

# A novel mutation in the major intrinsic protein (MIP) associated with autosomal dominant congenital cataracts in a Chinese family

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**Purpose:** To detect the underlying genetic defect in a Chinese family affected with bilateral congenital cataracts.

**Methods:** A detailed family history and clinical data were recorded. Mutation screening was performed in the nuclear cataract-related gene by bidirectional sequencing of the amplified products. The mutation was verified by denaturing high-performance liquid chromatography (DHPLC).

**Results:** Two cataract phenotypes were observed within this family: one eye exhibited Y-suture and nuclear pulverulent opacification of the lens, while the others exhibited complete opacification in the fetal nuclear region. Sequencing of the candidate genes detected a heterozygous c.319G>A change in the coding region of the major intrinsic protein (MIP), resulting in the substitution of a highly conserved Valine by Isoleucine (p.V107I). The mutation was confirmed by DHPLC.

**Conclusions:** This study has identified a novel MIP mutation, p.V107I in a Chinese family with congenital cataracts. To the best of our knowledge, this is the first reported case of cataracts caused by a mutation in the second extracellular loop domain of MIP.

The ocular lens is a transparent organ that focuses light onto the retina. Cataracts, including spontaneous onset (congenital or juvenile) and age-related, are clouding of the clear lens, which can eventually lead to loss of vision. Although congenital cataract is less common than age-related cataract, it is the leading cause of visual disability in children [1]. Statistic analyses have revealed approximately one third of congenital cataracts to be familial [2], among which the autosomal dominant type is the most common mode of inheritance [3]. To date, autosomal dominant congenital cataracts (ADCC) have been linked to mutations of several different genes [4]. Two types of these genes were shown to be related to congenital nuclear cataracts: (1) Genes encoding crystallins:  $\alpha$ A-crystallin (*CRYAA*) [5],  $\beta$ A1-crystallin (*CRYBA1*) [6],  $\beta$ B1-crystallin (*CRYBB1*) [7],  $\beta$ B2-crystallin (*CRYBB2*) [8],  $\gamma$ C-crystallin (*CRYGC*) [9], and  $\gamma$ D-crystallin (*CRYGD*) [10]; (2) Genes encoding membrane transport proteins: *GJA3* (Connexin46, Cx46) [11], *GJA8* (Connexin50, Cx50) [12], and *MIP* (major intrinsic protein or Aquaporin 0, AQP0) [13].

The connexins form gap junction channels for the intercellular transfer of small molecules and ions [14], while AQP0 functions as lens-specific water channel [15]. The lens, in the absence of a vascular supply, relies on metabolic co-

operation through transmembrane channels, which have been proposed to supply deeper-lying fiber cells with nutrients and to clear waste products [14]. Therefore these channels formed by the connexins and AQP0 play essential roles in the maintenance of lifelong lens transparency.

In this study, we screened nuclear-cataract-associated genes by direct sequencing in a Chinese family with congenital Y-sutural and nuclear cataracts. In the first exon of *MIP*, We detected a novel G>A transition, which leads to a missense mutation in the extracellular space of this transmembrane protein.

## METHODS

**Clinical evaluation and collection of genetic materials:** A three-generation family with congenital cataracts was studied at the Eye Center of the 2nd Affiliated Hospital, Medical College of Zhejiang University, Hangzhou, China. Appropriate informed consent in accordance with the Declaration of Helsinki and the Zhejiang Institutional Review Board approval was obtained from all participants. Nine individuals from the family participated in the study, 4 affected and 5 unaffected individuals, of whom 3 were spouses. The status was determined by a history of cataract extraction or ophthalmologic examination, including visual acuity, slit lamp, and fundus examination. The phenotypes were documented by slit lamp photography. Blood samples were obtained by venipuncture, collected in a BD Vacutainer (BD, San Jose, CA) containing EDTA. Genomic DNA was

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Figure 1. Cataracts in the family. **A:** Pedigree of the family with autosomal dominant cataract. The black arrow indicates the proband. **B:** A slit lamp photograph shows complete opacification of the lens fetal nucleus in the proband (II:4). **C:** A slit lamp photograph of the right eye lens of the proband's father (I:1) reveals the Y sutural and nuclear pulverulent cataract.

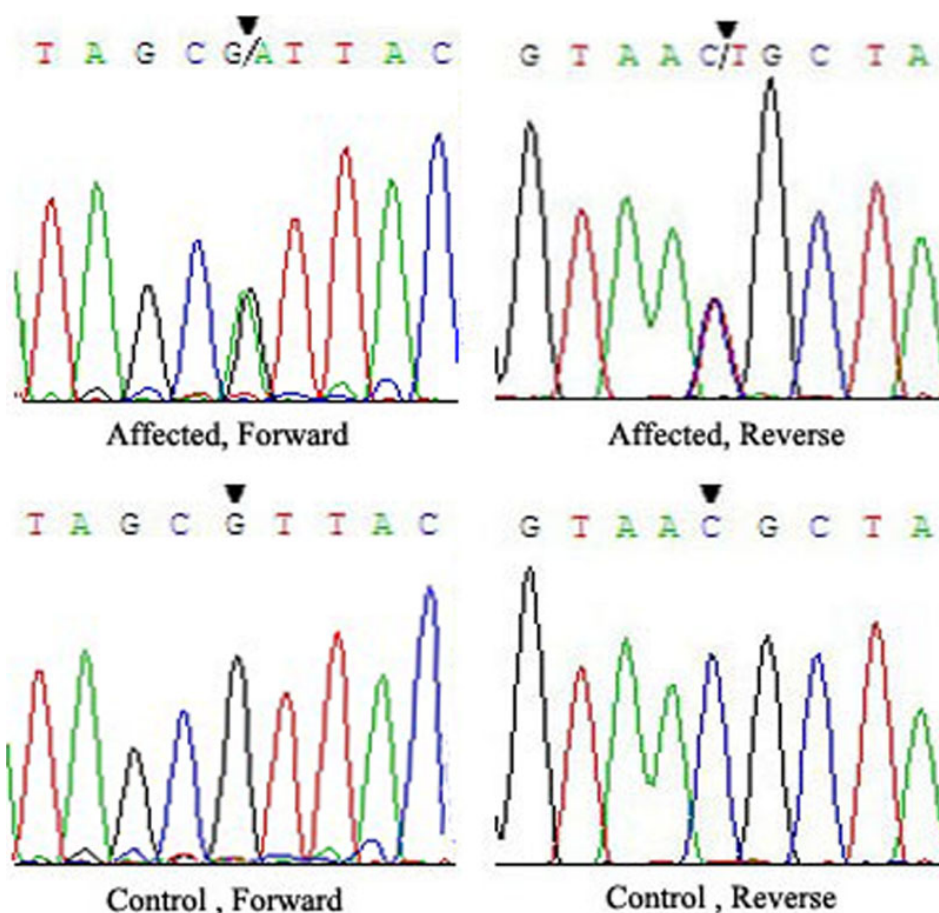


Figure 2. Forward and reverse sequence analysis of the affected and unaffected individuals in this ADCC Chinese family. A heterozygous mutation (c. 319G>A) in exon 1 of *MIP* (black triangles) is shown.

extracted using the QIAmp Blood kit (Qiagen, Hilden, Germany) following the manufacturer's instructions

**PCR and DNA sequencing:** Mutation screening was performed in the exon regions of the following candidate genes: *CRYAA*, *CRYBA1*, *CRYBB1*, *CRYBB2*, *CRYGC*, *CRYGD*, *GJA3*, *GJA8*, and *MIP*. The coding regions were amplified using previously published primer sequences [5,6,8,10,16,17]. PCR reactions were performed under the following conditions: 95 °C preactivation for 5 min, 10 cycles

of touchdown PCR with 0.5 °C down per cycle from 60 °C to 55 °C, followed by 25 cycles with denaturation at 95 °C for 45 s, annealing at 55 °C for 45 s and extension at 72 °C for 45 s. PCR products were isolated by electrophoresis on 3% agarose gels and sequenced using the BigDye Terminator Cycle sequencing kit V 3.1 (ABI Applied Biosystems, Sangon Co, Shanghai, China) on an ABI PRISM 3730 Sequence Analyzer (ABI), according to the manufacturer's directions

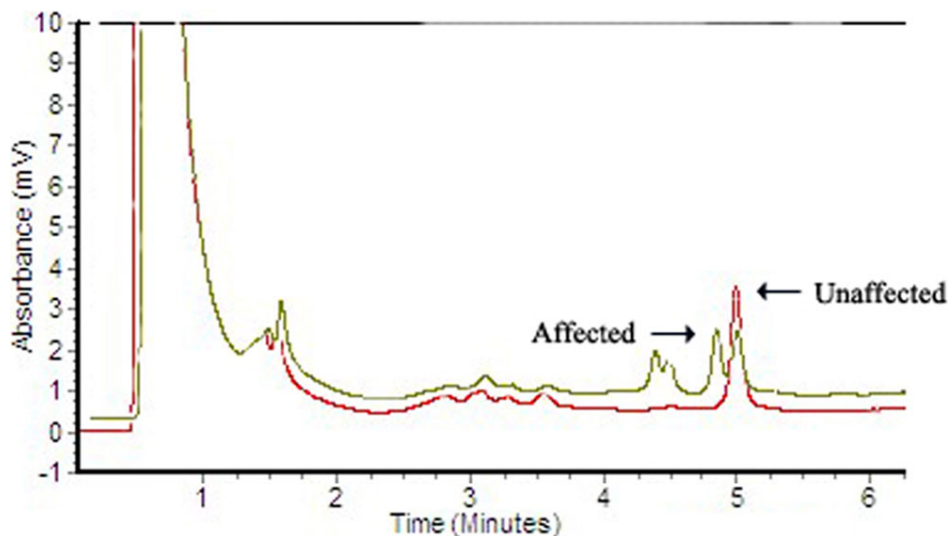


Figure 3. Denaturing high-performance liquid chromatography results of wild-type and mutated *MIP*. The DHPLC results shows variant traces for *MIP* compared to the wild-type (WT) trace. Profiles in brown contain the mutation; the profile in red is the wild type.

Species	LoopC sequence
<i>Homo sapiens</i> (human)	LYS <b>V</b> TPPAVRGNLALNTLH <b>P</b> AVS
<i>Bos taurus</i> (bovine)	LYS <b>V</b> TPPAVRGNLALNTLH <b>P</b> GV <b>S</b>
<i>Ovis aries</i> (sheep)	LYS <b>V</b> TPPAVRGNLALNTLH <b>P</b> GV <b>S</b>
<i>Canis familiaris</i> (dog)	LYS <b>V</b> TPPAVRGNLALNTLH <b>P</b> GV <b>S</b>
<i>Rattus norvegicus</i> (rat)	LYS <b>V</b> TPPAVRGNLALNTLH <b>A</b> GV <b>S</b>
<i>Mus musculus</i> (mouse)	LYS <b>V</b> TPPAVRGNLALNTLH <b>A</b> GV <b>S</b>
<i>Gallus gallus</i> (chicken)	LYG <b>V</b> TPAAVRGTLGLS <b>A</b> LH <b>P</b> SV <b>G</b>
<i>Xenopus tropicalis</i> ( <i>X.tropic</i> )	LYG <b>V</b> TP <b>T</b> AVRGNLALNTI <b>H</b> PGV <b>S</b>
<i>Danio rerio</i> (zebrafish)	LYG <b>V</b> TP <b>T</b> NMRGNLALNTL <b>Q</b> PGI <b>S</b>

Figure 4. Multiple-sequence alignment of *MIP* from different species. Multiple-sequence alignment of the different species reveals that codon 107, where the mutation (p.V107I) occurred, is highly conserved.

**Denaturing high-performance liquid chromatography:** Denaturing high performance liquid chromatography (DHPLC) was used to screen exon 1 of *MIP* in the affected patients, other family members, and 100 control subjects using a commercial system (Wave DHPLC; Transgenomic, San Jose, CA). The conditions were as follows: initial concentration at 44% of buffer A (0.1 M triethylammonium acetate, TEAA; Transgenomic) and 56% of buffer B (0.1 M TEAA containing 25% acetonitrile; Transgenomic) at 61.0 °C

**RESULTS**

**Clinical evaluation:** We identified a three-generation family with autosomal dominant congenital cataracts (Figure 1A). Opacification of the lens was bilateral in all of the affected individuals. There was no family history of other ocular or systemic abnormalities. The patients’ visual acuity ranged from finger count to 20/40 in the unoperated eyes. The impaired vision had been present since childhood and no complaint of decreased visual acuity with age from any of the patients. The proband was a 39-year old female (II:4). All of the affected individuals, except for individual I:1, exhibited

complete opacification of the fetal nucleus (Figure 1B). However, the cataracts of individual I:1 were very special: the left eye lens appeared to have complete opacification of the fetal nuclear region, while the right eye lens exhibited Y-suture opacification surrounded by a nuclear pulverulent cataract (Figure 1C).

**Mutation detection:** Bidirectional sequencing of the coding regions of the candidate genes revealed a heterozygous change, G>A, at position 319 (c.319G>A) in *MIP* in all of the affected individuals (Figure 2), resulting in the replacement of highly conserved Valine by Isoleucine (p.V107I).

**DHPLC analysis:** DHPLC confirmed this mutation, which cosegregated in all the affected individuals in the family, and this mutation was not observed in any of the unaffected family members or 100 unrelated control individuals (Figure 3).

**Multiple-sequence alignment and mutation analysis:** Using the NCBI website, we obtained the multiple sequence alignment of the AQP0 protein in various species including *Homo sapiens* (NP\_036196.1), *Bos taurus* (NP\_776362.1), *Ovis aries* (NP\_001153230.1), *Canis familiaris*



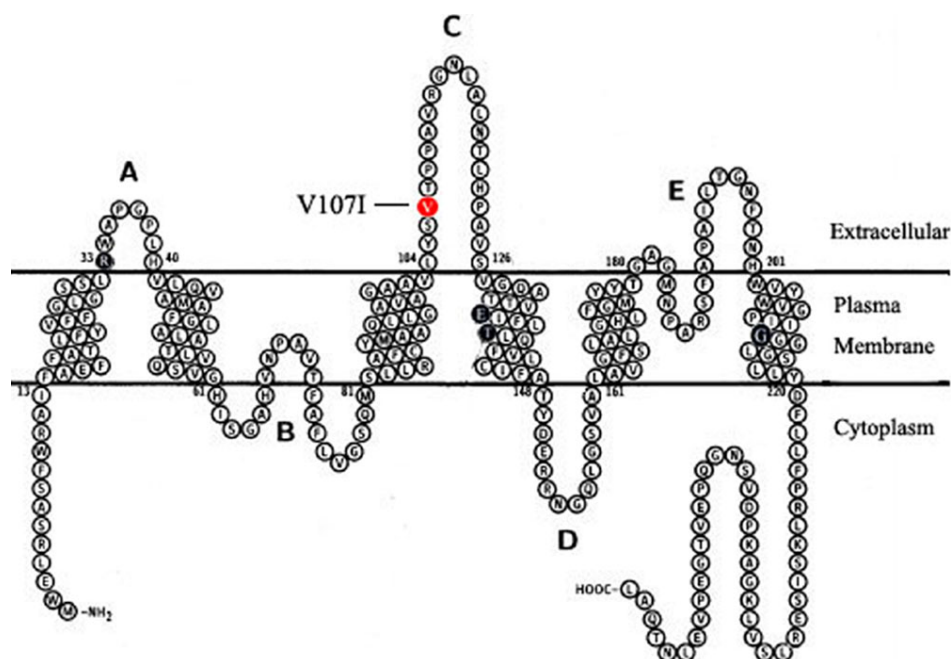


Figure 5. Topology of AQP0 and mutation analysis. Four reported missense mutations are marked in black: R33C, E134G, T138R, R233K. The novel mutation, V107I, is marked in red. This mutation located at the extracellular loop C of AQP0. (Modified from [36], permission granted by Prof. Peter Agre).

TABLE 1. PREVIOUSLY REPORTED MUTATIONS IN MIP GENE ASSOCIATED WITH CATARACTS

DNA change	Protein change	Mode of inheritance	Location/ MIP domain	Phenotype description	Origin of family	References
c. A401G	E134G	AD	H4 TM $\alpha$ -helices	Lamellar and sutural	English	[24]
c.C413G	T138R	AD	H4 TM $\alpha$ -helices	Polymorphic	English	[24]
A deleted G at nt.3223	Delete mutation at codon 213	AD	H6 TM $\alpha$ -helices	Radiating, vacuolar, or dense embryonal nuclear	American	[25]
c.G698A	R233K	AD	COOH-terminus	Posterior of the right, anterior polar in the left	Chinese	[27]
c.C97T	R33C	AD	Loop A	Total	Chinese	[26]
IVS3-1 G>A		AD	COOH-terminus	Snail-like	Chinese	[13]

(NP\_001074369.1), *Rattus norvegicus* (NP\_001099189.1), *Mus musculus* (NP\_032626.2), *Gallus gallus* (NP\_989597.1), *Xenopus tropicalis* (NP\_001090816.1) and *Danio rerio* (NP\_001003534.1). We found that codon 107, where the mutation (p.V107I) occurred, was phylogenetically conserved (Figure 4).

## DISCUSSION

AQP0 is a member of the aquaporin family, which forms pores that are either highly selective for water or permeable to other small neutral solutes, such as glycerol and urea [18]. As the water pores confer rapid movements of water across the plasma membranes, they are considered essential for the lens microcirculation system. Besides the water permeability function, AQP0 sometimes plays a cell-to-cell adhesion role [19,20], that helps compact the highly ordered fiber cells, thus minimizing extracellular space and light scattering. Moreover, AQP0 has been reported to interact with many other lens components including crystallins, lipids, and cytoskeletal proteins. These interactions were demonstrated to be important in maintaining the lens structure and

homeostasis [21-23]. Mutation in *MIP* in humans and mice has been reported to induce genetic cataracts in various studies [24-28]. To date, several mutations in human *MIP* have been identified, most of which are missense mutations (Figure 5). The cataracts induced by *MIP* mutation are usually located in the lens nuclear region (Table 1).

*MIP* expression starts as soon as the first primary fibers begin filling the lens vesicle, and continues to be expressed as the secondary fibers are differentiated from the equatorial epithelial cells [29]. When the terminal ends of the secondary fibers abut each other, lens sutures form [30]. Deletion of the *MIP* gene in mice leads to a lack of suture formation, resulting in the perturbed accommodation and focusing properties of the ocular lens [31]. These data highlight the important role that AQP0 plays in fiber adhesion and suture formation. The special cataract phenotype observed in this family, Y suture and nuclear opacities, is consistent with the localization and function of the AQP0 protein. Abnormal development of sutures has been reported in association with specific types of cataracts. Sutural cataract may occur as either an isolated type of cataract [32] or in association with opacities involving other

lens regions [33,34]. In this family, Y suture and nuclear pulverulent opacities were observed in one affected individual, while the others were total opacification in the fetal nuclear region, including the Y suture. The diverse cataract phenotypes caused by the same *MIP* gene suggests that other genetic modifiers are likely to influence the expression and function of AQP0 in lens development and Y suture formation.

Structural studies have shown that the transmembrane (TM) AQP0 contains two tandem repeats, each of which has three TM $\alpha$ -helices and a hydrophobic loop with a conserved asparagine-proline-alanine (NPA) motif. Six TM domains are connected by 5 loops, three of which are extracellular (loop A, C, E), while the others are intracellular (loop B, D) [35]. The extracellular loopC, which connects the third and fourth helices, mediates most of the junction-forming interactions of AQP0. The novel c.319G>A transition results in the substitution of a Valine for an Isoleucine (p.V107I), in loopC of AQP0 (Figure 5). The high conservation of V107 from zebrafish to humans indicates the importance of this residue.

There has been little functional investigation of the mutant AQP0 protein. Research on a *Xenopus* oocyte expression system showed that both the E134G and T138R mutations result in the loss of membrane water channel activity [36]. The deletion mutation at codon 213 created a frame-shift, and was demonstrated to interfere with the permeability of the water channel and the trafficking of proteins, thus leading to cataracts [37]. Electron crystallography research on the core of the sheep lens showed that the junction formation contacts are formed by the residues in loopC, including Pro109 and Pro110, and Arg113 and Pro123 [38]. Therefore, the Valine at site 107 may lie close enough to participate in or stabilize the contacting junction. Given that the mutation affects the connections of the neighbor helices, it is likely that it affects the tight gap junction formation by affecting the adhesion and regulation of the extracellular space volume. Water channel gating and the microcirculation may also be interrupted due to the improper organization of fibers. Further investigation is required to confirm that this is the mechanism by which the mutation affects the protein.

In summary, we identified a novel mutation of the human *MIP* gene segregated with Y sutural and nuclear cataract. This expands the spectrum of *MIP* mutations causing autosomal dominant nuclear cataract, both in terms of ethnicity and in terms of the location of the mutation in the loopC region of the protein.

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