

Evaluation of *PRSS56* in Chinese subjects with high hyperopia or primary angle-closure glaucoma

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Purpose: Mouse serine protease 56 (*Prss56*) mutants show a phenotype of angle-closure glaucoma with a shortened ocular axial length. Mutations in the human *PRSS56* gene are associated with posterior microphthalmia and nanophthalmos. In this study, variations in *PRSS56* were evaluated in patients with either primary angle-closure glaucoma (PACG) or high hyperopia.

Methods: A total of 561 participants were enrolled in this study, including 189 individuals with PACG, 110 individuals with simple high hyperopia (sphere refraction $\geq +5.00$ D), and 262 normal control subjects (-0.5 D < sphere refraction < $+0.5$ D). Polymerase chain reaction (PCR) and Sanger sequencing were performed to detect sequence variations in *PRSS56*. Novel variations were evaluated using online tools, such as PolyPhen-2 and SIFT. The frequencies of the variations were compared between patients and controls using Fisher's exact test ($\alpha=0.05$).

Results: Eleven variants including ten novel variants and one known variant, involving 15 alleles, were detected in 14 patients (five patients with PACG and nine patients with high hyperopia). Of the 11 variants, two novel variants were detected in four out of 262 normal controls, involving four alleles. The frequency of the variants in the patients with high hyperopia significantly differed from that in the controls ($p=0.003$).

Conclusions: The results indicate that variants in *PRSS56* may be implicated in PACG and high hyperopia.

Primary angle-closure glaucoma (PACG) is the most common form of primary glaucoma in Chinese [1-3]. Several studies have shown that genetic factors play an important role in the development of PACG [4-6]. Although several susceptible loci and genes have been investigated for PACG, the precise genes underlying PACG have not been identified [7-12]. PACG has been shown to be associated with a shallow anterior chamber depth (ACD), a thick lens, and a short axial length (AL) of the eye [13-16]. A high heritability of ACD has been found in various studies [6,17-19], and ACD shares common genetic determinants with AL and anterior angle distance [20]. Thus, genes regulating the growth of the ocular axial length might be good candidates for PACG.

Hyperopia is a common refractive error associated with a shortened ocular axial length [21-24]. Infants are usually born hyperopic with refractions ranging from 1.0 D (± 1.5 D) to 2.5 D (± 2.5 D) [25-28]. The degree and variance of hyperopia are decreased by emmetropization within the first year of life, with few changes thereafter up to at least 3 years

of age [27,29-32]. By the age of 3 years, the average spherical refraction ranges from 0.38 D (± 1.15 D) to 1.40 D (± 1.56 D) [33-35]. In children of different ethnicities 36 to 47 months old, approximately 6.3% to 10.6% carry refractions above +3.00 D, while 0.8% to 1.9% are above +5 D [33-35]. People with high hyperopia often suffer from blurred vision, asthenopia, accommodative dysfunction, binocular dysfunction, amblyopia, and strabismus [36,37]. There is much support for a genetic basis in the development of hyperopia [38-41], particularly for high hyperopia [42,43]. Several genes have been investigated with hyperopia in association studies and mutation studies, but the genes responsible for high hyperopia alone have not been identified [44-49]. Because ocular axial length is a critical determinant of refractive errors, genes regulating growth of the ocular axial length may be good candidates for high hyperopia [20,22,23,50].

Recently, a homozygous mutation in the serine protease 56 (*Prss56*) gene has been associated with angle-closure glaucoma and posterior microphthalmia in mice [51]. Mutations in *PRSS56* are also responsible for some cases of autosomal recessive posterior microphthalmos and nanophthalmos in humans [51-53]. Posterior microphthalmia and nanophthalmos are characterized by extreme hyperopia ranging from +8.00 D to +25.00 D due to a shortened axial length between 14 and 20 mm (23.44 mm in normal adults [54]) [42,43,55-58].

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Thus, the aim of this study was to evaluate *PRSS56* variations in patients with PACG or high hyperopia. Eleven variants were detected in 14 out of 299 patients, and two of the 11 variants were detected in four out of 262 normal controls. The results suggested that *PRSS56* variants may be implicated in PACG and high hyperopia in humans.

METHODS

Subjects: A total of 561 subjects were enrolled in this study, including 189 probands with PACG, 110 probands with high hyperopia, and 262 normal controls. Written informed consent conforming to the tenets of the Declaration of Helsinki was obtained from each participant or his or her guardian before clinical data and peripheral venous blood were collected. This study was approved by the institutional review board of Zhongshan Ophthalmic Center.

PACG was diagnosed according to the criteria of the Congress of International Society for Geographical and Epidemiological Ophthalmology (ISGEO) definition and classification of glaucoma [1]. Individuals with PACG who were enrolled in this study met the criteria as previously described [11,12]. 1) They exhibited more than two of the following symptoms and signs: eye pain, headache, blurred vision, conjunctival congestion, cornea epithelial edema, mild-dilated pupil with inactive response to illumination, and iris atrophy. 2) They had an anterior chamber angle closure of at least 180 degrees in gonioscopy and 3) had intraocular pressure (IOP) over 21 mmHg in at least one eye as assessed using Goldmann applanation tonometry. Patients with secondary glaucoma of ocular trauma, uveitis, diabetic, hypertension, and any other disease predisposed to glaucoma were excluded. Subjects with high hyperopia recruited in this study had bilateral cycloplegic sphere refraction $\geq +5.00$ D at or after 3 years old and no other known ocular or systemic diseases. Normal control subjects consisted of students recruited from 12 universities in Guangzhou, China, who met the following criteria: 1) bilateral cycloplegic sphere refraction between -0.50 D and $+0.50$ D; 2) bilateral visual acuity of 1.0 or better; 3) no family history of glaucoma, high myopia, or high hyperopia; and 4) no other ocular or systemic diseases.

All of the subjects received routine ophthalmological examinations, including visual acuity, slit-lamp, and direct ophthalmoscopy. Visual field defects were detected using a static automated white on white threshold perimetry (SITA fast strategy, program 30-2, model 750, Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA). Refractive errors were measured using an auto refractometer (Topcon KR-8000, Paramus, NJ) after cycloplegia (Mydrin-P, Santen

Pharmaceutical, Osaka, Japan). The ocular axial length was measured using an IOL master V5 (Carl Zeiss Meditec AG, Jena, Germany). Additional examinations, such as obtaining a fundus photograph, were performed in selected individuals. All subjects and their clinical data were collected from the Zhongshan Ophthalmic Center at Sun Yat-sen University.

Mutation screening: Genomic DNA was prepared from the venous blood of each participant as we previously described [59]. The coding exons and adjacent intronic regions of *PRSS56* were amplified with polymerase chain reaction (PCR). Primers used to amplify the genomic fragments of *PRSS56* have been previously described [51,52] with modifications (Appendix 1). The amplicons were sequenced with a cycle sequencing kit (ABI BigDye Terminator Cycle Sequencing Kit v3.1, Applied Biosystems, Foster City, CA) and electrophoresed on a Genetic Analyzer (ABI 3100 Genetic Analyzer, Applied Biosystems). The sequencing results from the subjects were compared with *PRSS56* consensus sequences (National Center for Biotechnology Information, [NC_000002.11](#) Reference GRCh37.p10 Primary Assembly [233,385,173...233390426]). To identify sequence variations, the SeqMan II program of the Lasergene package (DNASar, Madison, WI) was used.

Variation analysis: The variations were described according to the recommendations of the [Human Genomic Variation Society](#). Polymorphism Phenotyping v2 ([PolyPhen-2](#)) and Sorting Intolerant From Tolerant ([SIFT](#)) online tools were used to predict the effects of missense variations. Each variant was initially confirmed with bidirectional sequencing and then evaluated in the 262 normal control subjects. The frequency of the variations in the patients was compared to that in the controls using [Fisher's exact test](#) with $\alpha=0.05$.

RESULTS

The sequencing analysis of *PRSS56* coding exons and adjacent intronic regions was successful for all subjects. A total of eleven different variations involving 15 alleles were detected in 14 of 299 patients (five with PACG and nine with high hyperopia), including one known and ten novel variations (Table 1, Figure 1). One patient with PACG demonstrated homozygous variants, while the remaining 13 patients showed heterozygous variants. In addition, two of the 11 variants were detected in four of the 262 normal controls, involving four alleles. The frequency of the variants in the patients with high hyperopia ($9/220=4.09\%$) significantly differed from that in the controls ($4/524=0.76\%$, $p=0.003$, Table 2). Significant p value remained when the frequencies of the variants were compared between the total patients (PACG and high hyperopia) and the normal controls ($p=0.024$, Table 2). Although

no significant *p* value was obtained when the frequencies of the variants were compared between patients with PACG and normal controls (*p*=0.336, Table 2), four variants were found in patients with PACG but not in normal controls, including a known mutation and a homozygous variation.

The c.1066dupC (p.Gln356Profs*152) mutation, which has been known to cause nanophthalmos in homozygous individuals, was found in a heterozygous state in a patient with PACG and a patient with high hyperopia but was not observed in any of the 262 normal control subjects. The patient with PACG and the c.1066dupC mutation exhibited bilateral anterior chamber angle closure above 180 degrees and an ocular axial length of 23.05 mm and 22.95 mm in the right and left eyes, respectively. The patient with high hyperopia and a c.1066dupC mutation was a 4-year-old boy, who carried spherical refractions of +6.25 D and +6.75 D.

A novel homozygous variation, c.431C>T (p.Ala144Val), was detected in a 61-year-old female patient with PACG. The ocular axial length was 15.9 mm in the right eye, but she had a phthisis bulbi of the left eye at the first clinical observation. The anterior chamber angle in the right eye was closed at 360 degrees on gonioscopy. This variation was predicted to be damaging by Polyphen-2 and SIFT analysis and was not observed in any of the 262 normal control subjects.

Two other variants cosegregated with high hyperopia in two families, further supporting the association between variations in the *PRSS56* gene and high hyperopia. The variant c.376G>T (p.Gly126Trp) was detected in a 36-year-old man and his daughter. The male patient carried refractions of +8.00 D and +7.00 D in the right and left eyes, respectively. His daughter was also hyperopic with +5.00 D and +4.00 D in the respective right and left eye by the age of 5 years. The daughter was not included in the initial screening because the refraction was less than +5.00 D in her left eye. However, because she was hyperopic and related to the proband, she was treated as an affected individual in the family. She was further screened, and the same variant as in the proband was detected. The mother in this family was normal without hyperopia, and her DNA sample was not available for further study. In addition, this variant was also found in a patient with PACG who had a bilateral anterior chamber angle closure of 360 degrees. Another novel variation, c.1687C>T (p.Arg563Cys), was detected in a 22-year-old male patient and his elder sister. They both showed high hyperopia of +6.00D at least in one eye with shortened ocular axial lengths, except the sister showed refraction +4.75D in her left eye. Based on detection of the variant c.1687C>T (p.Agr563Cys) in the brother in the initial screening, the sister was further sequenced, and the same variant was detected. The DNA samples and refraction

examinations of the parents in this family were not available. Neither of the two variants (c.376G>T and c.1687C>T) were found in 262 normal controls, and both were predicted to be damaging by Polyphen-2 and SIFT analyses.

The other seven variants (c.299G>A, p.Arg100Gln; c.656C>G, p.Pro219Arg; c.739C>A, p.Arg247Ser; c.746C>T, p.Pro249Leu; c.794G>A, p.Arg265His; c.827C>T, p.Ala276Val; and c.1019C>T, p.Ser340Phe) were detected in either two patients with PACG or six patients with high hyperopia. However, two of these variants (c.739C>A, p.Arg247Ser and c.1019C>T, p.Ser340Phe) were also observed in normal controls. The clinical data for all patients are listed in Table 3 and Table 4.

DISCUSSION

In this study, *PRSS56* was evaluated in Chinese patients with either PACG or high hyperopia. To the best of our knowledge, this is the first analysis of *PRSS56* in human subjects with PACG or high hyperopia. A total of 11 variations were detected in five patients with PACG and nine patients with high hyperopia, including ten novel variations and one known mutation, suggesting that the *PRSS56* gene is a good candidate gene for PACG and high hyperopia.

The *PRSS56* gene is classified as a member of the chymotrypsin family because the gene carries a catalytic triad consisting of Asp191-His145-Ser286 [52]. In this study, variations of Ala144Val, Pro219Arg, Phe249Leu, Arg265His, and Ala276Val were all located in the region of the catalytic triad (Asp191-His145-Ser280), and all of these residues were highly conserved. Furthermore, these variations may disrupt the catalytic activity of the protein. The Gln356Profs*152 and Arg563Cys variations were also predicted to be deleterious by affecting the C-terminal of the *PRSS56* gene. For example, in the *Grm4* mouse, the mutation located in the C-terminal of the *Prss56* gene resulted in increased expression of the *Prss56* gene and a phenotype of angle-closure glaucoma [51].

A known mutation, c.1066dupC (p.Gln356Profs*152), was found to be a heterozygous mutation in a patient with PACG and in a patient with high hyperopia but not in 262 normal controls. However, this mutation was previously found to be a homozygous mutation in patients with posterior microphthalmia and nanophthalmos [51-53]. Previous studies have also reported that heterozygous and homozygous mutations in the membrane frizzled-related protein (*MFRP*) gene have resulted in nanophthalmos [60]. Heterozygotes showed less severe phenotypes compared to homozygotes but were significantly different from the general population [58]. In this study, in the patient with PACG and the heterozygous mutation c.1066dupC, the ocular axial length was 23.05 mm

TABLE 1. VARIATIONS IN PRSS56 DETECTED IN 189 PROBANDS WITH PACG AND 110 PROBANDS WITH HIGH HYPEROPIA.

Number	Exon	Variation	Effect	Status	*Probands	Controls	Polyphen-2 (scores)	SIFT (scores)	Remarks
1	E4	c.299G>A	p.Arg100Gln	hetero	G106, G165	0/262 NC	benign(0.088)	tolerant(0.75)	novel
2	E4	c.376G>T	p.Gly126Trp	hetero	QT900; G228	0/262 NC	probably damaging(0.978)	intolerant (0.01)	novel
3	E4	c.431C>T	p.Ala144Val	homo	G207	0/262 NC	possibly damaging(0.754)	intolerant(0.00)	novel
4	E6	c.656C>G	p.Pro219Arg	hetero	Q1488	0/262 NC	possibly damaging(0.719)	tolerant (0.35)	novel
5	E7	c.739C>A	p.Arg247Ser	hetero	QT616	1/262 NC	benign(0.588)	tolerant (0.27)	novel
6	E7	c.746C>T	p.Pro249Leu	hetero	QT922	0/262 NC	possibly damaging(0.944)	intolerant (0.01)	novel
7	E7	c.794G>A	p.Arg265His	hetero	QT297	0/262 NC	benign(0.012)	tolerant (0.24)	novel
8	E7	c.827C>T	p.Ala276Val	hetero	QT490	0/262 NC	possibly damaging(0.572)	tolerant (0.10)	novel
9	E9	c.1019C>T	p.Ser340Phe	hetero	QT968	3/262 NC	possibly damaging(0.719)	tolerant (0.70)	novel
10	E9	c.1066dupC	p.Gln356Profs*152	hetero	QT316, G182	0/262 NC	/	/	Known [51-53]
11	E13	c.1687C>T	p.Arg563Cys	hetero	QT703	0/262 NC	probably damaging(0.930)	intolerant (0.00)	novel

* Probands with PACG: G106, G165, G228, G207, G95, G168, and G261. Probands with high hyperopia: QT900, QT488, QT616, QT922, QT297, QT490, QT968, QT316, and QT703. NC=normal controls.

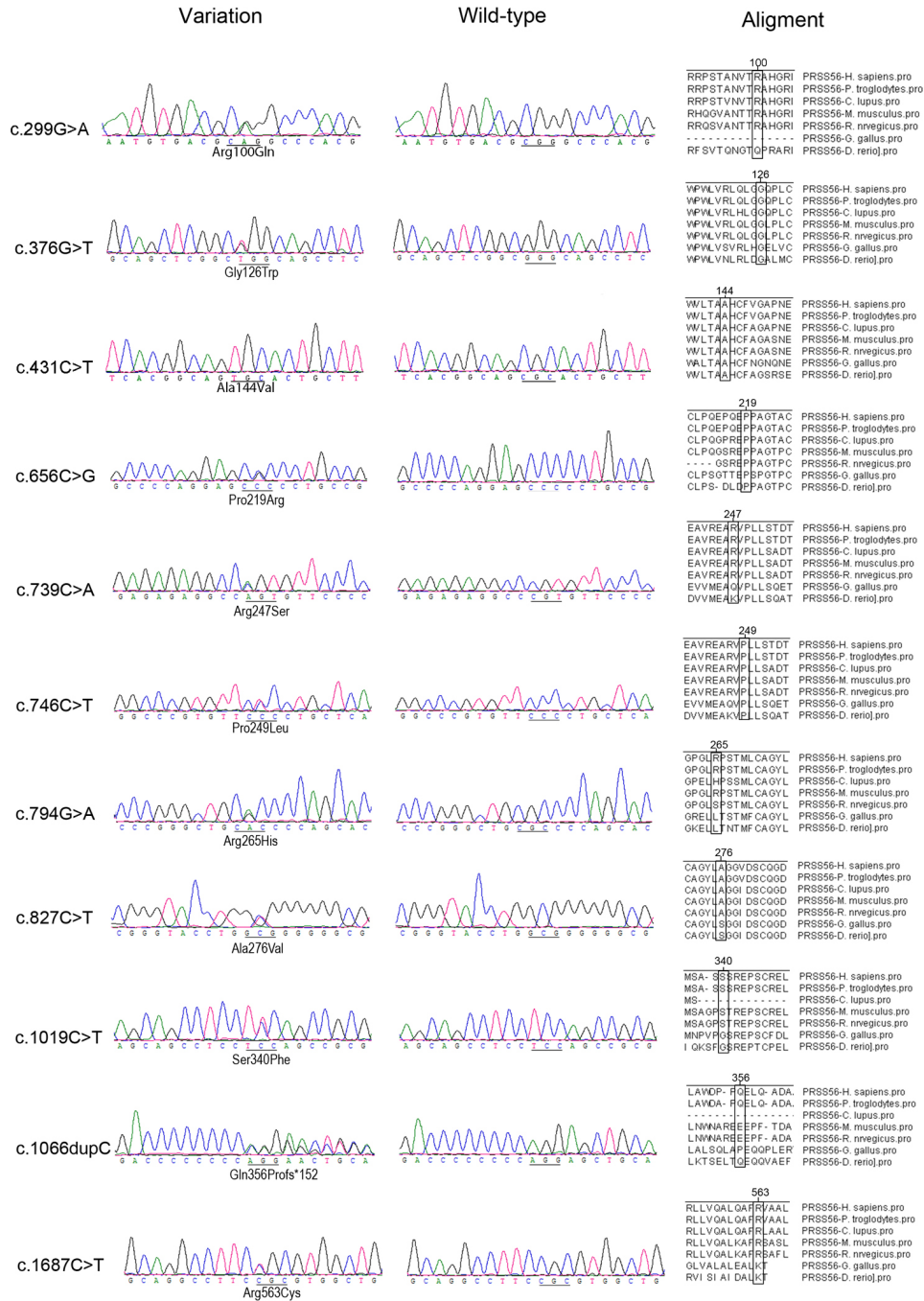


Figure 1. Eleven variations were detected in patients with high hyperopia or primary angle-closure glaucoma. From left to right, the columns represent the names of the variations, the sequences with variations, the corresponding normal sequences, and the protein sequence alignment of seven PRSS56 orthologs at the regions with variants. All of the variants were novel except c.1066dupC.

and 22.95 mm in the right and left eye, respectively, and the patient with high hyperopia and heterozygous mutation c.1066dupC had spherical refractions of +6.25 D in the right eye and +6.75D in the left eye. These features were similar to but less severe than the findings in posterior microphthalmia and nanophthalmos, in which the refractive errors ranged

from +10 D to +18 D and the ocular axial length varied from 14 mm to 20 mm [51,52,56]. The patient with PACG who carried a homozygous mutation (c.431C>T, p.Ala144Val) in the PRSS56 gene also presented a more severe phenotype of PACG, with an ocular axial length of 15.9 mm. Furthermore, the frequency of the variations in the patients with high

TABLE 2. COMPARISON OF PRSS56 VARIATIONS BETWEEN PROBANDS AND CONTROL SUBJECTS.

Samples	Total alleles	Variant alleles	Normal alleles	Frequency of variants	P
189 PACG	378	6	372	1.59	0.336
262 NC	524	4	520	0.76	
110 HH	220	9	211	4.09	0.003
262 NC	524	4	520	0.76	
189 PACG and 110 HH	598	15	583	2.51	0.034
262 NC	524	4	520	0.76	

PACG: primary angle-closure glaucoma; HH: high hyperopia; and NC: normal control. Comparisons were performed using Fishers' exact test, $\alpha=0.05$.

hyperopia significantly differed from that in the controls ($p=0.003$). A significant p value was also obtained when the total patients (PACG and high hyperopia) and the normal controls were compared ($p=0.024$).

Taken together, our results suggest that heterozygous and homozygous mutations in *PRSS56* may be implicated in PACG and high hyperopia, as homozygous mutations observed in mice with angle-closure glaucoma or in humans with posterior microphthalmia or anophthalmia. Further studies are required to confirm the association of our findings.

APPENDIX 1. PRIMERS USED FOR AMPLIFICATION AND SEQUENCING OF THE PRSS56 GENE.

To access the data, click or select the words "[Appendix 1.](#)" Note: The # and * marks indicate that the primers were the same as those in previous studies [51,52].

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TABLE 3. CLINICAL DATA OF PROBANDS AND AFFECTED FAMILY MEMBERS WITH HIGH HYPEROPIA AND PRSS56 VARIATIONS.

Patient	Variation	Gender	Age*	Best visual acuity		Refraction (diopters)		AL (mm)	
			(years)	OD	OS	OD	OS	OD	OS
QT900	c.[376G>T];[=]	M	36	0.05	0.8	8	7	20.12	20.17
QT900D#	c.[376G>T];[=]	F	5	1.00-	1.00-	5	4	20.87	21.21
QT488	c.[656C>G];[=]	M	7	0.4	0.1	9.5	9.75	N/A	N/A
QT616	c.[739C>A];[=]	M	23	0.4	0.5	10.5	10.25	20.5	20.41
QT922	c.[746C>T];[=]	F	3	FVS	FVS	6.5	6	18.98	18.92
QT297	c.[794G>A];[=]	M	9	0.6	0.3	9.25	9.25	N/A	N/A
QT490	c.[827C>T];[=]	M	7	0.1	1	8	7	N/A	N/A
QT968	c.[1019C>T];[=]	M	4	0.3	0.3	13	13	16.97	17.11
QT316	c.[1066dupC];[=]	M	4	1	0.8	6.25	6.75	N/A	N/A
QT703	c.[1687C>T];[=]	M	22	0.05	1	6	6	21.61	21.7
QT703S#	c.[1687C>T];[=]	F	27	0.5	0.4	6.25	4.75	20.06	20.41

*Age at diagnosis #QT900D is the daughter of QT900; QT703S is the sister of QT703. FVS=follow the visual stimulus; AL=axial length; N/A=not available.

TABLE 4. CLINICAL DATA OF PROBANDS WITH PACG AND PRSS56 VARIATIONS.

Patient	Variation	Gender	Age* (years)	Visual acuity		IOP (mmHg) [#]		C/D		ACD		AL		Angle closure		Visual field defects	
				OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
G106	c.[299G>A]; [=]	F	65	0.6	0.6	19	9	1	0.8	1.4	1.6	NA	180°	360°	temporal island	Photo sensitivity ↓	
G165	c.[299G>A]; [=]	F	65	0.3	0.3	71	58	0.3	0.6	1.78	1.65	NA	120°	360°	temporal island	nasal stepped	
G228	c.[376G>T]; [=]	F	73	0.2	0.3	35.8	65.8	NA	NA	1.354	0.984	NA	360°	360°	NA	NA	
G207	c.[431C>T]; [431C>T]	F	61	0.1	NLP	11.7	25	NA	NA	1.49	NA	15.9	360°	360°	NA	NA	
G182	c.[1066dupC]; [=]	M	65	1	0.1	22	24	NA	0.8	1.2	1	23.05	180°	360°	tunnel	tunnel	

* Age at diagnosis. # IOP for G106, G207 and G182 were measured after PACG surgery. NA: not available

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