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GJA3 Genetic Variation and Autosomal Dominant Congenital Cataracts and Glaucoma Following Cataract Surgery

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IMPORTANCE The p.Asp67Tyr genetic variant in the *GJA3* gene is responsible for congenital cataracts in a family with a high incidence of glaucoma following cataract surgery.

OBJECTIVE To describe the clinical features of a family with a strong association between congenital cataracts and glaucoma following cataract surgery secondary to a genetic variant in the *GJA3* gene (NM_021954.4:c.199G>T, p.Asp67Tyr).

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective, observational, case series, genetic association study from the University of Iowa spanning 61 years. Examined were the ophthalmic records from 1961 through 2022 of the family members of a 4-generation pedigree with autosomal dominant congenital cataracts.

MAIN OUTCOMES AND MEASURES Frequency of glaucoma following cataract surgery and postoperative complications among family members with congenital cataract due to the p.Asp67Tyr *GJA3* genetic variant.

RESULTS Medical records were available from 11 of 12 family members (7 male [63.6%]) with congenital cataract with a mean (SD) follow-up of 30 (21.7) years (range, 0.2-61 years). Eight of 9 patients with congenital cataracts developed glaucoma, and 8 of 8 patients who had cataract surgery at age 2 years or younger developed glaucoma following cataract surgery. The only family member with congenital cataracts who did not develop glaucoma had delayed cataract surgery until 12 and 21 years of age. Five of 11 family members (45.5%) had retinal detachments after cataract extraction and vitrectomy. No patients developed retinal detachments after prophylactic 360-degree endolaser.

CONCLUSIONS AND RELEVANCE The *GJA3* genetic variant, p.Asp67Tyr, was identified in a 4-generation congenital cataract pedigree from Iowa. This report suggests that patients with congenital cataract due to some *GJA3* genetic variants may be at especially high risk for glaucoma following cataract surgery. Retinal detachments after cataract extraction in the first 2 years of life were also common in this family, and prophylactic retinal endolaser may be indicated at the time of surgery.

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Invited Commentary
Supplemental content

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Congenital cataracts are among the leading causes of treatable blindness in children with an estimated prevalence of 1.03 per 10 000 (range, 0.32-22.9).[1] The most common cause of permanent vision loss secondary to congenital cataracts is deprivation amblyopia, which is minimized with early lensectomy. Unfortunately, glaucoma risk is inversely correlated with the age at the time of lensectomy.[2,3] The incidence of glaucoma following cataract surgery is approximately 15% to 45%,[4-7] and has a median age at onset of 6.8 years.[6] The strongest risk factor is age at lens extraction, with surgery occurring at younger than 3 months conferring the highest risk.[3,8]

Congenital cataracts are inherited in approximately one-half of cases.[9,10] One hundred fifteen genes and loci have been associated with inherited cataracts,[11] but only 39 of these loci are associated with primary or isolated congenital cataract.[12] The majority of genetic variants have been detected in genes encoding crystallins (approximately 50%) and connexins (approximately 25%).[12] The *GJA3* gene encodes connexin 46, a critical component of gap junctions within lens fibers. Gap junctions help to maintain osmotic and metabolic hemostasis of avascular crystalline lenses.[13-15] Many *GJA3* genetic variants are known to cause autosomal dominant nuclear and zonular pulverulent cataracts.[14,16-18] Herein, we report a 4-generation family with congenital cataracts and the discovery of an NM_021954.4:c.199G>T, p.Asp67Tyr *GJA3* genetic variant associated with their disease.

Key Points

Question What is the rate of glaucoma development following cataract surgery in a family with congenital cataracts from a NM_021954.4:c.199G>T, p.Asp67Tyr genetic variant within the *GJA3* gene?

Findings In this genetic association study of the medical records of 11 family members, 8 of 9 patients with congenital cataracts within this family developed glaucoma, and 8 of 8 patients who had surgery in early childhood for congenital cataracts developed glaucoma following cataract surgery. One family member with congenital cataracts did not develop glaucoma but had cataract surgeries after 12 years of age.

Meaning These findings suggest a high incidence of glaucoma following early childhood lensectomy for congenital cataracts caused by a *GJA3* genetic variant.

Methods

Study Design

We tested family members for disease-causing genetic variants in known congenital cataract genes and retrospectively conducted an observational, case series, genetic association study to establish genotype-phenotype correlations. We examined the ophthalmic records from 1961 through 2022 of family members of a 4-generation pedigree with autosomal dominant congenital cataracts. Limited information was available about the pedigree's founders (I-1 and I-2). All family members self-identified as Non-Hispanic White race and ethnicity. The study was approved by the University of Iowa institutional review board and followed the tenets of the Treaty of Helsinki. Adults provided written informed consent, and parents provided informed consent for children. Patients did not receive a stipend or incentive to participate in the study. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guidelines.

Genetic Analysis

DNA samples were collected from 10 members of the pedigree, including 9 with congenital cataract. DNA was prepared from blood samples using the QIAamp Blood Maxi Kit (Qiagen). Targeted DNA sequencing and whole-exome sequencing on 1 family member's (III-6) DNA (**Figure 1**) was used to assess several known congenital cataract genes for disease-causing genetic variants. We performed Sanger DNA sequencing of *CRYAA*, *CRYBA1*, *CRYBB2*, *CRYGD*, *BFSP2*, *EPHA2*, *FAM126*, and *FYCO1* with a 3730 automated capillary sequencer (Illumina) and whole-exome analysis using the SureSelect Human All Exon V5 exome kit (Agilent) and the Illumina HiSeq4000 with previously described methods.[19,20] The exome sequence data was analyzed with attention to the coding sequences of known autosomal dominant congenital cataract genes (*EPHA2*, *CRYGD*, *CRYGC*, *CRYGB*, *BFSP2*, *CRYGS*, *RRAGA*, *VIM*, *MIP*, *TMEM114*, *HSF4*, *CRYBA1*, *UNC45B*, *PRX*, *FTL*, *CHMP4B*, *CRYBB3*, *CRYBB2*, *CRYBB1*, and *GJA3*). Coding sequence variants in these genes with an allele frequency less than 1% in the gnomAD database[21-24] were evaluated for pathogenicity using the BLOSUM62 matrix,[25] MutationTaster,[26] PolyPhen2,[27] SIFT,[28] and CADD[29] analyses. The *GJA3* genetic variant p.Asp67Tyr was assessed for its effects on conserved protein sequences by constructing homology tables with the University of California, Santa Cruz, browser.[30]

Computer Modeling of the *GJA3* Genetic Variant

The probable effects of the p.Asp67Tyr genetic variant on GJA3 protein structure were evaluated based on biophysical modeling as we have previously described.[31] First, a homology model of human GJA3 was obtained from the Swiss Model Repository, which was based on a recent Ovis Aries (sheep) experimental structure from the Protein Data Bank (identification, 7JKC).[32] Next, the Asp67Tyr variant was introduced into the homology model followed by repacking of nearby residues using a rotamer optimization algorithm[33,34] and a potential energy function defined by the polarizable atomic multipole AMOEBA force field[35] in the program Force Field X.[36] Finally, a neural network, DeepDDG[37] analyzed the effect of p.Asp67Tyr on GJA3 protein stability.

Statistical Analysis

Statistical analyses were performed using Excel, version 16.73 (Microsoft). Paired and unpaired 2-tailed *t* tests were used with $P < .05$ as the threshold for significance. Data were analyzed from 1954 to April 2023.

Results

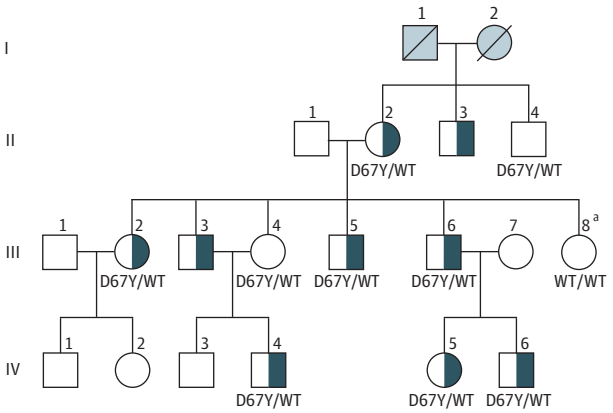
Congenital Cataracts

Medical records were available from 11 of 12 family members (7 male [63.6%]; 4 female [36.4%]) with congenital cataracts: II-2, II-3, II-4, III-2, III-3, III-5, III-6, III-8, IV-4, IV-5, and IV-6 (Figure 1). Patients had a mean (SD) follow-up of 30 (21.7) years (range, 0.2-61 years). Description of cataracts was available from 8 of 11 family members (**Table**). Of these 8 family members, 4 (50%) had cataracts described as cortical, and 3 (37.5%) had cataracts described as nuclear or embryonic cataracts. One family member (III-8) had a cataract that was described as a visually insignificant speck of anterior polar cataract in the right eye only. Consequently, individual III-8 was judged to be unaffected with regard to her family's congenital cataract. Three individuals (II-2, II-3, and II-4) were reported to have congenital cataract, but no description of the cataract was available. Three individuals (III-3, IV-4, and IV-5) required a second surgery related to their cataract extraction; III-3 and IV-5 needed a repeat surgery shortly after for retained lens fragments, whereas IV-4 had retained cortical material removed as part of the pars plana vitrectomy 16 years later. No patients had a secondary intraocular lens placed at any time.

Genetic and Molecular Analysis

No genetic variants were detected in several crystallin genes (*CRYAA*, *CRYBA1*, *CRYBB2*, and *CRYGD)* and other genes associated with cataract (*BFSP2*, *EPHA2*, *FAM126*, and *FYCO1*) using

Figure 1. Pedigree of 4-Generation Congenital Cataract/Glaucoma Following Cataract Surgery



Patients 2, 3, and 4 in generation II, patients 2, 3, 5, and 6 in generation III, and patients 4, 5, and 6 in generation IV were diagnosed with congenital cataracts. Patients that were diagnosed with glaucoma following cataract surgery are indicated by half-shaded symbols. Square symbols indicate male individuals, and round symbols indicate female individuals based on self-report. A gray symbol indicates patients without genetic or clinical data, and in this case, deceased. Roman numerals indicate the generation. D67Y indicates p.Asp67Tyr variant; WT, wild type.

[a] Denotes the patient who had only a visually insignificant speck of anterior polar cataract in 1 eye and was judged to be unaffected with regard to her family's congenital cataract presentation.

Sanger sequencing. Whole-exome sequencing was subsequently used to analyze 20 known autosomal dominant cataract genes. Only 1 plausible disease-causing variant was detected, a heterozygous missense variation in the *GJA3* gene, NM_021954.4:c.199G>T, p.Asp67Tyr . Sanger sequencing was used to confirm the p.Asp67Tyr genetic variant and showed that all family members with congenital cataract have the heterozygous p.Asp67Tyr *GJA3* genetic variant (Figure 1 and Table).

Several control populations were tested for the p.Asp67Tyr genetic variant in *GJA3*. No instances of the p.Asp67Tyr genetic variant were identified in the exomes of 362 previously reported normal control participants from Iowa.[38] Moreover, the p.Asp67Tyr genetic variant was not present in large public genomic databases including gnomAD (with >125 000 participants) and ClinVar,[21-24] further supporting its pathogenicity.

Several DNA algorithms were used to assess the potential pathogenicity of the p.Asp67Tyr genetic variant on the encoded connexin 46 protein. Five gene variant algorithms all suggested that the p.Asp67Tyr causes disease, including Polyphen2 (1.0 = probably damaging), SIFT (0 = deleterious), MutationTaster (disease causing), Blosum62 (−3), and CADD (C = 27.5). Moreover, the aspartate amino acid at position 67 of connexin 46 is highly conserved across evolution (**Figure 2**), suggesting that this sequence is essential for normal function. Finally, the tertiary structure of connexin 46 was modeled with and without the p.Asp67Tyr genetic variant using its known crystal structure (Protein Data Bank identification, 7JKC)[32] and refinement algorithms based on the polarizable AMOEBA force field as we have previously described.[34] The p.Asp67Tyr genetic variant significantly changes the structure of the connexin 46 (**Figure 3**), which is a critical gap junction protein required for lens clarity. Moreover, 2 different variations that alter the Asp67 amino acid of GJA3 (NM_021954.4:c.199G>C, p.Asp67His[39,40] and NM_021954.4:c.200A>G, p.Asp67Gly[40,41]) have also been reported in patients with congenital cataract. These data suggest that the p.Asp67Tyr genetic variant is responsible for the lens abnormalities in our congenital cataract pedigree, and based on American College of Medical Genetics and Genomics–Association for Molecular Pathology criteria (PM2, PM5, PP1, PP3, PP4), the variant is considered likely pathogenic.[42]

All 9 patients with the p.Asp67Tyr genetic variant were diagnosed with congenital cataracts at ages ranging from 0 to 6 days. One patient (II-2) with limited records was not available for genetic testing and was reportedly diagnosed at younger than 2 months. Patient II-4 had cataract surgery at a much later age (12 years in the right eye and 21 years in the left eye). This delay was a purposeful decision made by the parents after his sibling (II-3) had complications following cataract surgery. This deviated significantly from the other patients where the mean age of cataract extraction was 4.9 months (range, 0.2-24 months) (Table).

Glaucoma Following Cataract Surgery

Eight of 9 patients developed glaucoma following cataract surgery, and 8 of 8 patients who had cataract surgery performed at 2 years or younger developed glaucoma (mean [SD] age, 4.9 [7.7] months; range, 6 days-2 years). The remaining patient (II-4), whose cataract surgery was delayed until 12 and 21 years, developed dense amblyopia with best-corrected visual acuity (BCVA) of 20/400 OD and counting fingers at 2 feet OS but did not develop ocular hypertension or glaucoma following cataract surgery in either eye.

In patients who developed glaucoma following cataract surgery, the mean (SD) age at glaucoma diagnosis was 6.2 (7.7) years (range, 1 month-19 years) as defined by the age when ocular hypertension treatment was started. The maximum recorded IOP was 36.8 mm Hg (range, 25-50 mm Hg). The mean (SD) age at glaucoma surgery was 23.7 (21.4) years (range, 0.8-59 years). The mean (SD) age at glaucoma surgery was 58.0 (1.4) years for generation II, 28.3 (15.4) years for generation III, and 4.7 (6.4) years for generation IV without significant difference in maximum IOP. Eight of 13 eyes (62%) had pars plana 350-mm^2 Baerveldt glaucoma implant (BGI) surgeries combined with a pars plana vitrectomy (PPV). Pars plana tube placement was selected due to the thick corneas and crowded anterior chambers. The mean (SD) central corneal thickness was 664 (76) µm (Table), and no gonioscopic abnormalities were noted on any patients from examinations done under anesthesia or in clinic. Five of 13 eyes (38%) had pars plana FP7 Ahmed glaucoma valve (AGV) surgeries. Overall, 6 of 13 eyes (46%) had more than 1 glaucoma surgery, including revisions and second tubes (Table).

In addition to the high incidence of glaucoma, family members also had a high incidence of RD, which was attributed in part to an adherent vitreous base. Of the 11 patients with clinical information, 5 eyes of 5 patients (45.5%) had retinal detachments (RDs) that required surgical repair (II-2, II-3, II-4,

Table. Patient Details of a 4-Generation Congenital Cataract/Aphakic Glaucoma Pedigree

Patient No./age, y/sex[a]	Cataract/ glaucoma	p.Asp67Tyr	Age at cataract dx	Age at cataract extraction, y	Type of cataract	Maximum IOP, mm Hg (age, y)	Age at glaucoma treatment, y	Glaucoma surgery (age, y)	History of RD (age, y) and/or tx with endolaser	Snellen VA at most recent visit	Central corneal thickness, µm
II-2/69/F	Yes/yes	+	Limited records	OD: ~2	NA	OD: 47 (58)	OU: 19	OD: PP Ahmed[b] (59)	Yes, OS (50)	OD: 20/100	OD: 707
				OS: ~2		OS: 25 (50)		OS: Baerveldt[c] 350 (55), removal with CPC (57)		OS: 20/50	OS: 597
II-3/M	Yes/no	–	NA	NA	NA	NA	NA	One eye (unclear), resulted in RD and enucleation	Yes	NA	NA
II-4/61/M	Yes/no	+	2 d OU	OD: 12 OS: 21	NA	OD: 19 OS: 25	NA	NA	Yes, OS (42)	OD: 20/400 OS: CF	NA
III-2/52/F	Yes/yes	+	1 d OU	OD: 8 mo	Central cortical + posterior polar OU	OD: 36 (26)	OD: 9	OD: PP Baerveldt 350 (40), replaced with Ahmed (41)	Yes, OD (40)	OD: 20/200	OD: 612
				OS: 5 mo		OS: 29 (26)	OS: 9	OS: PP Ahmed (48)		OS: 20/30	OS: 730
III-3/50/M	Yes/yes	+	<2 mo OU	OD: 2 mo	Embryonic dense + zonal OD > OS	OD: 27 (31)	OD: 8	OS: PP Baerveldt 350 (38)	(Endolaser OS)	OD: 20/40	OD: 625
				OS: 2 mo, 3 mo (repeat)		OS: 40 (31)	OS: 8			OS: 20/400 eccentric fixation	OS: 620
III-5/37/M	Yes/yes	+	Limited records	OD: 19 d OS: 31 d	Nuclear + micro-spherophakia OU	OD: 44 (13) OS: 44 (13)	OD: 1 mo OS: 1 mo	OD: trab (13), PP Baerveldt 350 (13) OS: trab (13)	NA	OD: 20/60 OS: 20/30	OD: 855 OS: 801
III-6/35/M	Yes/yes	+	3 d OU	OD: 6 d	Gray/white nuclear OU	OD: 25 (6)	OD: 9	OD: NA	(Endolaser OS)	OD: 20/30	OD: 620
				OS: 17 d		OS: 35 (8 mo)	OS: 8 mo	OS: PP Baerveldt 350 (18)		OS: 20/30	OS: 594
III-8/33/F	Yes/no	+	6 d OD	NA	Visually insig-nificant small anterior polar OD	NA	NA	NA	NA	OD: 20/20 OS: 20/20	NA
IV-4/22/M	Yes/yes	+	0 d	OD: <1 mo, 16 (retained cortical material)	Dense white cortical OU	OD: 45 (11)	OU: 2.5	OD: PP Ahmed (16), PPV (16), and MP (17)	Yes OS (13) (endolaser OD)	OD: 20/25	OD: 630
				OS: 1 mo		OS: 49 (8)		OS: PP Ahmed (4), enucleation 19)		OS: NA	OS: 701
IV-5/7/F	Yes/yes	+	6 d OU	OD: 58 d	Dense white cortical OU	OD: 30 (8 mo)	OU: 7.5 mo	OD: Baerveldt 250 (17 mo)	(Endolaser OU)	OD: 20/30	OD: 629
				OS: 54 d, 58 d (fragment removal)		OS: 38 (9 mo)		OS: Baerveldt 250 (9 mo)		OS: 20/100	OS: 622
IV-6/4/M	Yes/yes	+	2 d OU	OD: 73 d	Central cortical OU	OD: 16 (13 mo)	OD: NA	OD: NA	(Endolaser OS)	OD: 20/200	OD: 623
				OS: 78 d		OS: 50 (13 mo)	OS: 9 mo	OS: PP Baerveldt 350 (14 mo), PP Baerveldt 350 (4 y)		OS: 20/100	OS: 650

Abbreviations: CF, counting fingers; CPC, cyclophotocoagulation; F, female; IOP, intraocular pressure; M, male; MP, micropulse cyclophotocoagulation; NA, not available; PP, pars plana; RD, retinal detachment; trab, trabeculectomy with mitomycin C; tx, treatment; VA, visual acuity; +, present; –, absent.

[a] Sex is based on self-report.

[b] Notation 250/350 refers to Baerveldt plate size in mm^2.

[c] All Ahmed tubes are FP7.

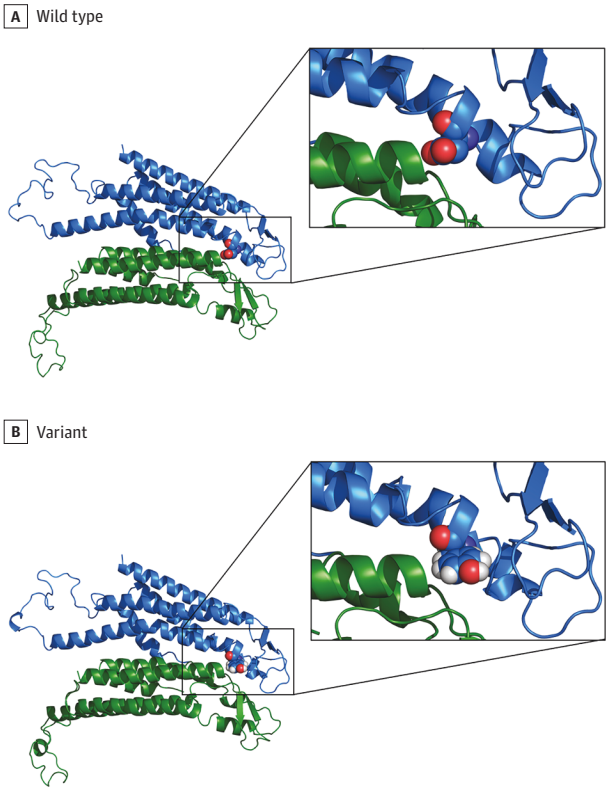
III-2, and IV-4), including PPV and scleral buckle placement. Given this strong family history, 4 eyes of 4 patients in the younger generations (patients III-3, III-6, IV-5, IV-6) had 360 degrees of prophylactic endolaser placed at the time of PPV (Table). To date, no RDs have been noted after prophylactic endolaser.

Figure 2. Connexin 46 Conservation of Amino Acid Sequence

Amino acid position	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76
Human *(Homo sapiens)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Gorilla *(Gorilla gorilla)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Monkey *(Macaca mulatta)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Mouse *(Mus musculus)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Rat *(Rattus norvegicus)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Dog *(Canis lupus)*	Q	P	G	C	E	N	V	C	Y	D	R	A	F	P	I	S	H	I	R
Elephant *(Loxodonta africana)*	Q	P	G	C	E	N	V	C	Y	D	Q	A	F	P	I	S	H	I	R
Cat *(Feline cattus)*	Q	P	G	C	E	N	V	C	Y	D	K	A	F	P	I	S	H	I	R
Chicken *(Gallus gallus)*	Q	P	G	C	E	N	V	C	Y	D	K	A	F	P	I	S	H	I	R
Frog *(Xenopus tropicalis)*	Q	P	G	C	E	N	V	C	Y	D	K	A	F	P	I	S	H	I	R
Zebrafish *(Danio rerio)*	Q	P	G	C	E	N	V	C	Y	D	E	A	F	P	I	S	H	I	R
Lamprey *(Petromyzon marinus)*	Q	P	G	C	E	N	V	C	Y	D	E	A	F	P	I	S	H	I	R

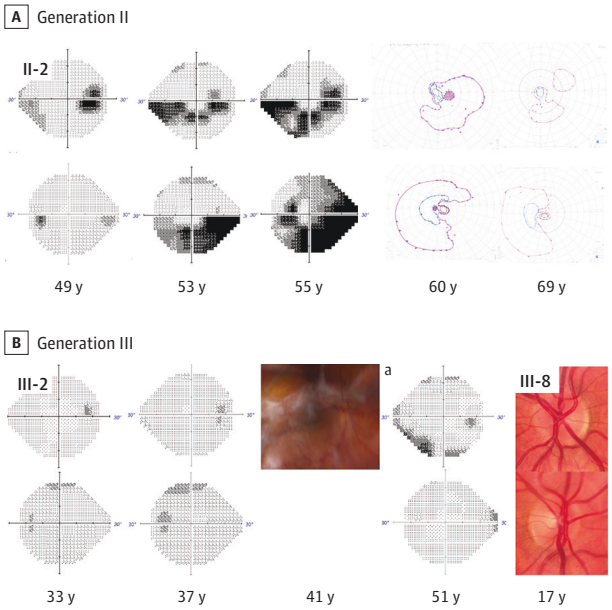
Aspartate amino acid at position 67 of connexin 46 is highly conserved across evolution. A indicates alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; V, valine; Y, tyrosine.

Figure 3. Dimer Models for the *GJA3* Protein



A, Dimer of a wild-type *GJA3* protein model. The aspartic acid at residue 67 is shown in spheres. B, Dimer of *GJA3* protein with variant p.Asp67Tyr shown in spheres and resulting structural change.

Figure 4. Clinical Data From the Congenital Cataract Pedigree



Visual fields (VFs), optic nerve photos, and B-scan ultrasonography images from 3 patients (II-2, III-2, III-8). Humphrey VF using the 24-2 Swedish interactive thresholding algorithm (SITA)–standard size III protocol. Some patients were followed up with Goldmann VFs (GVF), often obtained due to the severity of vision loss or limited visual acuity. On the GVFs, the color purple denotes the V4e isopter, blue the I4e isopter, and red the I2e isopter. Patient III-8 is the only patient with imaging that is negative for the *GJA3* genetic variant (and negative for congenital cataract).

[a] Indicates that a size V stimulus was used instead of a 24-2 SITA-III.

Case Descriptions

Except for patients I-1, I-2, II-3, and II-4, family members were followed up at our institution with records dating back to 1961. The clinical courses of 6 patients are subsequently detailed to highlight key features of congenital cataract and glaucoma following cataract surgery in this family. Clinical features and imaging for all family members are outlined in the Table, **Figure 4** (II-2, III-2, III-8), and the eFigure in Supplement 1.

Patient II-2, the proband of the family, had cataract surgery in both eyes at approximately 2 years old. Ambyopia limited her childhood BCVA to 20/40 OD and 20/70 OS. She

developed ocular hypertension (28 mm Hg in both eyes) at 19 years old and was treated medically. In her left eye, she had an RD at age 50 years that was treated with a scleral buckle. Later, a BGI was placed over that buckle at the age of 55 years. She developed myositis from the plate, requiring device removal and cyclophotocoagulation for IOP control at 57 years old. In the right eye, her IOP rose to 47 mm Hg despite maximum medical therapy, and she underwent an urgent AGV at 59 years old. Two weeks later, she had a PPV and a replacement of the AGV due to vitreous plugging and valve dysfunction. At her last follow-up, her IOP was 11 mm Hg in both eyes using latanoprost, brimonidine, timolol, and dorzolamide bilaterally. The patient's (II-2) VFs declined between the ages of 50 and 60 years despite aggressive surgical and medical treatment (Figure 4). Her Goldmann VFs have since stabilized with significantly constricted visual fields in both eyes: less than 20 degrees in the right eye and 10 degrees with a fixation-spitting defect in the left eye at last follow-up. Her BCVA at last follow-up was 20/100 OD and 20/50 OS.

Patient II-3 was not followed up at our institution, and limited clinical information was available. He had congenital cataracts and developed immediate postoperative complications after the cataract extraction in 1 eye during early childhood, which ultimately led to enucleation. The parents chose not to pursue cataract surgery on his other eye until he was much older (>12 years). Per family report, that eye has never developed an elevated IOP.

Patient II-4 was diagnosed with congenital cataracts in both eyes at 2 days of age but given his brother's complicated surgical history (II-3), his parents declined cataract surgery until he was much older (12 years in the right eye and 21 years in the left eye). His right eye was complicated by corneal decompensation in adulthood, which was managed with a penetrating keratoplasty (PKP) at 43 years and a repeat PKP at 55 years. One year later, corneal wound dehiscence resulted in endophthalmitis (*Staphylococcus epidermidis*) requiring PPV, corneal wound repair, and injection of vancomycin and ceftazidime. His left eye developed an RD, which subsequently required a pneumatic retinopexy, scleral buckle, and subsequent PPV with endolaser. He never developed elevated IOP in either eye. His BCVA at his last visit was 20/400 OD and counting fingers OS.

Patient III-2 was diagnosed with dense central posterior cataracts bilaterally when she was 1 day old. She underwent cataract extraction in the right eye at 5 months old and in the left eye at 8 months old. She developed rotary nystagmus, right hypertropia, and amblyopia in the right eye. Her IOP increased to 30 mm Hg in the right eye and 23 mm Hg in the left eye at 9 years old, and timolol, 0.25%, treatment was initiated in both eyes twice daily. Topical medical treatment was escalated until she required a PPV and pars plana BGI in the right eye at 40 years old. A large capsule over the BGI plate resulted in globe deformation, which was treated by tying off the BGI tube. Days after the repair, the patient developed a macula-on RD in the right eye requiring a PPV and scleral buckle (Figure 4) and later replacement of the BVI with an AGV. She subsequently developed corneal decompensation requiring a PKP at 43 years old and repeat PKP at 44 years old. Her left eye fared better with a pars plana AGV placed at 48 years old, done in combination with a prophylactic 360-degree endolaser. At her most recent visit, her vision was stable at 20/200 OD and 20/30 OS, with IOPs at 8 mm Hg in the right eye and 12 mm Hg in the left eye. Her last Humphrey VF was full in the left eye and had an inferior defect in the right eye consistent with an area of prior RD (Figure 4).

Patient III-8 had a tiny anterior polar cataract that was discovered in her right eye at 6 days old that was considered insignificant. Her BCVA was 20/20 OU without symptoms at 21 years old. She does not have glaucoma (Figure 4) and has not required any eye surgeries. She does not carry the familial *GJA3* (p.Asp67Tyr) genetic variant.

Patient IV-6 was the youngest family member to develop glaucoma following cataract surgery. He was diagnosed with dense cortical cataracts in both eyes at 2 days old and underwent lensectomy with anterior vitrectomy at 10 weeks old in the right eye and 11 weeks old in the left eye. Topical glaucoma treatment was initiated in both eyes at 9 months old. At 14 months old, he developed acute eye pain, nausea, and vomiting with an IOP of 50 mm Hg in the left eye and had an urgent pars plana BGI and PPV with prophylactic endolaser. At 3.5 years old, he had an acute tube obstruction, which was treated with a repeat PPV. Finally, he required a second pars plana BGI tube inferonasally in his left eye when his IOP acutely rose again at 4 years old. His right eye continues to have well-controlled IOP measurements without medications and stable optic nerves, depicted as patient IV-2 in eFigure in Supplement 1. His BCVA at his most recent visit was 20/200 OD and 20/100 OS.

Discussion

Genetic variants in the *GJA3* gene have been previously associated with congenital cataract.[14,16-18] However, there are little to no data about the frequency of subsequent glaucoma for most of these reports. It remains unclear whether the unusually high rate of glaucoma is specific to p.Asp67Tyr or is a feature of all *GJA3* variants. However, we report a *GJA3* genetic variant, p.Asp67Tyr, that was associated with congenital cataract and a remarkably high frequency of glaucoma following cataract surgery and cataract extraction. All patients who had cataract extraction in their first 2 years of life developed glaucoma following cataract surgery, which is much greater than the incidence in prior reports.[4-7] Although our cohort is small for making generalizations, there are statistical analyses that have been applied to data sets such as these. With a sample size of 11 family members, one can be 95% confident that no more than 27% of patients in this pedigree might avoid developing glaucoma following cataract surgery based on our findings.[43] Strong evidence suggests the p.Asp67Tyr genetic variant is pathogenic, including the results of 5 gene variant analysis algorithms, conservation of the p.Asp67 amino acid, structural analyses, and its absence in more than 125 000 control participants and ClinVar. These data suggest that p.Asp67Tyr is the likely cause of congenital cataract in our pedigree. Moreover, our study discovered a clinically important

genotype-phenotype correlation. Ophthalmologists should consider counseling the parents of children with congenital cataract caused by the p.Asp67Tyr genetic variants about the unusually high likelihood of glaucoma following cataract extraction.

Over the 3 generations of clinical data, the expressivity of glaucoma following cataract surgery appears to slightly increase with each generation (early disease, higher IOP, earlier surgeries). However, such patterns may be difficult to recognize with the small number of people in each generation. Ascertainment bias might also be a factor in our observations as younger generations may have received closer monitoring.

Delaying cataract extraction reduced the risk for glaucoma following cataract surgery in some family members but as expected, led to severe amblyopia. Both eyes of patient II-4 and 1 eye of patient II-3 delayed cataract surgery until 12 years of age or older. These eyes did not develop ocular hypertension or glaucoma following cataract surgery but did develop dense amblyopia (20/400 to hand motions). A recent meta-analysis suggested that placement of an intraocular lens at the time of surgery may reduce the incidence of glaucoma following cataract surgery.[44] However, no patient within this observational case series had an intraocular lens placed at any point.

No genetic information and limited clinical information are available from the first generation of the pedigree. These founders did not have glaucoma following cataract surgery. Interestingly, one was noted to be blind from infantile-onset glaucoma without cataracts, and the other was noted to have cataracts at a very young age without glaucoma. The timing of this individual's cataract surgery is unknown. Unfortunately, DNA was not available from the pedigree's founders to investigate the genotypes of these pedigree founders at the *GJA3* gene and at other loci. However, no additional genetic variants were detected in genes associated with childhood glaucoma (ie, *CYP1B1* and *MYOC*) in other family members. These results suggest that other known glaucoma variants are not contributing to the phenotype of the pedigree's founders.

Strengths and Limitations

The number of family members with both clinical data and genetic testing is a strength of this study. Another strength is the remarkably long follow-up at 1 institution. The main limitation of this study is that it is a retrospective observational case series of 1 family. The genetic variant identified in this family may be rare, and the genotype-phenotype correlations may not be directly relevant to many patients. Moreover, the biological mechanism that is responsible for the remarkably high rate of glaucoma following cataract surgery in this family is unknown. It is also unclear if the *GJA3* genetic variant is directly or indirectly responsible for the increased incidence of glaucoma following cataract surgery or if there are other genetic modifiers not yet identified.

Conclusions

In this genetic association study, all 8 patients within this family with autosomal dominant congenital cataracts developed glaucoma following cataract surgery by the age of 19 years. Genetic testing revealed a pathogenic genetic variant p.Asp67Tyr within the *GJA3* gene, which has been previously associated with congenital cataract.[14,16-18] This genetic variant causes significant structural change in connexin 46, a critical component of gap junctions responsible for maintaining osmotic and metabolic hemostasis of avascular crystalline lenses.[13-15] Current dogma suggests a 50% risk for glaucoma by 10 years following congenital cataract extraction.[4-7] However, in this specific family, the risk of glaucoma in this family was estimated to be 88% by 10 years following congenital cataract extraction and 100% by the age of 19 years, with one-half of cases (50%) occurring at 2.5 years or younger. Although this family may not be completely representative of others with this genetic variant, pediatric ophthalmologists should consider genetic testing in all children with bilateral congenital cataracts and consider closer follow-up of some families. Further studies to identify the biological mechanisms behind this high incidence of glaucoma may give insight into the pathogenesis of glaucoma following cataract surgery.

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