



Identification of a novel *MYOC* variant in a Hispanic family with early-onset primary open-angle glaucoma with elevated intraocular pressure

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Abstract Primary open-angle glaucoma (POAG) is the leading cause of irreversible blindness worldwide. Most cases are multifactorial in etiology, but some are associated with variants in the myocilin gene, *MYOC*. Here, we report the identification of a novel *MYOC* variant, c.1153G>A, in a 24-yr-old female patient with a personal and family history of juvenile/early-onset POAG. Further genetic testing within her family demonstrated that this variant segregates with the POAG phenotype in an autosomal dominant pattern. Identification of this *MYOC* variant in multiple affected relatives provides evidence for its pathogenicity, supporting previous findings linking *MYOC* mutations, in particular in the third exon's olfactomedin domain, to juvenile-onset POAG. This case also emphasizes the potential value of genetic testing in families with histories of eye disorders.

CASE PRESENTATION

With a global prevalence of ~3% and cases projected to reach 53–65.5 million by 2020, primary open-angle glaucoma (POAG) is the leading cause of irreversible blindness worldwide (Tham et al. 2014; Weinreb et al. 2014; Kapetanakis et al. 2016; Weinreb et al. 2016).

Most cases of POAG are multifactorial in etiology. However, monogenic autosomal dominant inheritance patterns may account for up to 10% of glaucoma cases, including certain presentations of POAG (Kwon et al. 2009). Of particular note, juvenile-onset high-tension POAG with intraocular pressure (IOP) typically ≥ 40 mmHg (normal < 20 mmHg) has been associated with mutations in the myocilin gene *MYOC* (NM_000261), which may also account for up to 5% of adult-onset disease (Stone et al. 1997; Alward et al. 2002; Wang et al. 2019).

Our proband (Fig. 1A, patient IV-2) is a 24-yr-old female who was diagnosed with bilateral POAG at age 9 yr. Her condition was medically managed until age 18 yr when IOP rose to 42 mmHg. Increased disc cupping was also noted at this time.

She underwent trabeculectomy procedures at age 18 (oculus sinister) and 20 (oculus dexter) yr. Both procedures were complicated by hypotony maculopathy requiring two revisions. Since then, her glaucoma has been managed without medications. Upon exam at age 24 yr,

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Ontology term: primary open angle glaucoma

Published by Cold Spring Harbor Laboratory Press

doi:10.1101/mcs.a004374

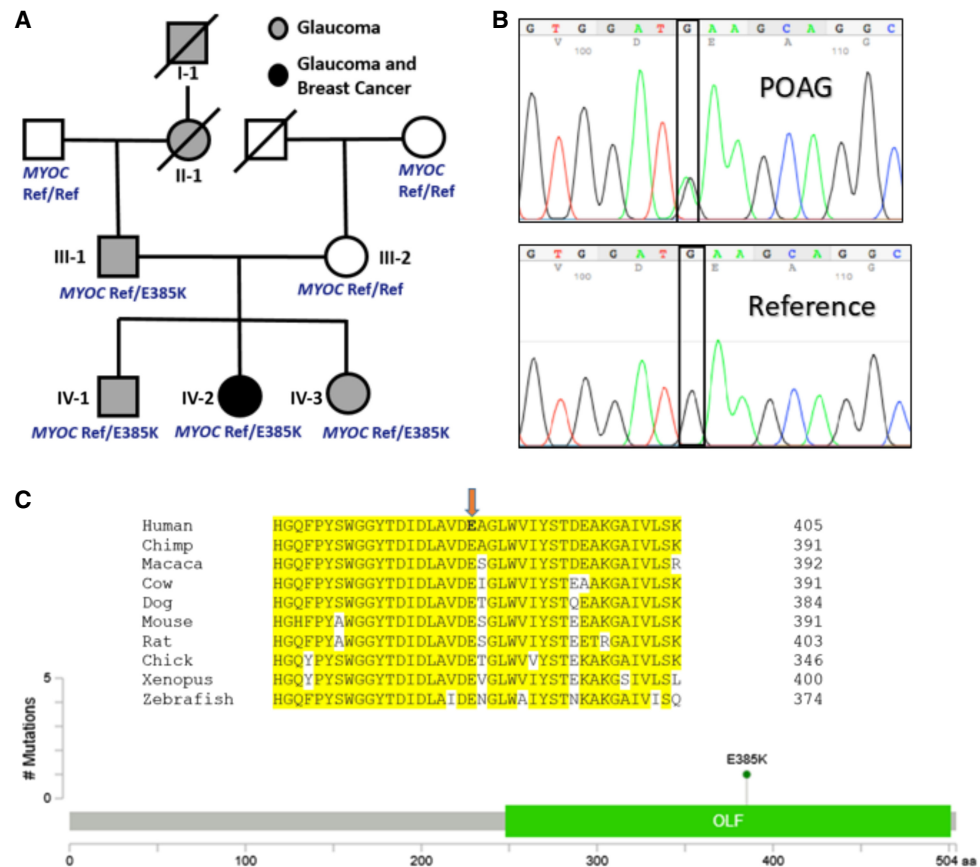


Figure 1. (A) The IV-2 family pedigree. The proband, IV-2, has a four-generation family history of early-onset glaucoma, including her great-grandfather (I-1), her grandmother (II-1), her father (III-1), and her siblings (IV-1 and IV-3). All living relatives with POAG are heterozygous for the p.Glu385Lys *MYOC* mutation, whereas unaffected relatives are homozygous wild-type. IV-2 does not have a family history of breast cancer or any known genetic risk factors for breast cancer. (B) Sanger sequencing. The c.1153G>A, p.Glu385Lys variant found in the proband and affected family members with POAG is demonstrated in comparison to the G/G reference sequence. (C) Conservation and location of the c.1153G>A, p.Glu385Lys variant. The p.Glu385Lys variant, which exchanges a highly conserved negatively charged glutamic acid for a positively charged lysine residue, occurs in the olfactomedin exon 3 of *MYOC*, the same region as a majority of previously identified POAG-associated *MYOC* mutations.

she had 20/25 vision in both eyes, corrected with glasses. Her IOP is currently stable at ~9–13 mmHg in both eyes.

The proband is one of three siblings born to nonconsanguineous Hispanic parents. Her brother was diagnosed with bilateral juvenile-onset POAG at age 19 yr and her sister received the same diagnosis at age 20 yr (patients IV-1 and IV-3). Her brother's condition is currently managed with medical therapy, but her sister has undergone a trabeculectomy. Her father (patient III-1) was diagnosed with juvenile-onset POAG in his 20s and received a trabeculectomy at age 26 following initial medical management. He also has adult-onset diabetes mellitus, but is otherwise healthy. Her mother (patient III-2) has adult-onset glaucoma.

The proband's paternal grandmother (patient II-1) had early-onset glaucoma and adult-onset diabetes. She began medical therapy in her 30s and later underwent trabeculectomy and laser surgery procedures. Her paternal great-grandfather (patient I-1) also had early-

onset glaucoma, which led to significant visual impairment by his mid-30s and eventually rendered him blind.

TECHNICAL ANALYSES

The proband was referred for genetic testing following a diagnosis of stage IIa ductal adenocarcinoma of the breast at age 23 yr. Prior to exome sequencing, a commercially available panel evaluating genes associated with hereditary cancer was sent and found to be negative.

Subsequent germline exome sequencing of the proband and her parents, which was completed under a research protocol at the Yale Center for Genome Analysis (Table 1), also failed to identify any known genetic risk factors for breast cancer. However, given that the proband and her father both have juvenile/early-onset POAG, we examined their sequences for rare heterozygous variants in common that were also not present in her mother's sequence (Table 2). Among these, we identified a novel variant in *MYOC*, NM_000261.2: c.1153G>A, p.Glu385Lys, located at a highly conserved residue within the olfactomedin-homology domain in exon 3 (Table 3). Multiple in silico algorithms, including CADD, SIFT and PolyPhen, predict this to be a deleterious variant. Furthermore, this variant is extremely rare, given that it is absent from the gnomAD database.

Subsequently, we sequenced this locus in the proband and all available first- or second-degree family members using Sanger sequencing. All individuals with juvenile/early-onset POAG—the proband, her father, and her two siblings—were determined to be heterozygous

Table 1. Sequencing metrics

	Proband	Father	Mother
Read length	99	99	99
Num reads (M)	45.8	49.3	57.9
Num bases (G)	4.5	4.9	5.7
Mean coverage	41.6	43.8	50.7
Median coverage	39	40	48
PCR duplicates	20.38%	22.49%	24.71%
Multiply mapped	6.25%	6.57%	6.36%
Unmapped	0.05%	0.06%	0.04%
Reads on-target	53.63%	51.56%	51.55%
Bases on-target	42.65%	41.05%	41.12%
Mean error rate	0.24%	0.26%	0.22%
1× target base coverage	95.1%	95.1%	95.1%
2× target base coverage	94.9%	94.9%	94.9%
4× target base coverage	94.7%	94.7%	94.7%
8× target base coverage	94.1%	94.1%	94.3%
10× target base coverage	93.5%	93.6%	94.1%
15× target base coverage	90.4%	90.8%	92.7%
20× target base coverage	84.7%	85.4%	89.8%
30× target base coverage	67.9%	69.6%	78.8%
40× target base coverage	48.7%	51.5%	63.5%
50× target base coverage	31.7%	35.3%	47.3%
100× target base coverage	1.8%	2.7%	4.5%

Table 2. Rare heterozygous variants

Gene	Chromosome	HGVS cDNA	HGVS protein	Max freq	CADD	SIFT	PPH
WDR63	1:85589887	NM_145172:c.2065C>G	p.L689V	0	24.9	D	D
GOLPH3L	1:150667289	NM_018178:c.26G>A	p.R9H	1.66 × 10 ⁻⁰⁵	27.2	D	D
MYOC	1:171605427	NM_000261.2:c.1153G>A	p.E385K	0	26.2	D	D
RC3H1	1:173915647	NM_172071:c.2928G>T	p.Q976H	0	26.5	D	D
PRKD3	2:37486821	NM_005813:c.2050C>T	p.L684F	0	29.6	D	D
LRP1B	2:141660657	NM_018557:c.3598C>A	p.P1200T	0	25.5	D	D
NCKIPSD	3:48716342	NM_016453:c.1760C>T	p.S587F	0	28.3	D	D
NIPAL1	4:48032145	NM_207330:c.322G>A	p.G108R	0	34	D	D
CSF1R	5:149433678	NM_005211:c.2873A>T	p.D958V	8.81 × 10 ⁻⁰⁵	25.6	D	D
RPS6KA2	6:167275598	NM_001006932:c.61G>C	p.E21Q	0	22.4	T	D
FREM1	9:14845969	NM_144966:c.1382T>G	p.L461R	0	26.6	D	D
GCNT1	9:79118564	NM_001490:c.1267T>A	p.L423M	0	22.9	D	P
FANCF	11:22646752	NM_022725:c.604delC	p.L202X	0	.	.	.
MUC15	11:26587076	NM_001135092:c.410dupC	p.P137fs	0	.	.	.
SLC3A2	11:62648607	NM_002394:c.415G>C	p.E139Q	1.27 × 10 ⁻⁰⁵	25.9	T	D
SLC22A24	11:62849139	NM_001136506:c.1286-1G>A (splice site)		0	22.9	.	.
USPL1	13:31232910	NM_005800:c.2696A>G	p.E899G	0	23.6	D	B
FARP1	13:99083345	NM_005766:c.1954G>A	p.E652K	0	29.2	D	P
MLYCD	16:83932751	NM_012213:c.2T>C	p.M1T	0	23.3	D	B
CHMP1A	16:89713647	NM_001083314:c.325C>T	p.R109X	3.46 × 10 ⁻⁰⁵	.	.	.
ATG4D	19:10662583	NM_032885:c.977G>A	p.R326H	0	25	D	D
MYO9B	19:17263484	NM_004145:c.966G>T	p.K322N	0	27.6	D	P
KMT2B	19:36213545	NM_014727:c.2647C>T	p.R883W	9.01 × 10 ⁻⁰⁶	34	D	D
RASGRP4	19:38903346	NM_170604:c.1646G>A	p.R549Q	9.00 × 10 ⁻⁰⁶	25.8	T	D
ACTR5	20:37400367	NM_024855:c.1732C>G	p.R578G	0	23.7	D	B
FAM65C	20:49214136	NM_080829:c.1759G>C	p.G587R	0	25.5	D	D
ZMAT5	22:30127219	NM_019103:c.508G>A	p.G170S	3.53 × 10 ⁻⁰⁵	34	D	D

Following full exome sequencing, multiple rare heterozygous variations were identified in common between the proband and her father, with her mother's exome as a reference. This table details all shared variants (heterozygous in the proband and her father, a reference in proband's mother) with a population frequency of <0.1%. The MYOC variant is in bold.

(Max freq) the maximum frequency of a variant in any population in the public gnomAD database, (0) the particular variant has not be reported in gnomAD, (CADD, SIFT, PPH) in silico predictors of the likelihood that a variant is deleterious, (T) tolerated, (D) deleterious, (B) benign, (P) pathogenic.

for this missense variant (Fig. 1B). In contrast, all unaffected individuals—the proband's mother, maternal grandmother, and paternal grandfather—did not have this variant in MYOC. These results indicate that this variant segregates with the disease phenotype in this family.

Following ACMG guidelines for interpretation, we classified the MYOC p.Glu385Lys variant as Likely Pathogenic, based on two moderate and two supporting criteria: PM2 (absent from controls in gnomAD) and PP1_Moderate (cosegregation with disease with multiple family members); and PP3 (multiple lines of computational evidence) and PP4 (specificity of MYOC causing heritable early-onset POAG with elevated IOP, as opposed to other known genetic causes, OPTN and TBK1, that cause early-onset normal tension glaucoma with IOP ≤ 21 mmHg) (Richards et al. 2015; Kelly et al. 2018; Sears et al. 2019; Wang et al. 2019).

Table 3. Details of MYOC gene variant

Gene	Chr	HGVS DNA (GRCh37)	HGVS cDNA	HGVS protein	Variant type	Predicted effect	dbSNP ID	Genotype	ClinVar ID
MYOC	1	g.171605427C>T	NM_000261.2 c.1153G>A	p.Glu385Lys	Substitution	Deleterious	rs1033533679	Heterozygous	SCV000897705

DISCUSSION

MYOC is a three-exon gene located on Chromosome 1q23-24 that codes for myocilin. It is highly expressed in several eye structures—in particular, the trabecular meshwork (TM), which is known to play a role in regulating IOP (Ortego et al. 1997; Polansky et al. 2000; Hewitt et al. 2008; Kwon et al. 2009; Vranka et al. 2015). Myocilin contains several functional domains, including a carboxy-terminal peroxisomal targeting domain and an olfactomedin domain—a region homologous to a family of secreted glycoproteins with uncertain function (Fingert et al. 2002; Kwon et al. 2009).

Although the association of MYOC with POAG is well-established, the normal function of the myocilin protein remains unclear. In fact, the lack of a discernible ocular phenotype in mice homozygous for a targeted null *Myoc* mutation suggests that it may be dispensable for normal eye function (Kim et al. 2001). However, multiple studies suggest that mutations in the olfactomedin domain lead to toxic intracellular protein accumulation (Kwon et al. 2009; Sears et al. 2019; Wang et al. 2019). Mutations resulting in aberrant exposure of the peroxisomal targeting domain in the protein may reduce myocilin excretion (Jacobson et al. 2001; Shepard et al. 2007). POAG-associated MYOC variants have also been shown to decrease myocilin solubility (Zhou and Vollrath 1999). These processes, and possibly others, produce an accumulation of intracellular myocilin aggregates, which form amyloid-like fibrils, leading to endoplasmic reticulum (ER) stress (Zode et al. 2011; Orwig et al. 2012; Patterson-Orazem et al. 2019). This, in turn, leads to TM cell damage and dysfunction, resulting in impaired aqueous humor outflow and increased IOP (Alvarado et al. 1984).

Some variants in MYOC are well-described in association with autosomal dominant familial POAG in general, whereas other variants are specifically associated with early-onset POAG with elevated IOP. The majority of these variants are missense, with an apparent clustering in exon 3, in particular in the olfactomedin domain (Bruttini et al. 2003; Hewitt et al. 2008; Tomarev and Nakaya 2009). The NM_000261.2:c.1153G>A variant described here is also located in the olfactomedin domain, but has not been previously reported in association with POAG (Fig. 1C). In silico tools predict a deleterious effect of this variant, which exchanges a highly conserved, negatively charged glutamic acid for a positively charged lysine residue in the third exon of MYOC.

SUMMARY

The finding of this NM_000261.2:c.1153G>A variant provides a notable addition to our understanding of MYOC-associated POAG. Not only does it highlight the previously identified link between MYOC and POAG, but it also provides additional support for the localization of pathogenic variants to the olfactomedin domain.

Of more immediate significance, this case emphasizes the importance of encouraging and facilitating genetic testing in families with histories of eye disorders. Identification of

the NM_000261.2:c.1153G>A variant empowers this family to make more informed decisions for future generations. In particular, the proband and her siblings would be candidates to obtain early childhood genetic testing for any future children, which, if positive, may enable earlier POAG screening and intervention. Early diagnosis of MYOC-associated POAG may become increasingly important in the future, given current efforts to develop targeted interventions, such as TM-cell replacement from mesenchymal stem cells as well as proteostasis-based therapy to address ER stress from myocilin accumulation (Huard and Lieberman 2018; Snider et al. 2018).

Identification of this variant also provides an opportunity to connect genetic findings with clinical outcomes, especially if the proband and her family are followed over time. Furthermore, the proband identifies as Hispanic, an ethnic group overrepresented among glaucoma patients compared to Caucasians (Quigley et al. 2001). Thus, this case could inform future efforts to carry out genetic testing in Hispanic glaucoma patients, potentially identifying trends in MYOC variants within this population.

ADDITIONAL INFORMATION

Data Deposition and Access

The MYOC variant described in this family was submitted to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and can be found under accession number SCV000897705. Raw data were not deposited to public access databases in the absence of patient consent but may be available through correspondence with the authors.

Ethics Statement

This study was approved by the Yale University Institutional Review Board. All living individuals referenced in this case report have provided written consent to participate in our research protocol and its publication of de-identified data.

Acknowledgments

We thank the Yale New Haven Hospital for supporting the Pediatric Genomics Discovery Program, the Yale Center for Genome Analysis for performing whole-exome sequencing, and the Yale DNA Diagnostics Laboratory for confirming our de novo novel variant. We also thank Sara and Jeffery Buell for their generous contributions to the Pediatric Genomics Discovery Program. We finally thank our patient and her family for their willingness to share their stories with the medical community.

Author Contributions

J.C. analyzed data and wrote the manuscript. W.J. analyzed sequencing data and critically reviewed the manuscript. L.J. analyzed clinical data and contributed to writing the manuscript. J.M.M. analyzed clinical data and critically reviewed the manuscript. S.S. analyzed clinical data and critically reviewed the manuscript. L.P. analyzed data and critically reviewed the manuscript. S.L. guided experimental design and data analysis and contributed to writing the manuscript.

Funding

This study was funded internally by the Yale New Haven Hospital.

Competing Interest Statement

S. Lakhani is part owner of Qiyas Higher Health, a startup company unrelated to this work.

Referees

Heidi Rehm
Anonymous

Received May 13, 2019; accepted in revised form August 9, 2019.

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