Molecular Vision 2006; 12:649-54 <http://www.molvis.org/molvis/v12/a73/>
Received 10 February 2006 | Accepted 2 June 2006 | Published 12 June 2006

Evaluation of the association between *OPA1* polymorphisms and primary open-angle glaucoma in Barbados families

Wenliang Yao,[1] Xiaodong Jiao,[1] J. Fielding Hejtmancik,[1] M. Cristina Leske,[2] Anselm Hennis,[2,3] Barbara Nemesure,[2] the Barbados Family Study Group

[1]Ophthalmic Genetics and Visual Function Branch, National Eye Institute, Bethesda, MD; [2]School of Medicine, Stony Brook University, Stony Brook, NY; [3]Ministry of Health and University of the West Indies, Bridgetown, Barbados

Purpose: To investigate whether single nucleotide polymorphisms (SNPs) in the *OPA1* gene are associated with two primary open-angle glaucoma (POAG) subgroups: those with elevated intraocular pressure (POAG/IOP) and those with normal tension glaucoma (NTG) in the African-Caribbean population of Barbados, West Indies.

Methods: SNPs at intervening sequence (IVS) 8, +4, and +32 of the *OPA1* gene were directly sequenced from 48 individuals with POAG/IOP, 48 nonglaucomatous controls, and 61 people with NTG. The remaining exons of *OPA1* were screened for sequence variations in the same 48 POAG/IOP participants and 48 controls by denaturing high performance liquid chromatography (dHPLC), and identified variations were confirmed by bidirectional sequencing. Genotype and allele frequencies of all SNPs were compared for statistically significant differences using the χ^2 and Fisher's exact test. Haplotypes and compound genotypes were also analyzed to evaluate the combined effect of the two IVS8 SNPs.

Results: The analyses of the genotype and haplotype frequencies of IVS8 +4 and +32 do not show statistically significant differences between those with POAG/IOP or NTG and controls. At IVS8 +32, although there are suggestions of possible associations of the CC genotype with NTG (χ^2=3.81, p=0.05), and the TC genotype with POAG/IOP (χ^2=4.23, p=0.04), these differences do not reach statistical significance at the level of 0.017 after a Bonferroni correction. In addition, the combined genotype comparisons at IVS8 +32 do not support the association (for controls compared to NTG χ^2=4.19, p=0.12, df=2; and for controls compared to POAG χ^2=4.83, p=0.09, df=2). Sixteen variants are observed in the OPA1 gene, of which 10 are novel. Neither genotype nor allele frequencies of any SNP are found to be associated with POAG/IOP.

Conclusions: Although some results are suggestive, there is not sufficient evidence to support an association of the SNPs evaluated in *OPA1* with POAG/IOP or NTG in the African-Caribbean population of Barbados, West Indies.

Glaucoma is one of the leading causes of blindness worldwide [1]. Primary open angle glaucoma (POAG), a major type of glaucoma, is characterized by progressive optic disc cupping and loss of retinal ganglion cells, resulting in gradual damage to the peripheral visual fields. POAG is a genetically heterogeneous disease. So far, at least three genes, myocilin (*MYOC*), optineurin (*OPTN*), and WD40-repeat 36 (*WDR36*) [2-4], and four other chromosomal loci have been implicated in POAG [5-8].

POAG is more prevalent in African-derived than European-derived populations. The prevalence of POAG in African-Caribbean populations is particularly high, approximately 7% in Barbados and 8.8% in St. Lucia, West Indies, as compared to 1% in most white populations [9-11]. A genome-wide scan was previously performed for POAG in a total of 146 Barbadian families comprising 1,327 individuals of African origin [12]. Evidence for linkage of POAG in these families was found on chromosome arms 2q and 10p. *MYOC*, *OPTN*, the cytochrome P450 gene *CYP1B1*, and the retina-specific gene *MPP4* were excluded as candidate genes by direct sequencing.

Recently, two polymorphisms, IVS8+4C>T and IVS8+32T>C, within the *OPA1* gene were reported to be associated with normal tension glaucoma (NTG), a subgroup of POAG, in a Caucasian population [13,14]. Mutations in *OPA1* previously have been shown to cause autosomal dominant optic atrophy (ADOA), a neuropathy resulting from degeneration of the retinal ganglion cells and optic nerve atrophy [15,16]. In contrast, association of *OPA1* polymorphisms with NTG could not be demonstrated in either Japanese or Korean NTG patients [17]. The differing results might relate to ethnic differences in the genetic causes of NTG in the Caucasian and Asian populations studied. The possible association of *OPA1* with NTG or perhaps with all POAG in an African-derived population has not been evaluated previously. In this study, therefore, we investigated whether SNPs in the *OPA1* gene were associated with NTG or POAG with elevated intraocular pressure (POAG/IOP) in the African-Caribbean population of Barbados.

METHODS

Study population: Institutional Review Board approval was obtained for this study by all participating institutions. Study participants gave informed consent consistent with the tenets

Correspondence to: J. Fielding Hejtmancik, MD, PhD, Ophthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD, 20892-1860; Phone: (301) 496-8300; FAX: (301) 435-1589; email: f3h@helix.nih.gov

of the Declaration of Helsinki. These participants were Barbados residents of African descent who represent a subset of individuals from the Barbados Family Study of Glaucoma (BFSG) [12,18]. All participants were Barbadians of African-Caribbean ethnic origin. As described in a previous report [12], all participants received a comprehensive ophthalmologic examination using standardized methods and procedures, including anthropometric and blood pressure measurements, best corrected visual acuity based on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart, Humphrey perimetry with the C64 suprathreshold program, C24-2 and C30-2 full threshold programs, applanation tonometry, pupil dilatation, lens gradings with the Lens Opacities Classification System II [19], and color stereo fundus photographs of the disc and macula.

In our previous study [12], we performed genotyping on 1,327 individuals from 146 families with a history of glaucoma. Of these, 350 participants were found to have POAG or suspect glaucoma. The diagnosis of POAG was conservative and required the presence of both visual field and optic disc abnormalities typical of glaucoma in at least one of eye after the exclusion of other possible causes. The majority of POAG cases in this study had an intraocular pressure (IOP) greater than or equal to 21 mmHg as well as a history of IOP-lowering treatment. Only 61 unrelated persons had NTG. For the present investigation, 48 randomly selected and unrelated POAG probands with an IOP >21 mmHg (classified as POAG/IOP; the average age in years was 67.1, ranging from 25-85), 48 randomly chosen and unrelated controls without glaucoma (the average age was 61.3, ranging from 52-76), and all of the 61 unrelated NTG participants (the average age was 52.1, ranging from 25 to 85) were chosen from among the BFSG families. The criteria for NTG in this study included the presence of glaucomatous optic disc changes as well as visual field changes in participants with IOP consistently below 21 mmHg without medical treatment. Controls were recruited from individuals seen for other eye diseases who had no diagnostic findings consistent with glaucoma and had an IOP strictly less than 21 mmHg without antihypertensive treatment. They were not excluded for having affected relatives, and were similar in this respect to the general nonglaucomatous population. Controls were matched as far as possible by average age rather than through a one-to-one matching procedure.

DNA analysis: Genomic DNA was extracted from blood samples by standard salting out and phenol-chloroform extraction procedures [20]. Exon 8, including the two polymorphisms (IVS8+4 and IVS8+32) of known interest, was sequenced directly in all samples. Haplotype analysis for these single nucleotide polymorphisms (SNPs) was straightforward because the T allele at IVS8+4 was only found in conjunction with the T allele at IVS8+32 (Table 1). The remaining 27 coding exons of the *OPA1* gene (GenBank NT_005612) and their adjacent intronic sequences were amplified by specific primers, and then were analyzed by denaturing high-performance liquid chromatography (dHPLC, Wave System; Transgenomic Inc., San Joes, CA) with two to three optimized melting temperatures predicted by WAVEMAKER™ (Transgenomic Inc.). During the analyses, different chromatographic patterns were detected and assembled automatically if variations were harbored in the sequences. The variations were confirmed by direct sequencing using dye-labeled terminators (BigDye Terminator version 1.1; Applied Biosystems, Inc., Foster City, CA). Sequencing reactions were purified by gel filtration (Performa DTR System; Edge Biosystem, Gaithersburg, MD), before electrophoresis on an ABI 3100 Genetic Analyzer.

Statistical analysis: Genotype and allele frequencies for individual polymorphisms were compared for statistically sig-

Table 1. Haplotype and compound genotype frequencies of the single nucleotide polymorphisms (SNPs) at IVS8 +4 and +32

Haplotype						
IVS8 +4	IVS8 +32	NTG n (%)	POAG/IOP n (%)	Controls n (%)	p (NTG)	p (POAG)
C	T	55 (45.1)	55 (57.3)	56 (58.3)	0.05	0.88
C	C	64 (52.5)	40 (41.7)	38 (39.6)	0.06	0.77
T	T	3 (2.4)	1 (1.0)	2 (2.1)	1.00*	1.00*
Combined comparison: p(NTG)=0.15, df=2; p(POAG)=0.82, df=2						
Compound genotype						
IVS8 +4	IVS8 +32	NTG n (%)	POAG/IOP n (%)	Controls n (%)	p (NTG)	p (POAG)
CC	TT	11 (18.0)	19 (39.6)	14 (29.2)	0.16	0.28
CC	TC	30 (49.2)	16 (33.3)	26 (54.2)	0.61	0.04
CC	CC	17 (27.9)	12 (25.0)	6 (12.5)	0.05	0.12
CT	TT	3 (4.9)	1 (2.1)	2 (4.2)	1.00*	1.00*
Combined comparison: p(NTG)=0.32, df=3; p(POAG)=0.14, df=3						

The significance for comparing normal tension glaucoma (NTG) participants with controls and for comparing POAG/IOP participants with controls are shown under the headings p (NTG) and p (POAG), respectively. For multiple comparisons, the significance p values are at the level of 0.017 for three comparisons and 0.013 for four comparisons. The asterisk indicates that Fisher's exact test was applied due to small sample size.

nificant differences between affected and control groups using the χ^2 test and Fisher's exact test. To account for multiple comparisons carried out on the *OPA1* IVS8 genotype polymorphisms, a Bonferroni correction was applied, and the p value was evaluated at the significance level of 0.013 for four comparisons and 0.017 for three comparisons (Table 1, Table 2).

RESULTS

The 48 participants with POAG/IOP and 48 normal controls showed a total of 16 sequence variations in the exons and flanking intronic sequences of *OPA1* (Table 3), of which 10 were novel. Two sequence changes, S158N and A210V, resulted in amino acid changes in the protein, and two more occurred in the coding sequence but did not change the amino acid sequence. As can be seen from Table 3, the differences in genotype and allele frequencies between individuals with POAG/IOP and controls were not significant for any of these polymorphisms.

The genotype frequencies of *OPA1* alleles in this study are in Hardy-Weinberg equilibrium except for the polymorphisms at position IVS18 +51, where both the POAG and control groups show a paucity of heterozygotes (5-6 individuals fewer than predicted) and IVS 26 +25, where both POAG and control groups show a paucity of heterozygotes (2-5 individuals fewer than predicted) and ex21 + 96 where the control group only shows a paucity of 5 heterozygotes (Table 3). A marginally significant (χ^2=4.74, p=0.03) lack of Hardy-Weinberg equilibrium was also detected in the POAG group at position IVS8 +32, where there is a deficit of 7 heterozygotes (Table 2). These are not significant when tested for multiple testing, and in any event none of these alleles appear to be associated POAG or NTG.

As seen in Table 2, the χ^2 analysis for the TC genotype at +32 showed a possible association with POAG/IOP (χ^2=4.23, p=0.04), and the CC genotype frequency was more prevalent in the NTG group (χ^2=3.81, p=0.05), but these differences did not reach statistical significance at the level of 0.017 after a Bonferroni correction for three comparisons. In addition, the combined genotype comparisons at +32 did not support the association (χ^2=4.19 p=0.12, df=2; χ^2=4.83, p=0.09, df=2) and the C allele frequency at +32 indicated a marginal but not statistically significant difference (χ^2=3.58, p=0.06). Testing of the IVS8+4 and IVS8+32 polymorphisms in the BFSG samples revealed no significant differences in the frequency distributions between the affected groups (NTG and POAG/IOP) and the control group.

It was noted that the IVS8+4C>T polymorphism was very rare in this study. The T allele only contributed to 2.5% of alleles in persons with NTG, 1.0% of alleles in individuals with POAG/IOP, and 2.1% of alleles in unaffected controls (Table 2). Furthermore, we could not find the TT genotype, and the TC haplotype did not occur in this study (Table 1).

Since the compound genotype at IVS8+4 and IVS8+32 has been reported to be strongly associated with NTG in other populations, the haplotypes for the IVS8 +4/+32 SNPs were examined further. As seen in Table 1, the χ^2 analysis for the CT and CC haplotypes between individuals with NTG and controls showed marginal differences (χ^2=3.78, p=0.05; χ^2=3.58, p=0.06; respectively). A comparison of the combined haplotypes indicated that there was no significant difference between NTG and controls (χ^2=3.79, p=0.15, df=2). Similarly, in comparing the compound genotype CC/TC of POAG/IOP participants with the control group, the difference (p=0.04) was marginally significant, but this significance was lost after adjustment of the required p value to 0.013 for four comparisons using a Bonferroni correction.

DISCUSSION

In this work we examine possible associations between polymorphisms of the *OPA1* gene and individuals with POAG/IOP or NTG in the African-Caribbean population of Barbados, West Indies. Although such a relationship has been suggested for Caucasians [13,14], no significant association of

Table 2. Genotype and allele frequencies of the SNPs at IVS8 +4 and +32

Location	Allele	Genotype	NTG n (%)	POAG/IOP n (%)	Controls n (%)	p (NTG)	p (POAG)
IVS8 +4	C		119 (97.5)	95 (99.0)	94 (97.9)		
	T		3 (2.5)	1 (1.0)	2 (2.1)	0.11*	1.00*
		CC	58 (95.1)	47 (97.9)	46 (95.8)		
		CT	3 (4.9)	1 (2.1)	2 (4.2)	0.11*	1.00*
IVS8 +32#	T		58 (47.5)	56 (58.3)	58 (60.4)		
	C		64 (52.5)	40 (41.7)	38 (39.6)	0.06	0.77
		TT	14 (22.9)	20 (41.7)	16 (33.3)	0.23	0.40
		TC	30 (49.2)	16 (33.3)	26 (54.2)	0.61	0.04
		CC	17 (27.9)	12 (25.0)	6 (12.5)	0.05	0.12

Combined comparison: p(NTG)=0.12, df=2; p(POAG)=0.09, df=2

The significance for comparing normal tension glaucoma (NTG) participants with controls and for comparing POAG/IOP participants with controls are shown under the headings p (NTG) and p (POAG), respectively. For three comparisons, significant p values are at 0.017. The asterisk indicates that Fisher's exact test was applied due to small sample size and the sharp (hash mark) indicates that the IVS8 +32 alleles show a marginally significant deviation from Hardy-Weinberg equilibrium in the POAG group only.

SNPs in the *OPA1* gene is seen with POAG/IOP or NTG in the BFSG. This lack of association includes the 10 novel sequence changes identified in this study, as well as the two IVS8 polymorphisms for which associations have been reported in the Caucasian population. Similarly, the various combined haplotypes of the IVS8 polymorphisms fail to show significant associations with either POAG/IOP or NTG. The lack of association between alleles and haplotypes of *OPA1* SNPs and POAG/IOP or NTG in the Barbados population is consistent with the absence of linkage to the *OPA1* region seen in our previous study [12], although linkage and association studies provide complementary information regarding the genetic pathogenesis of diseases.

Aung et al. [13] and Powell et al. [14] reported that polymorphisms of the *OPA1* gene are associated with NTG in a Caucasian population. However, this association was not seen in Korean and Japanese populations [17], suggesting that differences may exist with regard to the genetic pathogenesis of POAG in Caucasian and Asian populations. Such differences had already been noted with regards to the roles of myocilin and optineurin in POAG in the BFSG [12]. Together, these findings raised the question of whether *OPA1* polymorphisms, especially those in IVS8, might be associated with NTG specifically or perhaps with POAG in general, in an African-Caribbean population.

The results seen by Powell et al. [14] and Aung et al. [13] in Caucasian populations differ somewhat. Aung et al. [13] reported that the IVS8+4 CT genotype and the compound genotype IVS8+4 CT, +32 TC were strongly associated with NTG, whereas Powell's data only supported an association of the IVS8+32TC genotype with NTG, for which no independent association was seen by the Aung group. In addition, the Powell group reported 6 of 9 possible genotypes at the +4/+32 position, but only four were seen in the study by Aung et al. [13] which did not identify CC/CC and TT/TT homozygotes. It is notable that the IVS8+4C>T polymorphism is common in Caucasians, accounting for about 30% of genotypes in Caucasians with NTG and 12.4% to 33.9% in Caucasian controls [13,14]. However, this polymorphism is rare in the African-Caribbean population, contributing less than 5.0% of geno-

Table 3. OPA1 SNPs and the allele and genotype frequencies

Location	Nucleotide change	Genotype	Codon changes	POAG/IOP n (%)	Controls n (%)	p (gene)	p (allele)
IVS 3a -21	g.23940A>G*	A/G		8 (16.7)	7 (14.6)	0.57	0.45
		G/G		1 (2.1)	0 (0)		
		A/A		39 (81.2)	41 (85.4)		
ex3b +25	g.23985A>G	A/G	S158N	25 (52.1)	24 (50.0)	0.96	0.88
		G/G		7 (14.6)	8 (16.7)		
		A/A		16 (33.3)	16 (33.3)		
IVS 3b -104	g.24463T>A*	T/A		2 (4.2)	5 (10.4)	0.44**	0.44**
		T/T		46 (95.8)	43 (89.6)		
IVS 3c -19	g.25633T>C*	T/C		18 (37.5)	25 (52.1)	0.28	0.66
		C/C		12 (25.0)	7 (14.6)		
		T/T		18 (37.5)	16 (33.3)		
ex4 +19	g.25670C>T*	C/T	A210V	1 (2.1)	1 (2.1)	1.00**	1.00**
		C/C		47 (97.9)	47 (97.9)		
IVS4 -8	g.32867C>T*	C/T		2 (4.2)	0 (0)	0.49**	0.50**
		C/C		46 (95.8)	48 (100)		
IVS8 +37	g.44101A>C*	A/C		10 (20.8)	6 (12.5)	0.27	0.3
		A/A		38 (79.2)	42 (87.5)		
IVS8 -74	g.44661A>C*	A/C		5 (10.4)	8 (16.7)	0.37	0.39
		A/A		43 (89.6)	40 (83.3)		
ex17 +18	g.53866A>C*	A/C	A536A	2 (4.2)	3 (6.3)	1.00**	1.00**
		A/A		46 (95.8)	45 (93.7)		
IVS18 +13	g.54930T>C*	T/C		2 (4.2)	1 (2.1)	1.00**	1.00**
		T/T		46 (95.8)	47 (97.9)		
IVS18 +51#	g.54968G>T	T/T		3 (6.3)	3 (6.3)	1.00**	1.00**
		G/G		45 (93.7)	45 (93.7)		
ex21 +96#	g.63958T>C	T/C	A703A	10 (20.8)	5 (10.4)	0.35	0.52
		C/C		2 (4.2)	3 (6.3)		
		T/T		36 (75.0)	40 (83.3)		
IVS 26+25#	g.73197T>A	T/A		4 (8.3)	2 (4.2)	0.43	0.58
		A/A		1 (2.1)	3 (6.3)		
		T/T		43 (89.6)	43 (89.6)		
IVS 27 +23	g.74086T>C*	T/C		4 (8.3)	4 (8.3)	1.00**	1.00**
		T/T		44 (91.7)	44 (91.7)		

The significance for comparing the genotype frequencies and for comparing the allele frequencies are shown under the headings p (gene) and p (allele), respectively. Both tests are estimated by a χ^2 test (df=2). The double asterisk indicates that the Fisher exact test was applied due to small sample size. The single asterisk indicates a novel variation. The sharp (hash mark) indicates that the polymorphisms show mild deviations from Hardy-Weinberg equilibrium. The table summarizes data from 48 POAG patients and 48 controls.

types in either affected individuals or unaffected controls in this study (Table 2). This suggests that the rare T allele of IVS8+4 in the Barbados population may explain the lack of association seen with POAG/IOP in this study, consistent with results in Asian populations [17].

One limitation of this study is the relatively small sample size. There are only 61 unrelated NTG individuals among 350 POAG cases. This is a relatively low ratio. Generally, NTG accounts for approximately one-third of all POAG cases. Small sample size in this study could be a possible reason why Hardy-Weinberg disequilibrium at a boundary level was detected in the POAG group at IVS8+32. However, even from the analysis of 157 participants (48 POAG/IOP, 61 NTG and 48 controls), the distributions of the *OPA1* genotype frequencies in the affected and control groups are comparable. None of the distributions are significantly different, although there are possible associations noted with the IVS8+32TC genotype and POAG/IOP and with the IVS8+32CC genotype and NTG. Thus, while this study cannot completely eliminate the possibility of a contribution of the IVS8 polymorphisms to POAG/IOP or NTG, it suggests that these polymorphisms do not exert a major risk in this African-Caribbean population. Similarly, this study cannot address the possibility of risk contributed by the IVS8+4 C/T polymorphism in other studies, since the T allele is rare in the African-Caribbean population of Barbados. However, even with the small sample sizes available, these results can exclude an effect giving relative risks less than 0.1 or greater than 4 for all of the polymorphisms studied with 95% power, placing an effective limit on their importance in this population.

In summary, we were unable to demonstrate any significant associations of SNPs in *OPA1* (chromosome 3q28) with POAG/IOP or NTG in the BFSG. This is consistent with previous results mapping POAG in Barbados to loci on chromosomes 2q and 10p [12], although the possibility of additional loci was not excluded in that study. While *OPA1* does not appear to have a major role in determining risk to POAG in this population, a small effect could not be excluded. More genes will be evaluated as candidates for contributing to POAG in this population, especially those in the linked regions on chromosomes 2q and 10p. The African-Caribbean population in Barbados provides a unique opportunity to evaluate potential genetic contributions to glaucoma, as it is a relatively isolated population with a high rate of POAG when compared with Caucasians and other ethnic groups.

ACKNOWLEDGEMENTS

We thank the study participants, The Ministry of Health, and the Department of Ophthalmology, Queen Elizabeth Hospital, Bridgetown, Barbados, for their assistance. This research was supported by the National Eye Institute (EYO11000). The BFSG Study Group; M. Cristina Leske, MD, MPH (Principal Investigator), Coordinating Center-University at Stony Brook, Stony Brook, NY (M. C. Leske, MD, MPH, Barbara Nemesure, PhD, Qimei He, PhD, Suh-Yuh Wu, MS, Nancy Mendell, PhD, Lixin Jiang, MS, Kasthuri Sarma, Koumudi Manthani). Data Collection Center-Ministry of Health, Bridgetown, Barbados, West Indies (Anselm Hennis, MRCP (UK), PhD, M. Ann Bannister, MB, BS, DO, MRCOphth, Muthu Thangaraj, MB, BS, DO, MRCOphth, Rajiv Luthra, MD, MPH, Coreen Barrow, Anthanette Holder). Fundus Photography Reading Center-The Johns Hopkins University, Baltimore, MD (Andrew P. Schachat, MD, Judith A. Alexander, Deborah Phillips, Reva Ward-Strozykowski). Laboratory Center-The National Eye Institute, Bethesda, MD (James Fielding Hejtmancik, MD, PhD, Xiaodong Jiao, PhD). Local Advisory Group-Trevor Hassell, MBBS, FRCP, FACC, GCM (Department of Cardiology) and Henry Fraser, FACP, FRCP (UK), PhD, GCM (Chronic Diseases Research Centre) School of Clinical Medicine and Research, University of the West Indies, Barbados, West Indies; Clive Gibbons, FRCS (Ed), FRCP, FCOph (UK; Department of Ophthalmology) Queen Elizabeth Hospital, Barbados, West Indies.

REFERENCES

1. Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. Bull World Health Organ 1995; 73:115-21.
2. Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, Heon E, Krupin T, Ritch R, Kreutzer D, Crick RP, Sarfarazi M. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science 2002; 295:1077-9.
3. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, Nishimura D, Clark AF, Nystuen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC. Identification of a gene that causes primary open angle glaucoma. Science 1997; 275:668-70.
4. Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, Liebmann J, Ritch R, Heon E, Crick RP, Child A, Sarfarazi M. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. Hum Mol Genet 2005; 14:725-33.
5. Stoilova D, Child A, Trifan OC, Crick RP, Coakes RL, Sarfarazi M. Localization of a locus (GLC1B) for adult-onset primary open angle glaucoma to the 2cen-q13 region. Genomics 1996; 36:142-50.
6. Trifan OC, Traboulsi EI, Stoilova D, Alozie I, Nguyen R, Raja S, Sarfarazi M. A third locus (GLC1D) for adult-onset primary open-angle glaucoma maps to the 8q23 region. Am J Ophthalmol 1998; 126:17-28.
7. Wirtz MK, Samples JR, Kramer PL, Rust K, Topinka JR, Yount J, Koler RD, Acott TS. Mapping a gene for adult-onset primary open-angle glaucoma to chromosome 3q. Am J Hum Genet 1997; 60:296-304.
8. Wirtz MK, Samples JR, Rust K, Lie J, Nordling L, Schilling K, Acott TS, Kramer PL. GLC1F, a new primary open-angle glaucoma locus, maps to 7q35-q36. Arch Ophthalmol 1999; 117:237-41.
9. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA 1991; 266:369-74.
10. Mason RP, Kosoko O, Wilson MR, Martone JF, Cowan CL Jr, Gear JC, Ross-Degnan D. National survey of the prevalence and risk factors of glaucoma in St. Lucia, West Indies. Part I. Prevalence findings. Ophthalmology 1989; 96:1363-8.
11. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol 1994; 112:821-9.
12. Nemesure B, Jiao X, He Q, Leske MC, Wu SY, Hennis A, Mendell

N, Redman J, Garchon HJ, Agarwala R, Schaffer AA, Hejtmancik F, Barbados Family Study Group. A genome-wide scan for primary open-angle glaucoma (POAG): the Barbados Family Study of Open-Angle Glaucoma. Hum Genet 2003; 112:600-9.

13. Aung T, Ocaka L, Ebenezer ND, Morris AG, Krawczak M, Thiselton DL, Alexander C, Votruba M, Brice G, Child AH, Francis PJ, Hitchings RA, Lehmann OJ, Bhattacharya SS. A major marker for normal tension glaucoma: association with polymorphisms in the OPA1 gene. Hum Genet 2002; 110:52-6.
14. Powell BL, Toomes C, Scott S, Yeung A, Marchbank NJ, Spry PG, Lumb R, Inglehearn CF, Churchill AJ. Polymorphisms in OPA1 are associated with normal tension glaucoma. Mol Vis 2003; 9:460-4.
15. Alexander C, Votruba M, Pesch UE, Thiselton DL, Mayer S, Moore A, Rodriguez M, Kellner U, Leo-Kottler B, Auburger G, Bhattacharya SS, Wissinger B. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat Genet 2000; 26:211-5.
16. Delettre C, Lenaers G, Griffoin JM, Gigarel N, Lorenzo C, Belenguer P, Pelloquin L, Grosgeorge J, Turc-Carel C, Perret E, Astarie-Dequeker C, Lasquellec L, Arnaud B, Ducommun B, Kaplan J, Hamel CP. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nat Genet 2000; 26:207-10.
17. Woo SJ, Kim DM, Kim JY, Park SS, Ko HS, Yoo T. Investigation of the association between OPA1 polymorphisms and normal-tension glaucoma in Korea. J Glaucoma 2004; 13:492-5.
18. Leske MC, Nemesure B, He Q, Wu SY, Fielding Hejtmancik J, Hennis A. Patterns of open-angle glaucoma in the Barbados Family Study. Ophthalmology 2001; 108:1015-22.
19. Chylack LT Jr, Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). Arch Ophthalmol 1989; 107:991-7.
20. Smith RJ, Holcomb JD, Daiger SP, Caskey CT, Pelias MZ, Alford BR, Fontenot DD, Hejtmancik JF. Exclusion of Usher syndrome gene from much of chromosome 4. Cytogenet Cell Genet 1989; 50:102-6.

The print version of this article was created on 12 Jun 2006. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.