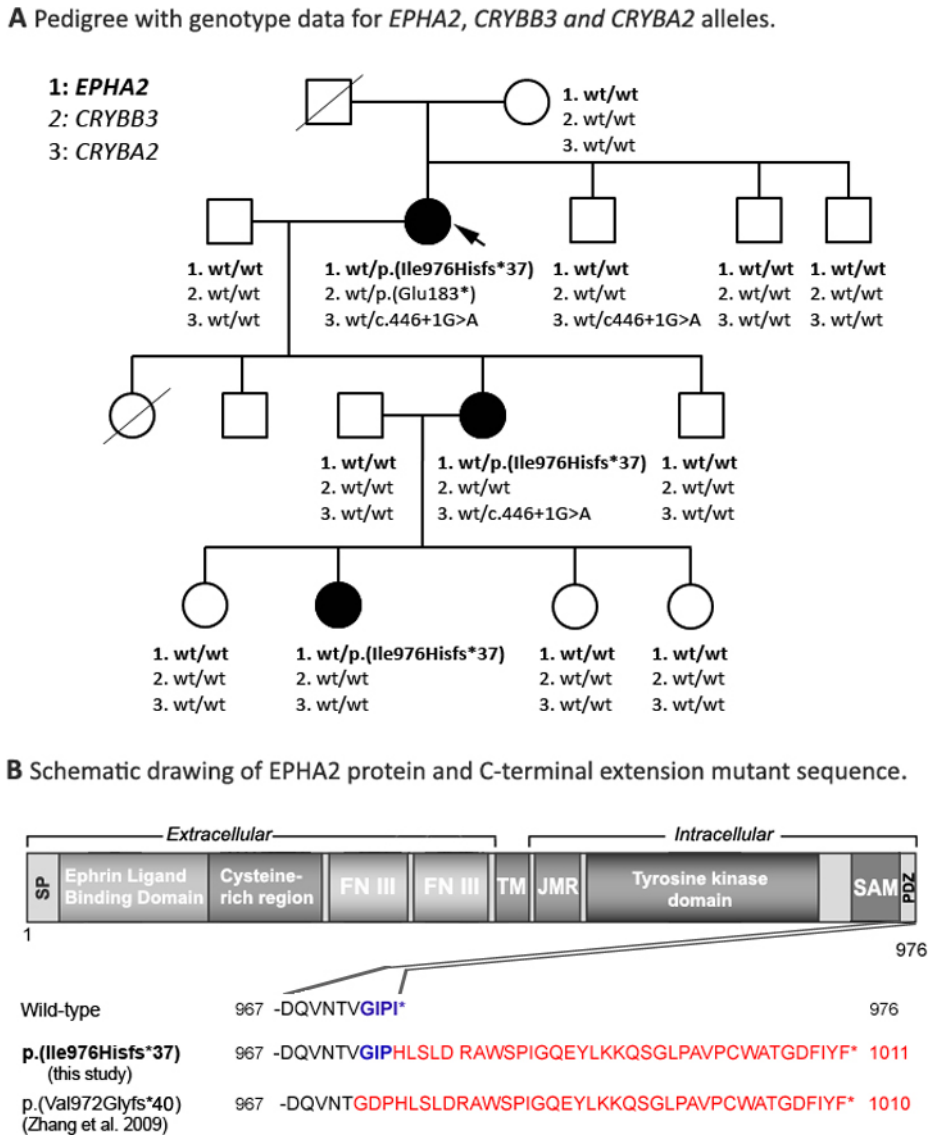

Figure 1. Cosegregation analysis of the identified alleles and schematic representation of EPHA2 wild-type and mutant proteins. **A**: Pedigree with genotype data for *EPHA2*, *CRYBB3*, and *CRYBA2* alleles. Individuals affected with congenital cataract are indicated by shaded symbols. Genotyping results for the three alleles identified in the family are shown below each individual tested: 1 = *EPHA2;* 2 = *CRYBB3;* 3 = *CRYBA2*. The pathogenic allele is indicated in bold. The proband is indicated with an arrow; wt, wild-type allele at the variant position. **B**: Schematic drawing of the EPHA2 protein and C-terminal extension mutant sequences. The EPHA2 domain structure is shown at the top; SP = signal peptide, FN III = fibronectin III type repeats, TM = transmembrane domain, JMR = juxtamembrane region, SAM = sterile alpha motif, PDZ = PDZ-binding motif. C-terminal sequences of EPHA2 wild-type and frameshift mutants are shown at the bottom with the PDZ-motif residues indicated in blue and erroneous amino acids in red.

African American alleles reported in EVS and is not reported in the dbSNP or 1000 Genomes. A logarithm of the odds (LOD) score of 2.71 was obtained using the available pedigree and the identified *EPHA2* allele as a rare phase known marker [25], which provides additional evidence to support pathogenicity.

The *CRYBB3* nonsense variant c.547G>T, p.(Glu183*; rs147328317) is located in the final exon of *CRYBB3* and thus would be expected to escape nonsense-mediated decay [26] and produce a CRYBB3 protein lacking 28 C-terminal amino acids. The *CRYBA2* splicing variant c.446+1G>A (rs142969645) affects the donor splice site between exons 3 and 4. These two rare variants are present in EVS in 0.08% (*CRYBB3*) and 0.07% (*CRYBA2*) of European Caucasian alleles (7/8,596 and 6/8,600 alleles, respectively).

Table 1. Primers and conditions for *EPHA2, CRYBB3* and *CRYBA2* PCR amplification.

Gene	Primers (5′-3′)	PCR size (bp)	Special conditions
EPHA2	F: CAGCGACATCAAGAGGATTG	285	Betaine solution; annealing at 60 °C
	R: TGGTCATCTCCTCAGTTCAG		
CRYBA2	F: AGTGAGGCAGAGGATGTATC	367	FailSafe Mix D; annealing at 60 °C
	R: TCCAGTCTGACTCCATCATC		
CRYBB3	F: TGTAGGCAGGCAGAGTGCAT	501	Betaine solution; annealing at 58 °C
	R: AGTCTCAGAACACTCAAGC		

Sanger sequencing results: All three variants were confirmed with Sanger sequencing in the proband. The novel frameshift mutation in *EPHA2* was present in all three affected family members and was not present in eight unaffected family members, including the unaffected mother, brothers, son, and granddaughters of the proband (Figure 1A). The *CRYBB3* variant was present in the proband only, and the *CRYBA2* variant was seen in the proband, her affected daughter, and an unaffected brother, but not the affected granddaughter (Figure 1A).

DISCUSSION

The novel *EPHA2* frameshift mutation identified in this family, c.2925dupC, p.(Ile976Hisfs*37), affects the intracellular region of the protein, specifically the potential PDZ-binding motif that encompasses amino acids 973–976 (Figure 1B); this motif is predicted to bind PDZ domain-containing proteins that promote the assembly of multiprotein signaling complexes at the membrane. Other intracellular domains include the sterile alpha motif (SAM), tyrosine kinase domain, and juxtamembrane region that are involved in interactions with signaling proteins and other important functions [27]. The c.2925dupC, p.(Ile976Hisfs*37) mutation disrupts the PDZ-motif and, because of the additional aberrant C-terminal sequence, might affect proper folding and function of other EPHA2 domains as well. This is only the second *EPHA2* mutation that specifically affects the potential PDZ-motif and the third pathogenic allele associated with an erroneous C-terminal extension beyond the normal stop codon. The previously reported alleles include frameshift mutation c.2915_2916delTG, p.(Val972Glyfs*40), located four codons upstream of the mutation reported here, which completely removes the potential PDZ-motif sequence (Figure 1B) [18]. In addition, the recurrent splicing mutation c.2826–9G>A, seen in three independent families, was shown to result in an insertion of a 7 bp intronic sequence into the mRNA and, consequently, the addition of 71 novel amino acid residues at the C-terminus; this mutation affects the SAM domain and the PDZ-binding motif [18,20]. Thirty-six residues of the erroneous C-terminal tail are identical between these three mutant alleles. Previous studies demonstrated reduced protein stability and function for the c.2915_2916delTG frameshift and c.2826–9G>A splicing mutations [27]. Interestingly, mutations that extend the length of the mutant protein have been reported in two other genes that cause dominant congenital cataracts, *PITX3* and *FOXE3* [28,29]. Although the *PITX3* mutations disrupt a significant portion of the

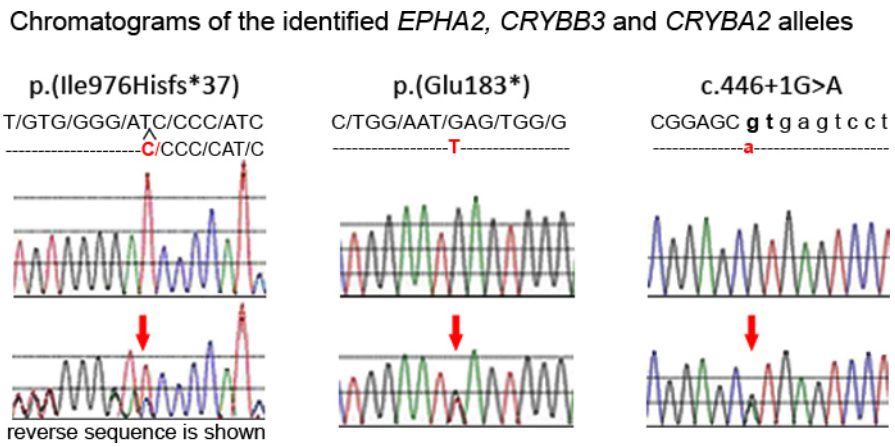

Figure 2. Chromatograms of the *EPHA2*, *CRYBB3*, and *CRYBA2* alleles. The variant position is indicated with a red arrow.

protein sequence in addition to extending the length of the protein [28,30-32], four dominant *FOXE3* mutations occur at or within five amino acids of the stop codon [29,33-35]. Given the evidence of pathogenicity and complete cosegregation in the pedigree, the *EPHA2* variant c.2925dupC, p.(Ile976Hisfs*37) was determined to be the pathogenic allele causing the congenital cataract in the family.

The congenital cataract phenotype reported in this family is consistent with the previously reported *EPHA2* mutations, but two individuals in the family were also affected with juvenile glaucoma, which has not been reported previously in families with *EPHA2* mutations [17-20]. Since glaucoma is reported in up to 30% of eyes following congenital cataract extraction [36,37], particularly when cataracts are removed early in life, it is possible that the glaucoma seen in two family members is simply a result of the cataract surgery. Review of whole exome data for the proband and her daughter for known congenital/juvenile glaucoma genes including *CYP1B1* (OMIM 601771), *MYOC* (OMIM 601652), *LTBP2*(OMIM 602091), and *TDRD7* (OMIM 611258) did not identify any rare/novel coding variants in these genes.

The two other rare likely loss-of-function variants in genes known to cause dominant congenital cataract, a nonsense variant in *CRYBB3* and a splicing variant in *CRYBA2*, were considered and excluded based on the control data and cosegregation analysis. Recessive and dominant missense mutations in *CYRBB3* have been reported in association with congenital cataract [3,38], and nonsense mutations in two other members of the *CRYBB* family, *CRYBB1* and *CRYBB2,* as well as *CRYGC* and *CRYGD*, are associated with autosomal dominant congenital cataracts [7]. A missense mutation in *CRYBA2* was recently reported to cause autosomal dominant congenital cataract with reduced penetrance [3], and multiple splicing mutations in another crystalline gene, *CRYBA1*, have been reported in association with autosomal dominant congenital cataracts [7]. Although both alleles have some evidence providing support for possible pathogenicity, both are present in EVS at about twice the frequency of congenital cataracts in the general population, which suggests these alleles are not highly penetrant dominant alleles for congenital cataracts. In addition, cosegregation analysis showed that neither variant was present in all three affected family members (Figure 1A). Based on these data, it was concluded that these variants are either rare polymorphisms or recessive alleles that do not contribute to the cataracts in this family.

Conclusion: In this paper, we report the identification of a novel *EPHA2* mutant C-terminal extension allele associated with dominant congenital cataracts and glaucoma. The other identified variants in known cataract genes, a nonsense change in *CRYBB3* and a splicing alteration in *CRYBA2,* were excluded as causative based on their frequency in the general population and cosegregation analysis and do not appear to have any effect on the cataract phenotype in the carriers of these additional alleles.

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