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A novel mutation in the connexin 46 (*GJA3*) gene associated with autosomal dominant congenital cataract in an Indian family

Kamlesh Guleria,[1] Karl Sperling,[2] Daljit Singh,[3] Raymonda Varon,[2] Jai Rup Singh,[1] Vanita Vanita[1]

[1]*Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar, India;* [2]*Institute of Human Genetics, Charité Humboldt University, Berlin, Germany;* [3]*Dr. Daljit Singh Eye Hospital, Amritsar, India*

Purpose: To identify the genetic defect in an autosomal dominant congenital cataract family (ADCC), having 18 individuals in four generations affected with embryonal cataract.
Methods: A genome wide scan using the GeneChip Human Mapping 10K Array, version 2 was performed on DNA samples from eight affected and two unaffected members of an ADCC family having 18 members in four generations affected with embryonal cataract. The region of potential linkage delimited by single nucleotide polymorphic (SNP) markers was analyzed using fluorescently labeled microsatellite markers. Mutation screening was performed in the candidate gene by bidirectional sequencing of amplified products.
Results: By whole genome screening linkage in this family, the genetic defect was located to a region of chromosome 13q11 which contains the candidate gene *connexin 46* (*GJA3*) for ADCC. Sequencing of the coding region of *GJA3* showed a novel heterozygous 98G>T change resulting in the substitution of highly conserved arginine by leucine at codon 33 (R33L), located in the first transmembrane domain of *GJA3*. This nucleotide change was not seen in any unaffected members of this family nor in 50 unrelated control subjects.
Conclusions: The present study describes a novel mutation (R33L) in the *GJA3* associated with finely granular embryonal cataract. These findings expand the mutation spectrum of *GJA3* in association with congenital cataract.

Congenital cataract is one of the significant causes of visual impairment in infants. It is clinically and genetically a highly heterogeneous lens disorder with autosomal dominant inheritance being most common. Congenital cataract can occur as an isolated anomaly or associated with other ocular or developmental anomalies. Its incidence is estimated to be between 2.2 and 2.49 per 10,000 live births [1,2]. In one-third of the cases, congenital cataract has been reported as a familial trait [3,4]. At least 35 loci and mutations in 15 genes have been identified to be involved in the pathogenesis of various forms of congenital and developmental cataracts [5].

The eye lens, an avascular organ, has developed an extensive cell to cell communication system via gap junction channels, which are encoded by connexin genes. The gap junction channels facilitate the exchange of ions, metabolites, signaling molecules, and other molecules with a molecular weight up to 1 kDa between adjacent cells [6]. In humans, more than 20 genes that code connexins of varying molecular mass, ranging between 25 and 62 kDa, have been identified. Three of these (connexin 43, connexin 46, and connexin 50; all belong to the α-connexin family) are expressed in the lens. Mutations in specific connexin genes have been associated with several diseases including genetic deafness, skin disease, peripheral neuropathies, heart defects, and congenital cataract [7]. Mutations in either connexin 46 or in connexin 50 have been linked with congenital cataract in humans [8,9] and mice [10-13]. In the present study, we detected linkage of finely granular embryonal cataract with the connexin 46 (*GJA3* gene, GenBank NM_021954) on chromosome 13q11 in a four-generation autosomal dominant congenital cataract (ADCC) family of Indian origin. Upon sequence analysis of *GJA3*, we identified a heterozygous G98T change resulting in the substitution of a highly conserved arginine by leucine at codon 33 (R33L) in the affected individuals of this family. This is a novel mutation not previously reported in congenital cataract.

Correspondence to: Dr. Vanita Vanita, Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar-143005, Punjab, India; Phone +183-2258802-09 Ext. 3277 or 3279; FAX: +183-2258863 or +183-2258820; email: vanita_kumar@yahoo.com

METHODS

Patient ascertainment and collection of genetic material: A four-generation family (CC-644) with autosomal dominant bilateral cataract was investigated at the Dr. Daljit Singh Eye Hospital, Amritsar, Punjab (India). Both affected and unaffected individuals underwent detailed ophthalmic examination including Snellen visual acuity, A-scan ultrasonography, and slit-lamp examination with dilated pupils. The phenotype was documented using slit-lamp photography. Twenty-five members of this family participated in the study and 15 of them were diagnosed as affected. The study protocols adhered to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of the Guru Nanak Dev University, Amritsar. After informed consent, 5-10 ml venous blood was collected from affected and unaffected members of this family and DNA was extracted for subsequent molecular genetic analysis.

Phenotype description: All unoperated affected family members showed bilateral cataract characterized as a band of

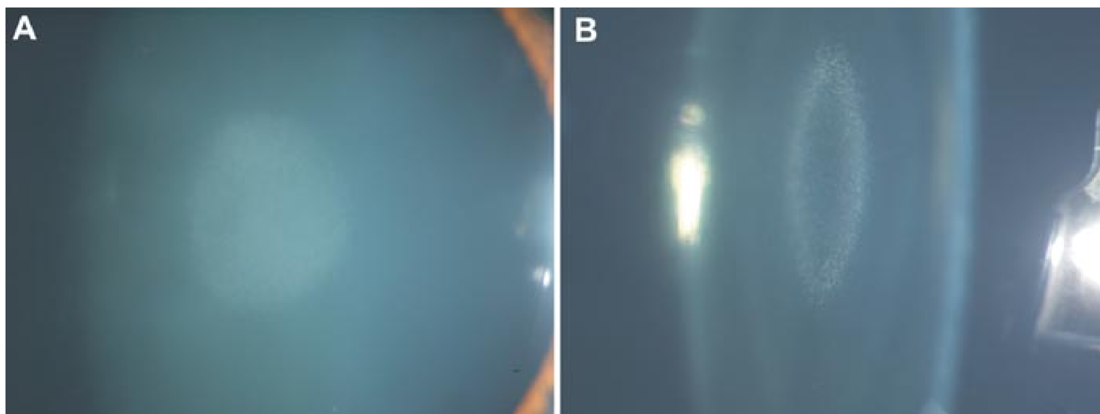

Figure 1. Slit-lamp photograph of affected individual 3-2. **A**: Oblique illumination showing a finely granular opacity in the embryonal nucleus. **B**: Optical section showing a slit-like or hollow discus-like clear area surrounded by a thick, finely granular opacity.

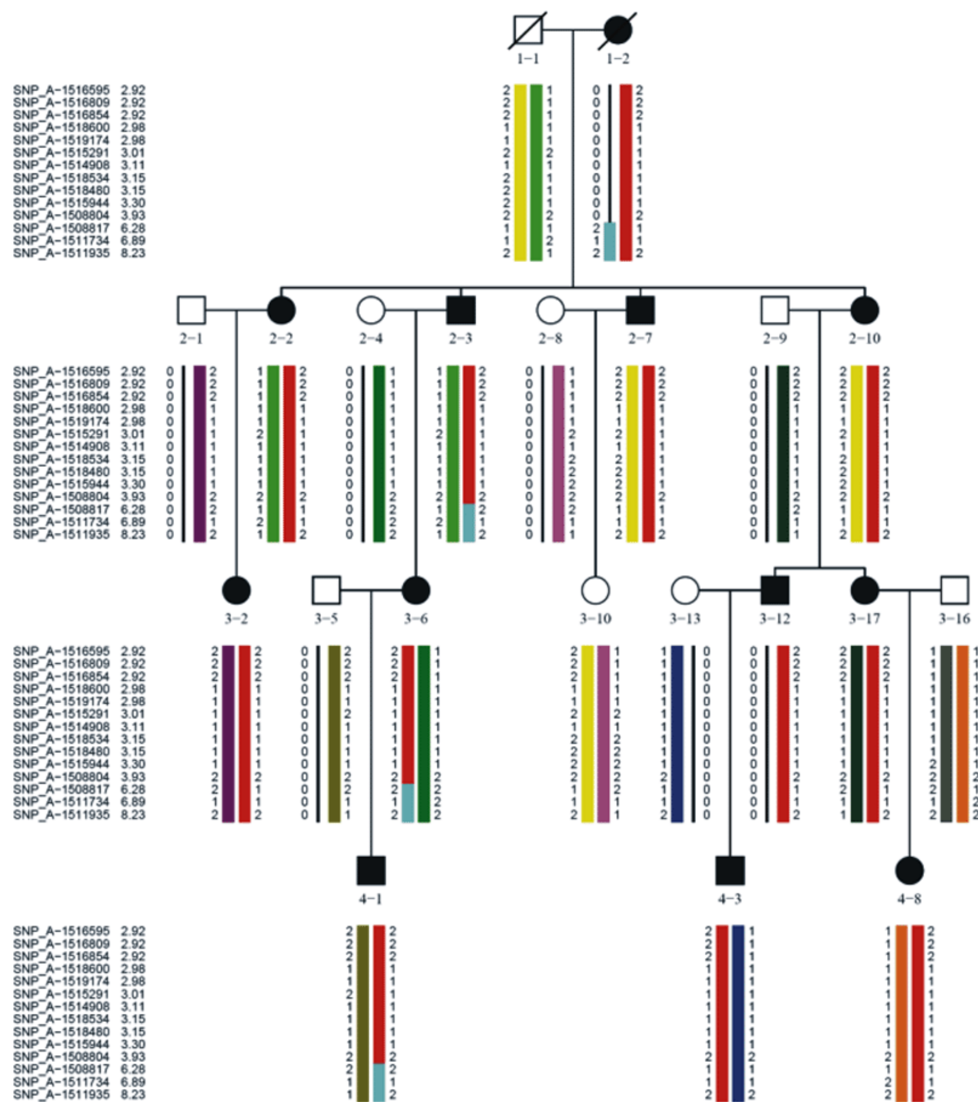

Figure 2. Haplotype analysis of a portion of family CC-644 using chromosome 13 single nucleotide polymorphic markers. Eight affected (2-3, 2-10, 3-2, 3-6, 3-17, 4-1, 4-3, and 4-8) and two unaffected (3-10 and 3-16) family members were analyzed. Recombination events were observed in three affected individuals (2-3, 3-6, and 4-1) at SNP_A-1508817 as inherited from father (2-3) to his daughter (3-6) and then to his grandson (4-1) placing the disease locus between SNP_A-1516595 and SNP_A-1508817. Red bars indicate the affected haplotypes.

numerous granular opacities involving the embryonal nucleus. The central biconvex area of the lens appeared to have no opacity. The edges of the granular band of opacity appeared to be diffused on either side. The optical section showed a slit-like or hollow discus-like clear area surrounded by a thick, finely granular opacity (Figure 1). The equatorial periphery of the lens showed many grey and blue dot opacities. The width and density of the opacity increased with age. Apart from cataract, there was no family history of other ocular or systemic abnormalities in the affected individuals.

Linkage analysis: A high density single nucleotide polymorphic (SNP) genome scan was performed using a whole genome sampling analysis approach [14] with the GeneChip Human Mapping 10K Array, version 2 (Affymetrix, Santa Clara, CA). This whole genome sampling comprised of 10,204 SNP markers with an average heterozygosity in Caucasians of 38% and a mean intermarker distance of 258 kb, equivalent to 0.36 cM. DNA samples from eight affected (2-3, 2-10, 3-2, 3-6, 3-17, 4-1, 4-3, and 4-8) and from two unaffected (3-10 and 3-16) family members (Figure 2) were analyzed following the Affymetrix protocol. Genotypes were called by the GeneChip® DNA Analysis Software version 2 (Affymetrix, Santa Clara, CA). Data was analyzed using the ALOHOMORA program [15]. Regions of potential linkage delimited by the

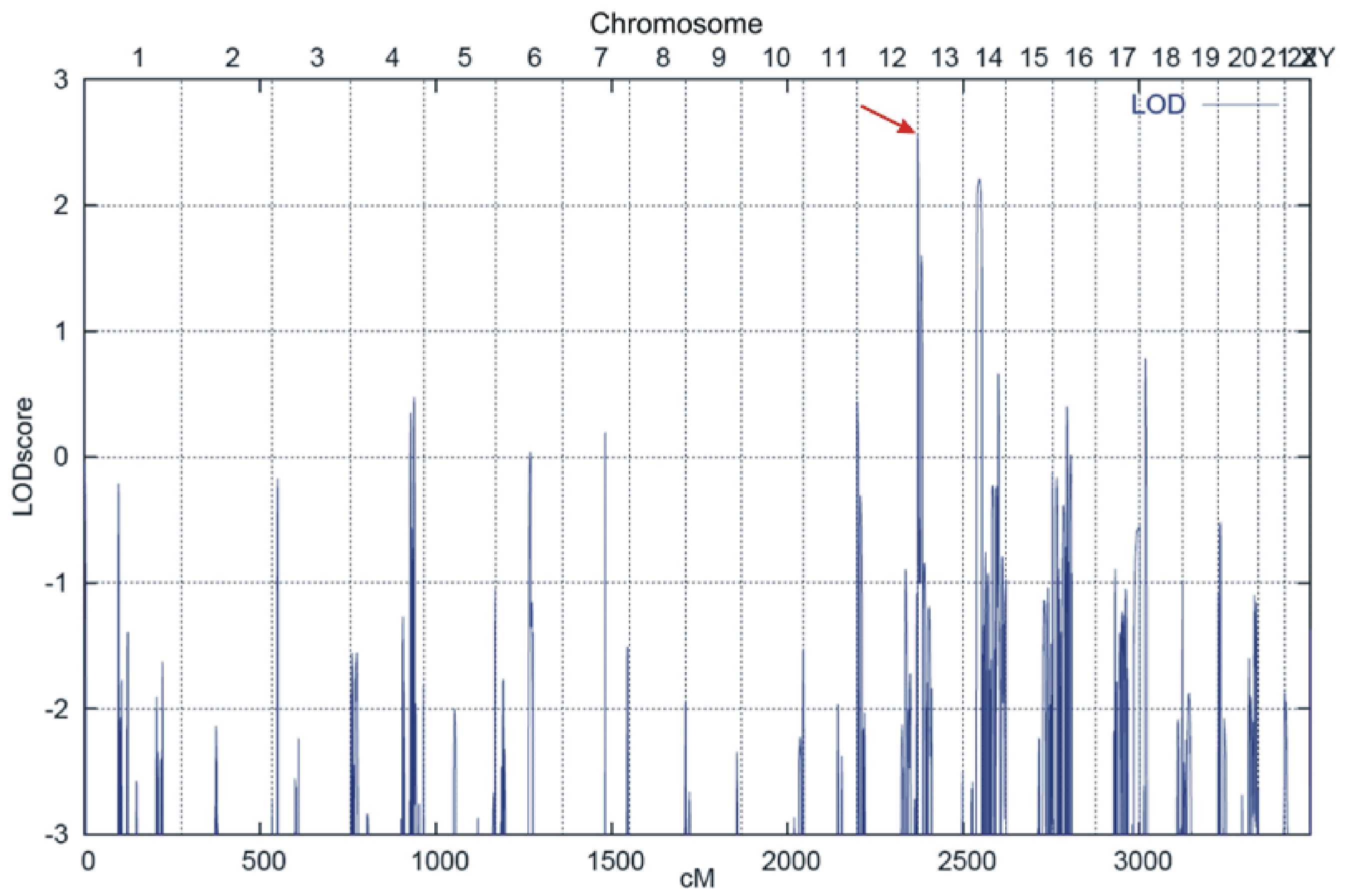

Figure 3. Graphical view of additive LOD score calculations of genome-wide single nucleotide polymorphism. The highest peak on chromosome 13 (indicated by red arrow) with lod score value of 2.56 indicates the region of potential linkage.

Table 1. Two-point LOD scores for linkage between the disease locus and chromosome 13 markers

Marker	Position (cM)	LOD scores at θ=								
		0.000	0.001	0.010	0.050	0.100	0.150	0.200	0.300	0.400
D13S1236	4.2	-0.087	0.948	1.856	2.301	2.273	2.104	1.864	1.255	0.537
D13S175	7.4	3.894	3.887	3.824	3.539	3.170	2.787	2.390	1.552	0.674

This table summarizes the two-point LOD scores for chromosome 13q11 markers close to *GJA3*. The highest LOD score 3.894 at θ=0.000 was obtained for marker D13S175. Position of the markers is based on the Genethon linkage map [16].

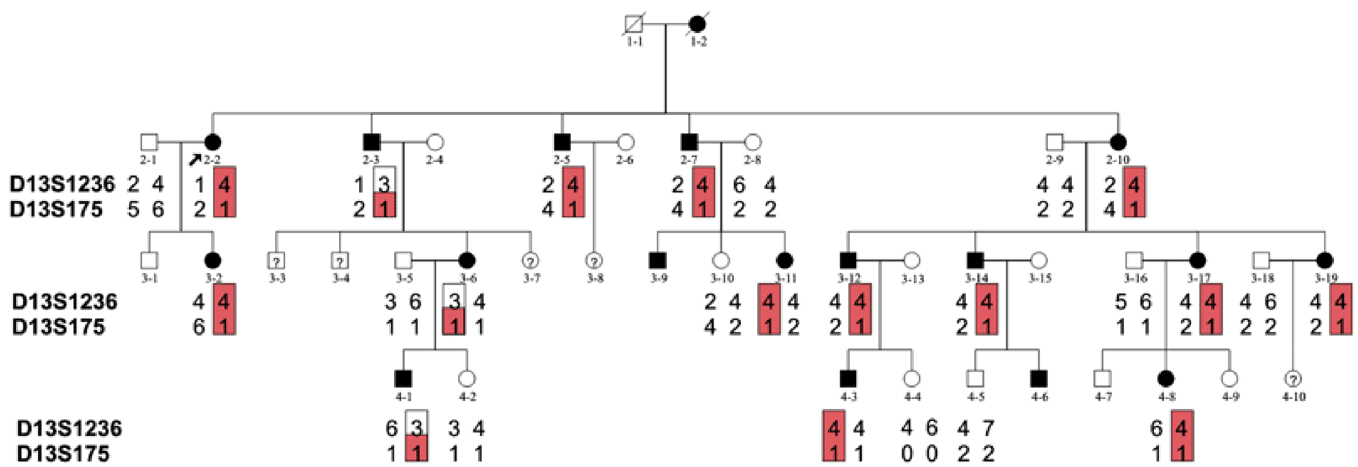

Figure 4. Haplotype analysis of the cataract family. Haplotypes segregating with the disease are indicated in the shaded boxes. Recombination events were observed in three affected individuals (2-3, 3-6, and 4-1) at D13S1236. Squares and circles symbolize males and females, respectively and filled symbols denote affected individuals. Proband (2-2) is indicated with a black arrow.

Figure 5. A portion of *GJA3* DNA sequence in an affected and an unaffected individual. **A**: DNA sequence electropherogram (forward strand) showing the heterozygous 98G>T transversion that replaces arginine by leucine at codon 33 in the affected individual (2-7). **B**: DNA sequence electropherogram of an unaffected individual (2-1) showing wild type G at position 98. The position of mutated (G>T) and wild type nucleotide G in an affected and an unaffected individual (2-7 and 2-1, respectively) is indicated with pink arrows.

SNP markers was further analyzed in 25 individuals of this ADCC family including 15 affected and 10 unaffected through the use of fluorescently labeled microsatellite markers (Genethon linkage map) [16] following the methods and conditions described [17]. Electrophoresis of PCR products was carried out on an ABI PRISM 3730 automated DNA sequencer (Applied Biosystems, Foster City, CA) and data were analyzed by GeneMapper software version 3.5 (Applied Biosystems). Autosomal dominant inheritance with complete penetrance of the trait and a disease gene frequency of 0.0001 were assumed. Recombination values (θ) were considered to be equal between males and females. Two-point linkage analysis was carried out with the LINKAGE program package [18].

Mutation screening: The coding region of *GJA3* was bidirectionally sequenced using previously published primer sequences [19]. Genomic DNA from two affected members and one unaffected member of the family were analyzed. PCR and sequencing reactions were performed following conditions detailed elsewhere [20]. Electrophoresis of the sequencing reaction products was performed on 5% urea-polyacrylamide gels on the ABI Prism 377 DNA sequencer (Applied Biosystems). The data were analyzed using the sequence analysis software version 3.4.1 (Applied Biosystems).

RESULTS

Linkage and haplotype analysis: In a genome-wide scan, a region of potential linkage with a maximum LOD score of 2.56 was identified on chromosome 13 (Figure 3) between the SNP markers SNP_A-1516595 (rs1947012) and SNP_A-1508817 (rs725600). This region on chromosome 13 harbors *connexin 46* (*GJA3*), earlier reported to be linked with congenital cataract. SNP haplotype analysis showed three affected individuals (2-3, 3-6, and 4-1) to be recombinant at SNP_A-1508817 thus placing the disease locus between SNP_A-1516595 and SNP_A-1508817. Further microsatellite marker analysis was carried out on 15 affected and 10 unaffected members of this family with markers D13S1236 and D13S175 in the mapped interval on chromosome 13q11. A maximum lod score of 3.894 at θ=0.000 was obtained with marker D13S175 (Table 1). Haplotype analysis with analyzed markers D13S1236 and D13S175 showed three affected individuals (2-3, 3-6, and 4-1) to be recombinant at marker D13S1236 (Figure 4). Individual 3-6 inherited this from her father (2-3) and then passed it onto her son (4-1).

Mutation analysis: By direct sequencing of the entire coding region of *GJA3*, a novel heterozygous G>T transversion at nucleotide position 98 (c. 98G>T) was detected in two affected members of this family (Figure 5). This transversion leads to the replacement of a highly conserved arginine with leucine at codon 33 (R33L). This substitution resulted in the gain of a *Sfa*NI restriction site. Analysis of all other members of this family showed cosegregation of this change with the disease phenotype in the affected individuals only. Further sequence analysis of fifty unrelated control subjects (100 chromosomes) from similar ethnic background showed only a wild type G at nucleotide position 98 (data not shown).

DISCUSSION

In the present study in a genome-wide screening, we identified a locus on chromosome 13 in an ADCC family of Indian origin having finely granular embryonal cataract. Further, we report a novel change (R33L) in *GJA3* in association with congenital cataract in this family. This change seems to be disease causative as it segregated completely with the disease phenotype and was absent in unaffected individuals in this family and in the 50 unrelated controls from a similar ethnic background.

GJA3 consists of a single exon encoding a 435 amino acid protein in humans and is predominantly expressed in lens fiber cells. All connexins have four transmembrane domains (M1, M2, M3, and M4), two extracellular loops (E1 and E2), and cytoplasmic NH_2- and COOH-termini (Figure 6). Thirteen mutations in *GJA3* involving the different domains have so far been reported to be associated with ADCC in humans (Table 2). Of these, seven mutations have been linked with nuclear or zonular pulverulent cataract that is mainly characterized as having dust-like opacities in developmental zones of the lens.

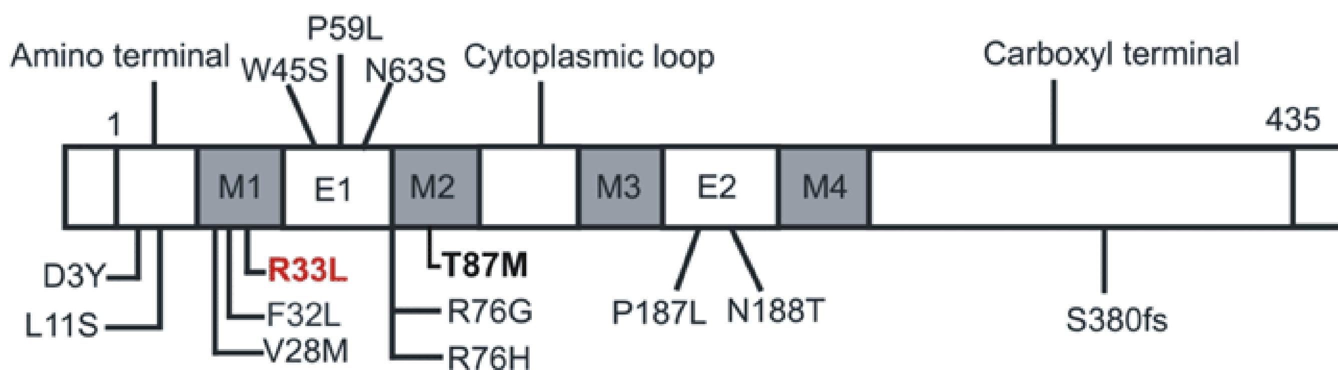

Figure 6. Schematic diagram of the connexin 46 polypeptide and locations of identified mutations. The connexin 46 polypeptide (435 amino acids) has nine structural domains including a cytoplasmic amino terminal, four transmembrane domains (M1-M4), two extracellular loops (E1, E2), a cytoplasmic loop, and a cytoplasmic carboxy terminal (figure modified from Bennett et al [33]). The location of R33L mutation observed in the present family (as highlighted in red) and other already known mutations associated with congenital cataract are indicated.

TABLE 2. MUTATIONS IN HUMAN CONNEXIN 46 (GJA3)

Amino acid change	Location	Cataract type	Phenotype description	Family origin	Reference
D3Y	NH2-terminal cytoplasmic loop	Zonular pulverulent	Progressive zonular pulverulent cataract	Hispanic	[34]
L11S	NH2-terminal cytoplasmic loop	Ant-egg	Lamellar cataract with dense ant-egg like structures imbedded in the lens, primarily confined to the perinuclear layers and to lesser degree in the fetal nucleus	Danish	[8]
V28M	First transmembrane domain	Variable	Variable cataract types like total, anterior capsular cataract with posterior cortical opacities in different individuals	Indian	[24]
F32L	First transmembrane domain	Nuclear pulverulent	Punctate opacities in the central zone of the lens limited to the embryonal nucleus	Chinese	[26]
R33L	First transmembrane domain	Finely granular embryonal	A band of opacities formed by numerous granular opacities with diffused edges on either side involving embryonal nucleus. Optical section of the lens shows slit like or hollow discus like clear area surrounded by thick finely granular opacity	Indian	Present study
W45S	First extracellular loop	Nuclear	Progressive nuclear cataract	Chinese	[35]
P59L	First extracellular loop	Nuclear punctate	Coarse punctate opacities located in the central or nuclear region of the lens	American	[33]
N63S	First extracellular loop	Zonular pulverulent	Coarse and granular opacities in the central zone of the lens. Fine dust-like opacities predominated in the peripheral zone of the lens.	Caucasian	[19]
R76G	Boundary of first extracellular loop and second transmembrane domain	Total	Total lens opacification	Indian	[24]
R76H	Boundary of first extracellular loop and second transmembrane domain	Nuclear pulverulent	Faint lamellar nuclear opacity surrounding pulverulent nuclear opacities, some with fine gold dots or haze and some with needle-like peripheral riders	Australian	[36]
T87M	Second transmembrane domain	Pearl box	A bunch of white spots in the embryonal nucleus. The central white spots distributed in a radial manner. The space between the surface opacity and central white spots was optically empty	Indian	[37]
P187L	Second extracellular loop	Zonular pulverulent	Central dust-like opacity affecting the embryonal, fetal and infantile nucleus of the lens surrounded by snowflake-like opacities in the anterior and posterior cortical region of the lens	Caucasian	[38]
N188T	Second extracellular loop	Nuclear pulverulent	Progressive, central pulverulent opacity affecting the embryonal, fetal and infantile nucleus of the lens	Chinese	[39]
S380fs	COOH-terminal cytoplasmic loop	Zonular pulverulent	Coarse and granular opacities in the central zone of the lens. Fine dust-like opacities predominated in the peripheral zone of the lens	Caucasian	[19]

Reported mutations in GJA3 associated with different congenital cataract phenotypes in different families.

The 98G>T substitution observed in the present study resulted in the replacement of a polar amino acid (arginine) to a nonpolar amino acid (leucine) at codon 33 (R33L), localized in the first transmembrane domain (M1) of the GJA3 polypeptide (Figure 6). A multiple amino acid sequence alignment showed that arginine at position 33 in the first transmembrane domain (M1) of the connexin 46 is phylogenetically conserved in different species (Figure 7A) as well as in different human α-connexins (Figure 7B). This suggests that arginine may play a key role in connexin function. In connexin 26 (*GJB2*), localized at 13q12, two corresponding mutations (R32C and R32H) in the first transmembrane domain have been reported to be associated with deafness [21,22]. Replacement of an arginine with leucine (R21L) in CRYAA, associated with congenital cataract and macular hypoplasia, has been reported by Graw et al. [23] in a German family. They further observed that this exchange alters the isoelectric point slightly and enhances the hydrophobicity significantly in the mutant. Similarly, substitution of arginine by the uncharged amino acid glycine at codon 76 (R76G) in the first extracellular loop of GJA3 has been reported in total congenital cataract [24]. Yeager and Nicholson [25] hypothesized that this might alter the charge on the surface of the extracellular loop thereby affecting the connexon docking. In connexin 46, two heterozygous mutations (V28M and F32L) are located within the first transmembrane domain (M1). These mutations, V28M and F32L, have been reported to cause variable [24] and nuclear pulverulent cataract [26], respectively (Figure 6). The transmembrane domains of the connexins are proposed to participate in the oligomerization into connexon hemichannels and are also essential for the correct transport of the protein into the plasma membrane [27]. It has been reported that residues in the first transmembrane domain are essential for the formation of the pore lining and therefore channel permeability [28]. Although the effect of the R33L mutation observed in the affected individuals of this ADCC family on the activity of connexin 46 has not been directly tested, we speculate that like P88S in GJA8 and other dominantly transmitted mutations in different connexins, R33L may also result in inappropriate association of connexins and alter the function of wild-type connexins in a dominant negative manner.

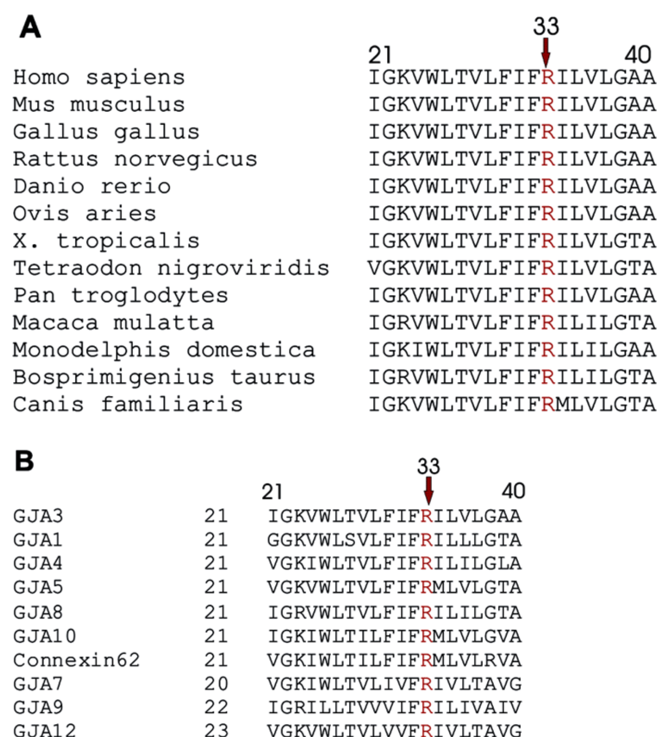

Figure 7. A multiple sequence alignment of a section of connexin 46 amino acids in different species and in different human α-connexins. Alignment data indicate that arginine at position 33 marked in red is highly conserved in different species (**A**) and in different human α-connexins (**B**)

Apart from humans, defects in the *connexin 46* and the *connexin 50* genes have also been reported to be linked with cataract in mice. A missense mutation (Glu42Lys) in the *connexin 46* gene has been reported to be associated with congenital cataract in rats [10]. Point mutations (G22R, D47A, and V64A) in the *connexin 50* gene have also been reported to result in dominant cataracts in mice [11-13]. Gong et al. [29] reported that mice homozygous for disrupted α3 connexin developed nuclear cataracts which resulted from proteolysis of γ-crystallin proteins and their conversion into insoluble forms, while *connexin 50* knockout mice had abnormal lens and eye growth along with nuclear cataract [30,31]. Targeted replacement of *connexin 50* with the *connexin 46* coding region in mice demonstrated that connexin 50 is required for normal lens and eye growth whereas connexin 46 is essential for maintenance of lens transparency [32].

The cataract phenotypes that have been reported to be linked with *GJA3* mutations share genotype-phenotype similarities to some extent but also exhibit some differences with respect to the appearance and location of opacities within the lens. The phenotype in the present family resembles to some extent with other cataracts linked to *GJA3* as having granular opacities (Table 2). However, the appearance and shape of the opacity, which is like a hollow discus (Figure 1B), differs from the other reported cataract types. The difference in the morphologies of cataract phenotypes associated with mutations in the *GJA3* may be attributed to the action of modifier genes or environmental factors that could affect the expression of *connexin 46*.

In conclusion, we describe a novel heterozygous R33L mutation in *GJA3* in an autosomal dominant congenital cataract family of Indian origin. These findings thus expand the mutation spectrum of *GJA3*.

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