Published in final edited form as:

Am J Ophthalmol. 2007 July ; 144(1): 75–80.

Clinical features associated with an Asp380His myocilin mutation in a USA family with Primary Open Angle Glaucoma

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Abstract

Purpose—To determine the glaucoma phenotype of an American pedigree with the *myocilin* Asp380His.

Design—An observational case series study

Methods—An observational case series study was used to examine a family in which an Asp380His *myocilin* mutation was segregating. Thirteen family members were examined and medical records were obtained on the remaining two individuals. Blood samples were collected from all 15 participants following the tenets of the Helsinki declaration under the auspices of the OH&SU IRB and screened for *myocilin* variants by denaturing high performance liquid chromatography (dHPLC). Any DNA samples with dHPLC data different from the control sample were sequenced for base pair analysis.

Results—An Asp380His *myocilin* mutation was identified in eight members, seven of whom had POAG. The eighth individual had high intraocular pressures. The disease presents in this family with extremely high intraocular pressures requiring trabeculectomies to control the pressure. The age at diagnosis ranged from 30 to 45.

Conclusions—This family with an Asp380His *myocilin* mutation presents with an intermediate phenotype between juvenile and adult onset glaucoma. The Asp380 amino acid residue appears to be important in myocilin function based upon the finding that substitution of this amino acid with four different amino acids, His, Ala, Asn or Gly, all result in a similar presentation of POAG, that is intermediate between the more severe clinical presentations observed in individuals with the Pro370Leu or Lys423Glu variant and the milder findings in patients with the Gln368Stop mutation.

INTRODUCTION

Primary open angle glaucoma (POAG) is a neurodegenerative disease of the optic nerve that can lead to blindness. This disease is the most common form of glaucoma; close to 3 million individuals in the USA will be affected by the year 2010.¹ Based upon the age of diagnosis, POAG is referred to as either adult- or juvenile-onset with 35 years being the boundary.² Juvenile glaucoma is usually a much more severe disease with high intraocular pressures requiring surgery to avoid loss of sight.²

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Mutations in *myocilin* (*MYOC*) account for 8% of juvenile glaucoma and 3–4% of adult onset POAG.^{2, 3} Over 73 mutations in *MYOC* have been reported with 93% of these located in the olfactomedin domain coded by exon 3.^{3, 4} Three different variants of the Asp380 residue have been reported including Asp380Ala, Asp380Asn, and Asp380Gly.^{5–8}

Myocilin is an acidic protein that contains at least two folding domains, an N-terminal coiled coil and a C-terminal globular domain with significant homology to an olfactomedin module.^{9, 10} The function of myocilin remains unknown in spite of intensive investigation by many groups. The cellular distribution of this protein is disperse ranging from endoplasmic reticulum, Golgi apparatus, intracellular vesicles, mitochondria, cytoplasmic filaments to extracellular secretion depending upon the cell or tissue type.^{11, 12} Myocilin undergoes specific endoproteolytic cleavage releasing the C-terminal end containing the olfactomedin module.¹³ The proportion of processed secreted myocilin may regulate the normal trabecular meshwork structure by interacting with the extracellular matrix.¹³ While the function of myocilin is unknown, it is intriguing that the majority of mutations are in the olfactomedin region.

Several functional studies of the Asp380Ala mutation have been reported including analysis of endoproteolytic processing, effect of temperature and triton insolubility.^{13, 14} The Asp380Ala mutation both significantly inhibits endoproteolytic processing of the myocilin protein and is only partially soluble in triton.¹³ Triton insolubility has been proposed to be a characteristic of glaucomatous forms of *MYOC* mutant proteins. In addition, the Asp380Ala mutant protein shows high secretion from cells at 30° C and low secretion at 37° C.¹⁴ Culturing cells at lower temperatures facilitates protein folding suggesting that the substitution at this residue results in abnormal folding. Thus the Asp380Ala substitution appears to alter folding of the myocilin protein with an expected resulting impact on function.

Herein, we describe the clinical findings in a family with a novel Asp380His *MYOC* mutation.

METHODS

This family was invited to participate in our Glaucoma Genetics Study at the Department of Ophthalmology, Casey Eye Institute, Oregon Health & Sciences University in Portland, Oregon. Dr. John Samples examined thirteen of the fifteen participants. Medical records were obtained from the remaining two members, who lived out of state. The clinical examination protocol included:

1. Applanation tonometry with a recently calibrated Goldmann applanation tonometer (Haag Streit AG, Bern, Switzerland). The anterior segment was examined by clinical slit-lamp biomicroscopy including gonioscopy.
2. Optic disc appearance was evaluated with a 78 diopter Hruby lens and by direct ophthalmoscope by JRS. Family members were classified as normal, suspicious (vertical cup/disc ratio [CDR] ≥ 0.5), or definitely glaucomatous (CDR ≥ 0.7). A CDR ≥ 0.5 has been shown to be a risk factor for POAG in ocular hypertensive patients in the Ocular Hypertension Study.¹⁵ The presence of one or more qualitative signs such as focal neuroretinal rim thinning or a notch extending to the margin, retinal nerve fiber layer defects, disc hemorrhages, and bared circumpapillary vessels were also regarded as glaucomatous.
3. Venous blood was obtained for DNA extraction.
4. The criterion for glaucoma diagnosis that was used has been previously described.¹⁶ Essentially, one of three criteria had to be met: (1) glaucoma diagnosis prior to our study with instigation of treatment, (2) definite bilateral nasal steps on Humphrey

glaucoma hemifield test, or (3) two or more of the following findings: (a) untreated IOP > 24 mm Hg, (b) characteristic optic nerve damage; (c) abnormal Humphrey glaucoma hemifield test.

Mutation Analysis

Mutation analysis of the three exons and the promoter region of MYOC was performed using denaturing high performance liquid chromatography (dHPLC) with the Transgenomic WAVE™ system. WAVEMaker or Navigator software (Transgenomic, Omaha, NE) were used to design amplicons that would be optimal for identifying heteroduplex DNA using the Transgenomic WAVE™ system. PCR reactions contained 1.9 units of Optimase polymerase (Transgenomic) in a 50 l volume containing 100 ng of DNA template, 25 pmole of each forward and reverse primer, 0.2 mM of each deoxyribonucleotide triphosphate (dATP, dCTP, dGTP, and dTTP), and 5 l of the 10X reaction buffer from Transgenomic containing 1.5 mM MgSO₄. Touchdown PCR was performed with the GeneAmp PCR System 9700 (PE Applied Biosystem, Foster City, CA) with the annealing temperature lowered by 0.5°C for 15 cycles followed by 20 cycles at a constant annealing temperature. The touchdown and annealing temperatures were designed specifically for each PCR product based upon the properties of the sequence. The denaturation and extension temperatures were kept constant at 95°C and 72°C, respectively. The final incubation for all of the primer sets was at 72°C for 5 min. Prior to applying the PCR products to the Transgenomic WAVE™ system, the samples were denatured by raising the temperature to 95°C and then lowering to 25°C by 1.5°C/min.

dHPLC analysis - The PCR amplicons were run individually on the Transgenomic WAVE™ system using 5 l of each sample. A linear gradient of 5% triethylammonium acetate (TEAA) (Buffer A) and 25 % acetonitrile + 5% TEAA (Buffer B) was used to elute the sample at a flow rate of 0.9 ml/min. All heteroduplex amplicons were sequenced at the Portland VAMC core facility to identify the specific MYOC base pair change.

The probability of multiple mutations at the Asp380 position was calculated by the ratio of $503C_{416}^{*87}C_{79}^{*8}C_7^{*1}C_1 / 504C_{416}^{*88}C_{79}^{*9}C_7^{*2}C_1^{*1}C_1$, where the denominator represents the number of combinations based on 504 is the number of amino acids in myocilin, 416 is the number that of residues with no known substitutions, 88 amino acids have been reported to be replaced, 79 of these replacements involve just one substitution, 7 have two different replacements, 1 has three substitutions and one has four replacements, and the numerator computes all possible combinations based on given the Asp380 has four replacements and 79, 7, and 1 amino acids involve with one, two different, and three different replacements, respectively, among the remaining 503 amino acids.

RESULTS

A MYOC Asp380His variant was identified in an American family comprised of four generations as shown in Figure 1. Seven subjects from this pedigree were found to have glaucoma (Table 1). The mean ± SD age at diagnosis was 37 ± 6.7 years (range 30–47 years). The highest recorded IOP ranged from 9 to 55 mmHg (mean 32 ± 15.5). Medical records were unavailable for three of the individuals prior to the start of their treatment. Two individuals were diagnosed before the age of 35, which would be consistent with juvenile glaucoma. All seven individuals with POAG have had trabeculectomies in both eyes.

DNA from fifteen of the family members was analyzed for the MYOC D380H mutation. All seven of the affected family members carried the MYOC D380H mutation. This variant was also found in two additional family members, one with ocular hypertension and the other with CDR ratios of 0.5 in both eyes. No other family members had the mutation. None of the 100 unaffected controls had the D380H variant nor did the random POAG population of 120 people.

The three other reports identifying variations at the Asp380 residue screened 60, 53, 596, and 152 control subjects, respectively, with no finding of changes at this site in these individuals.^{5–8}

Glaucoma segregates as an autosomal dominant trait in this family with all affected members having one parent with POAG with the exception of 99107 and 99062. No clinical information was available on their mother, who is deceased. Family member 99105, who was considered as a glaucoma suspect by her ophthalmologist, is being treated with timoptic XE 0.5 mgm qhs OU even though she has normal visual fields. Individual 99107 was diagnosed as POAG by her ophthalmologist. All of the family members without the D380H myocilin mutation have normal IOPs and CDRs.

The penetrance of the D380H mutation is 87.5% over the age of 40 in this family.

DISCUSSION

Four different amino acid variations of the Asp380 residue in *MYOC* have been reported, including Asp380His in this paper, Asp380Ala, Asp380Gly and Asp380Asn.^{5–8} The majority of *MYOC* mutations result in juvenile glaucoma with the exception of the Gln368Stop variant, which has a much less severe clinical phenotype. In the family with the Asp380His mutation reported herein, the onset of the glaucoma phenotype is intermediate between juvenile and adult onset glaucoma with a mean age of onset of 37 years with the youngest individual being 30 years old at diagnosis. The age range in the families with the Asp380Ala is a bit younger with the earliest diagnosis at the age of 21 years.^{5, 6} Two other variants, Asp380Gly and Asp380Asn were found in individuals. The age of the patient with Asp380Gly was not reported, while the ages of the two with the Asp380Asn were 36 and 76 years.^{7, 8} Without follow-up on the families of these three unrelated, it is difficult to assess the effect of these mutations on age of onset.

High intraocular pressures are a hallmark of juvenile glaucoma. The Asp380His phenotype exhibits maximum pressures ranging from 32 to 55 mm Hg. We were unable to obtain records on three of the affected individuals prior to treatment; however, the treatment of all seven affected individuals with trabeculectomies is consistent with all of them suffering from high pressures. The two individuals with the Asp380Asn also had high pressures of 43 and 35 mm Hg, respectively, as did the families with the Asp380Ala variant.^{5, 6, 8} Unfortunately, the intraocular pressures for the individual with the Asp380Gly mutation were not reported.⁷ However, the available evidence suggests that substitution of Asp380 with His, Ala, Asn or Gly appears to result in a similar clinical presentation of glaucoma that is intermediate between the more severe clinical presentations observed in individuals with the Pro370Leu or Lys423Glu variant and the milder findings in patients with the Gln368Stop mutation.^{17–19}

The Asp380 residue is in the olfactomedin region of myocilin where the majority of mutations (>90%) have been identified. Thus, disruption of the olfactomedin structure appears to be important in the pathophysiology of glaucoma. Functional studies of the Asp380Ala mutation have shown that this aberrant protein is retained within the cell.^{13, 20} When the cells were incubated at a lower temperature a small amount of the mutant protein was secreted extracellularly. This would suggest that the Asp380His protein most likely is also retained within the cell, although experiments will need to be done to determine this.

Asp380 with four different amino acids substitutions holds the record for reported *de novo* mutations for myocilin followed by Pro481^{29, 30} with three reported variants. Recurrent mutations of the same codon are extremely rare.^{21,22} The probability of four independent hits occurring at the Asp380 residue is 0.00198. A total of 100 amino acids in myocilin, which contains 504 residues, have been shown to be replaced by different amino acids.^{6–8, 17, 18,}

23–51 Regions in myocilin with multiple substitutions include Asp380 and Pro481 with four and three variants, respectively, and six regions with two different amino acids replacements, e.g., Gln337, Thr377, Ser393, Arg422, Arg470 and Ile499.^{7, 17, 23, 29, 30, 37, 41, 45, 48,}
 52 The sequence coding for Asp380 does not contain a CpG dinucleotide, which is the motif usually found in hot spot regions. Thus, it is unlikely that Asp380 represents a hot spot region but instead may reflect that this protein domain is important in myocilin function or dysfunction in POAG.

Acknowledgements

NIH Grants EY11650, 5P30EY010572, AHAF and an unrestricted grant from RPB to the Casey Eye Institute supported this work. There are no commercial relationships.

This work was supported by grants RO1 EY11650–07, 5P30EY010572 from the National Institutes of Health, Bethesda, MD; the American Health Assistance Foundation, Bethesda, MD; an unrestricted grant from Research to Prevent Blindness. There are no financial disclosures to be made. Contributions of authors: Design of the study (MW, JS); Conduct of the study (MW, JS, NDG); statistical analysis (DC). We would like to thank the family for their willingness to participate in this study. In addition, we would like to thank Mrs. Jennifer Man for contacting family members and organizing the glaucoma genetics clinics. This study and data accumulation was carried out with approval from the Oregon Health & Sciences University Institutional Review Board. Informed Consent was obtained from the subjects and the study is in accordance with HIPAA regulations.

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Biographies

Mary K. Wirtz, PhD is the Director of the Glaucoma Genetics Laboratory at the Casey Eye Institute, Oregon Health & Sciences University in Portland, Or. Dr. Wirtz obtained a Bachelor of Science degree in Biology at Portland State University (1976) and a doctoral degree from the Oregon Health & Sciences University (1983). Her laboratory research is focused on identifying glaucoma susceptibility genes.

John R. Samples, M.D. Biosketch

John R. Samples, M.D. is Professor of Ophthalmology at Oregon Health and Sciences University. He is a member of the American Academy of Ophthalmology's Basic and Clinical Science Course Committee and the Ophthalmic Technology Assessment Committee. Three of the autosomal dominant genetic loci for open angle glaucoma were initially discovered in his practice. He coauthored the recent report of the first genetic abnormality to be associated with angle closure glaucoma.

Figure 1.

A pedigree of the POAG family with the Asp380His *MYOC* mutation. Filled in symbols indicate individuals with POAG; lower right quadrant filled in indicates the person has a cup to disc ratio = 0.5; lower left filled-in quadrant indicates the individual has high intraocular pressures. Analysis of DNA was performed on those people with a number below the symbol. D380H is below each symbol representing a family member with the mutation.

Table

Clinical Findings in POAG family with the Asp380His MYOC mutation

ID #	Genotype	Diagnosis	Age at Diagnosis	Age at Exam	Max IOP OD/OS ⁺	CDR OD/OS [*]	Surgery
97084	D380H	POAG	47	62	54/55	0.8/0.9	trabeculectomy OU
99014 ⁺	D380H	POAG	30	55	35/32 ⁺	0.9 OU	trabeculectomy OU
99062	D380H	POAG	35	67	45/45	0.85/0.75	trabeculectomy OU
00002	D380H	POAG	37	42	36/40	0.9/0.7	trabeculectomy OU
97085 ⁺	D380H	POAG	45	90	9/13 ⁺	0.9 OU	trabeculectomy OU
99015 ⁺	D380H	POAG	30	51	12/19 ⁺	0.9 OU	trabeculectomy OU
99051 ⁺	D380H	POAG	35	52	20/13	0.55/0.6	trabeculectomy OU
99105	D380H	OHT		38	35/34	NA	trabeculectomy OU
99107	D380H	Suspect		76	20/20	0.5 OU	
99007	D380D	Normal		45	17/17	0.3 OU	
99012	D380D	Normal		66	21/22	0.2 OU	
99041	D380D	Normal		30	16/16	0.2 OU	
99042	D380D	Normal		30	15/15	0.1 OU	
99053	D380D	Normal		43	16/15	0.1 OU	
99104	D380D	Normal		54	16/15	0.1 OU	

⁺ Intraocular pressures before treatment were not available.^{*} NA= not available