OPA1 increases the risk of normal but not high tension glaucoma

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ABSTRACT

Background Primary open angle glaucoma is a progressive optic neuropathy characterised by the selective loss of retinal ganglion cells, pathological optic disc cupping and visual field defects. The *OPA1* gene encodes an inner mitochondrial membrane protein crucial for normal mitochondrial function, and pathogenic mutations cause autosomal dominant optic atrophy by specifically targeting retinal ganglion cells. This raises the distinct possibility that more subtle genetic variations in *OPA1* could alter the risk of developing glaucoma.

Methods 137 patients with primary open angle glaucoma (67 patients with high-tension glaucoma (HTG), 70 patients with normal-tension glaucoma (NTG)) and 75 controls from the North East of England were studied. Three single-nucleotide polymorphisms in intron 8 (IVS8+4c→t and IVS8+32t→c) and exon 4 (c.473A→G) of the *OPA1* gene were genotyped in the study group. In addition, the entire *OPA1* coding region was sequenced in 24 individuals with the CT/TT compound genotype using standard BigDye chemistries.

Results There was no difference in either allele or genotype frequency for the IVS8+32t→c single-nucleotide polymorphisms between patients and controls, but there was a significant association between the T allele at IVS8+4c→t and the risk of developing NTG (OR=2.04, 95% CI=1.10 to 3.81, p=0.004), but not HTG. Logistic regression analysis also confirmed a strong association between the CT/TT compound genotype at IVS8+4 and IVS8+32 with NTG (OR=29.75, 95% CI=3.83 to 231.21, p=0.001).

Conclusions The CT/TT compound genotype at IVS8+4 and IVS8+32 is a strong genetic risk determinant for NTG but not HTG.

INTRODUCTION

Primary open angle glaucoma (POAG) is the second most common cause of blindness in developed countries and accounts for about 10% of all blind registration in the UK.[1] It affects over 60 million people worldwide, and, with an ageing population, the prevalence of POAG is expected to increase by 30% in the next 20 years.[2] POAG is characterised by the selective, progressive loss of retinal ganglion cells (RGCs), leading to structural changes at the optic nerve head in the form of pathological cupping and visual field loss. The most significant risk factors for the development of glaucoma are raised intraocular pressure (IOP), increasing age, a positive family history in a first-degree relative and ethnicity (Black>Hispanic>Caucasian>Asian).[3 4] In the non-glaucomatous population, IOP follows a normal distribution with a mean of 16.0 mm Hg and a SD of 2.5 mm Hg, giving a statistical upper limit of 21.0 mm Hg. About two-thirds of patients with POAG have IOPs >21.0 mm Hg at initial presentation, referred to as high-tension glaucoma (HTG), whereas the remainder with IOPs ≤21.0 mm Hg are classified as having normal-tension glaucoma (NTG).[3 4]

POAG is a complex disease with a strong genetic component, and multiple susceptibility loci have been identified in populations from different ethnic backgrounds.[3 5] Four causative genes have been identified so far: *optineurin* (*OPTN*, OMIM 602432) on chromosome 10p14-15, *myocilin* (*MYOC*, OMIM 610652) on chromosome 1q24-25, *CYP1B1* (OMIM 601771) on chromosome 2p21-22, and *WDR36* (OMIM 609669) on chromosome 5q21-22, but these account for fewer than 5–10% of patients with sporadic, adult-onset POAG. Interestingly, a maternal family history of POAG is 6–8 times more likely than a paternal family history, which suggests a possible mitochondrial genetic influence.[6–8] Furthermore, mitochondrial abnormalities have been identified in patients with POAG, with an increase in mitochondrial DNA (mtDNA) content and a reduction in mitochondrial respiratory chain activities.[9] The preferential loss of RGCs in glaucoma is also a key pathological feature seen in Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA), the two most common inherited optic neuropathies. Both these conditions are the result of mitochondrial dysfunction; LHON comes from primary mtDNA mutations affecting the respiratory chain complexes, and the majority of DOA families have mutations in the *OPA1* gene (3q28-q29), which codes for an inner mitochondrial membrane protein critical for mitochondrial maintenance, oxidative phosphorylation and regulation of apoptosis.[10]

Two single-nucleotide polymorphisms (SNPs) within intron 8 of the *OPA1* gene (IVS8+4c→t and IVS8+32t→c) have been linked with an increased risk of developing POAG in some, but not all, populations studied.[11–15] To further clarify the influence of *OPA1* in modulating susceptibility to glaucoma, we have performed an analysis of *OPA1* SNPs in a well-characterised cohort of patients with POAG, and in addition reviewed the literature to compare the strength of the association identified in other study groups.

METHODS

Patient and control samples

We investigated a well-characterised Caucasian cohort consisting of 137 patients with POAG (mean (SD) age=71.6 (8.0) years) and 75 controls

(mean (SD) age=79.3 (4.4) years) from the North East of England, a region that has been relatively stable in terms of migratory flux.[16 17] The POAG group consisted of 67 HTG patients with a mean (SD) pre-treatment IOP of 23.1 (2.0) mm Hg (range 22–28) and 70 NTG patients with a mean (SD) pre-treatment IOP of 17.7 (2.2) mm Hg (range 13–21). Both cases and controls underwent a full ophthalmological examination including: (1) IOP measurement by Goldmann applanation tonometry, (2) gonioscopy to confirm open drainage angles, (3) dilated fundal examination, and (4) Humphrey full-threshold 24:2 visual field perimetry. All patients had unequivocal evidence of glaucoma, with both pathological optic disc cupping and characteristic visual field defects. HTG patients with IOPs >30 mm Hg were not included in this study. Control subjects were unaffected spouses of patients with POAG, and other ocular pathologies were carefully excluded. Genomic DNA was extracted from whole blood using established methods[16 17] and stored at −80°C for future molecular genetic investigations, with prior approval having been obtained from our local research ethics committee.

OPA1 genotyping

The two SNPs in intron 8 (IVS8+4c→t and IVS8+32t→c) were genotyped using the following primers to generate a 383 bp PCR product: (1) forward, 5′-TGAAGTTCTTGATGTTCTCTCTG-3′; (2) reverse, 5′-ATGGCTAATTTAATCCACTGTTC-3′. In the second phase of this study, the entire coding region of the *OPA1* gene was amplified in 24 individuals with the CT/TT compound genotype (HTG, N=10; NTG, N=12; controls, N=2), using a set of 27 M13-tagged primer pairs (available on request). Genotyping for the c.473A→G SNP located in exon 4 was also determined for the entire study cohort, using the following primers to generate a 341 bp PCR product: (1) forward, 5′-GGGTTGTCATGAGGATTAAACAA-3′; (2) reverse 5′-AAAAATGTCCTGTTTTTCATTGG-3′. For all three SNPs (IVS8+4c→t, IVS8+32t→c and c.473A→G) and the entire *OPA1* coding region, PCR products were purified and sequenced using BigDye terminator cycle chemistries on an ABI3100 Genetic Analyser (Applied Biosystems, Warrington, UK). Sequence results were then compared with the GenBank *OPA1* reference sequence (Accession number AB011139) using SeqScape software v2.1.

mtDNA haplogroups

The mtDNA haplogroup status for both patients and controls had previously been determined by restriction fragment analysis of amplified PCR fragments spanning specific informative sites within the mitochondrial genome.[18] Haplogroups K, W, I, V, X and M were present in less than 5% of our control population and these were analysed as a single group.

Statistical analysis

The Hardy–Weinberg equilibrium for *OPA1* genotypes was assessed for patients and controls (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl), and statistical analyses were performed using SPSS v15 statistical software. Allele and genotype SNP frequencies were compared using the Fisher exact test and χ^2 analysis, with Bonferroni correction for multiple comparisons where applicable. Binary logistic regression was also used for multivariate analysis of other possible confounding factors that could influence the risk of developing glaucoma. This form of analysis assumes that the logarithm of the odds ratio (OR) is a linear function of the predictor variables included in the model:

$$\mathrm{Log}(P/1-P) = B_0 + B_1X_1 + B_2X_2 + \ldots B_nX_n$$

where P is the probability of developing glaucoma, X_1, $X_2 \ldots X_n$ represent the chosen predictor variables, and B_0, $B_1 \ldots B_n$ are coefficients reflecting the nature of each predictor.[19] The independent variables used in our model were: (1) age, (2) gender, (3) maximum pre-treatment IOP, (4) mtDNA haplogroup and (5) IVS8+4 and IVS8+32 compound genotype.

RESULTS

Intron 8 SNPs

Both POAG and control groups were in Hardy–Weinberg equilibrium at IVS8+4c→t and IVS8+32t→c. The T allele at IVS8+4c→t was over-represented among NTG patients compared with controls (OR=2.04, 95% CI=1.10 to 3.81, p=0.03), but there was

Table 1 Allele and genotype frequencies for the IVS8+4c→t and IVS8+32t→c *OPA1* SNPs

	Controls (N=75)	Whole group (N=137)		HTG (N=67)		NTG (N=70)	
(A) IVS8+4c→t							
Allele			p Value		p Value		p Value
C	131 (87.3%)	222 (81.0%)		114 (85.1%)		108 (77.1%)	
T	19 (12.7%)	52 (19.0%)	0.096	20 (14.9%)	0.581	32 (22.9%)	0.030*
Genotype			p Value†		p Value†		p Value†
CC	59 (78.7%)	90 (65.7%)		49 (73.1%)		41 (58.6%)	
CT	13 (17.3%)	42 (30.7%)		16 (23.9%)		26 (37.1%)	
TT	3 (4.0%)	5 (3.6%)	0.106	2 (3.0%)	0.061	3 (4.3%)	0.025*
(B) IVS8+32t→c							
Allele			p Value		p Value		p Value
T	79 (52.7%)	155 (56.6%)		60 (44.8%)		59 (42.1%)	
C	71 (47.3%)	119 (43.4%)	0.440	74 (55.2%)	0.666	81 (57.9%)	0.375
Genotype			p Value‡		p Value‡		p Value‡
TT	21 (28.0%)	41 (29.9%)		12 (17.9%)		11 (15.7%)	
TC	37 (49.3%)	73 (53.3%)		36 (53.7%)		37 (52.9%)	
CC	17 (22.7%)	23 (16.8%)	0.578	19 (28.4%)	0.769	22 (31.4%)	0.566

χ^2 analysis of all three possible genotypes at †IVS8+4C→T and ‡IVS8+32T→C.
*Significant p value.
SNP, single-nucleotide polymorphisms.

Table 2 Compound genotype frequencies for the IVS8+4c→t and IVS8+32t→c *OPA1* single-nucleotide polymorphisms

IVS8+4	IVS8+32	Patients	Controls	p Value*	OR	95% CI
(A) Whole group						
TT	TT	5 (3.6%)	3 (4.0%)	1.000	0.91	0.21 to 3.92
CT	TT	22 (16.1%)	2 (2.7%)	0.003*	6.98	1.59 to 30.59
CT	TC	20 (14.6%)	11 (14.7%)	0.989	0.99	0.45 to 2.21
CC	TT	14 (10.2%)	16 (21.3%)	0.026	0.42	0.19 to 0.92
CC	TC	53 (38.7%)	26 (34.7%)	0.563	1.19	0.66 to 2.14
CC	CC	23 (16.8%)	17 (22.7%)	0.296	0.69	0.34 to 1.39
(B) HTG						
TT	TT	2 (3.0%)	3 (4.0%)	1.000	0.74	0.12 to 4.56
CT	TT	10 (14.9%)	2 (2.7%)	0.013	6.40	1.35 to 30.40
CT	TC	6 (9.0%)	11 (14.7%)	0.316	0.57	0.20 to 1.64
CC	TT	7 (10.4%)	16 (21.3%)	0.110	0.43	0.17 to 1.12
CC	TC	30 (44.8%)	26 (34.7%)	0.216	1.53	0.78 to 3.01
CC	CC	12 (17.9%)	17 (22.7%)	0.483	0.74	0.33 to 1.70
(C) NTG						
TT	TT	3 (4.3%)	3 (4.0%)	1.000	1.08	0.21 to 5.51
CT	TT	12 (17.1%)	2 (2.7%)	0.004*	7.55	1.63 to 35.10
CT	TC	14 (20.0%)	11 (14.7%)	0.396	1.46	0.61 to 3.46
CC	TT	7 (10.0%)	16 (21.3%)	0.062	0.41	0.16 to 1.07
CC	TC	23 (32.9%)	26 (34.7%)	0.818	0.92	0.46 to 1.84
CC	CC	11 (15.7%)	17 (22.7%)	0.289	0.64	0.27 to 1.48

*Significant with Bonferroni correction: $p<0.008$.

no significant difference in allele frequency for the HTG and whole POAG groups. Similarly, there was a significant difference in the distribution of the three IVS8+4c→t genotypes for the NTG group (p=0.025), but not for the HTG or whole POAG groups (table 1A). There was no significant difference in either allele or genotype frequency for the IVS8+32t→c SNP when comparing all POAG cases, HTG and NTG subgroups with controls (table 1B).

Compound genotype

Analysis of both IVS8+4c→t and IVS8+32t→c SNPs showed a significant increased risk of glaucoma in subjects with the CT/TT compound genotype for the whole POAG group (OR=6.98, 95% CI=1.59 to 30.59, p=0.003) and NTG group (OR=7.55, 95% CI=1.63 to 35.10, p=0.004). Although there was a trend towards a higher risk of HTG with the CT/TT compound genotype (p=0.013), this was not significant after Bonferroni correction (table 2). The CT/TT compound genotype was also not associated with higher pre-treatment IOPs or worse cup to disc ratios (CDRs), in both the HTG and NTG groups ($p>0.05$, data not shown).

Logistic regression

Binary logistic regression confirmed a significantly increased risk of developing glaucoma with the CT/TT compound genotype for the whole patient group (OR=56.52, 95% CI=5.98 to 533.78, $p<0.001$) and those with NTG (OR=29.75, 95% CI=3.83 to 231.21, $p<0.001$), but not for the HTG group (table 3). None of the mtDNA haplogroups were significant risk factors for glaucoma. Although haplogroup J was over-represented among NTG patients compared with controls (p=0.045), this fell below the level for statistical significance with Bonferroni correction.

OPA1 haplotype

We sequenced the entire *OPA1* coding region of all 24 individuals with the CT/TT compound genotype at IVS8+4 and IVS8+32 (HTG, N=10; NTG, N=12; controls, N=2), and no previously described pathogenic mutations were identified. However, all of them shared the same haplotype, with homozygosity at both the c.473A→G (p.N158S) and c.2109C→T (p.A703A) SNPs, except for one NTG patient (figure 1A). The latter was heterozygous for the c.473A→G and c.2109C→T SNPs, and also had two additional heterozygous SNPs at c.575C→T (p.A192V) and

Table 3 Logistic regression analysis comparing patients with POAG with controls

	Whole group		HTG		NTG	
Predictor variables	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
mtDNA haplogroup†						
H	0.62 (0.26 to 1.50)	0.292	0.97 (0.43 to 2.18)	0.934	0.51 (0.20 to 1.28)	0.151
T	0.42 (0.12 to 1.48)	0.176	0.65 (0.21 to 2.00)	0.457	0.37 (0.10 to 1.45)	0.154
J	3.79 (0.86 to 16.63)	0.077	1.64 (0.34 to 8.05)	0.540	4.42 (1.04 to 18.92)	0.045
U	1.68 (0.50 to 5.62)	0.401	2.02 (0.62 to 6.62)	0.246	1.85 (0.53 to 6.38)	0.332
Others	0.82 (0.24 to 2.82)	0.757	0.65 (0.19 to 2.21)	0.490	0.72 (0.21 to 2.52)	0.609
Compound genotype‡						
CT/TT	56.52 (5.98 to 533.78)	<0.001*	9.91 (1.74 to 56.57)	0.010	29.75 (3.83 to 231.21)	<0.001*

Our logistic regression models also incorporated the following predictor variables with the controls acting as the reference group: (1) age, (2) gender, and (3) maximum IOP, except in the HTG subgroup where maximum IOP was not included;
*Significant with Bonferroni correction: †$p<0.01$, ‡$p<0.008$.
IOP, intraocular pressure; HTG, high-tension glaucoma; mtDNA, mitochondrial DNA; NTG, normal-tension glaucoma; POAG, primary open angle glaucoma.

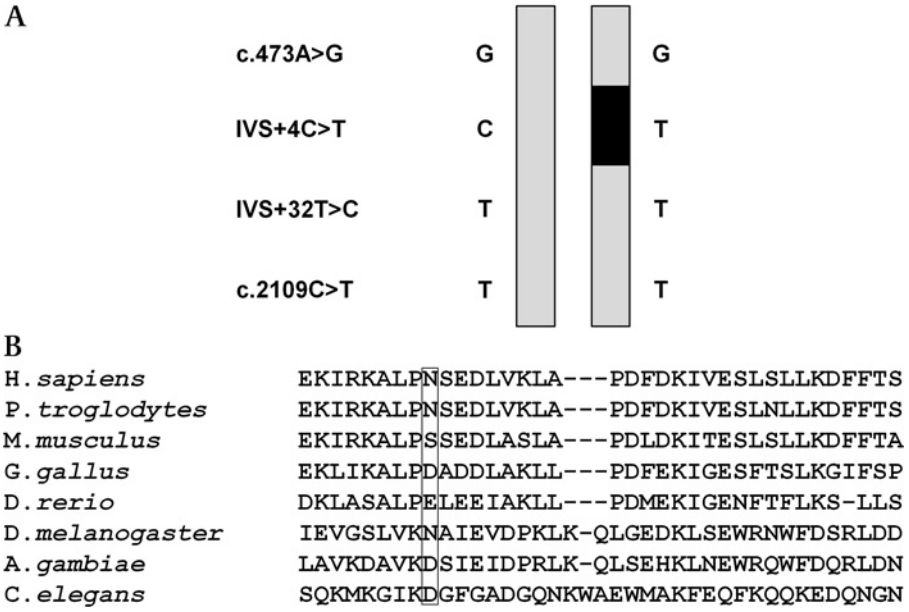

Figure 1 (A) Shared *OPA1* haplotype in individuals with the IVS8+4 and IVS8+32 CT/TT compound genotype. (B) Alignment of the 36 amino acids encoded by exon 4, indicating the poor evolutionary conservation of the codon altered by the c.473A→G SNP (p.N158S) in both lower vertebrates and invertebrates.

c.1608A→C (p.A536A). Further analysis of the non-synonymous c.473A→G (p.N158S) SNP in our entire study cohort did not show any statistically significant difference between our patient and control groups (table 4).

DISCUSSION

This study has identified a strong association between specific *OPA1* polymorphisms at IVS8+4c→t and IVS8+32t→c and the risk of glaucoma. Subgroup analysis based upon pre-treatment IOPs further indicated that the susceptibility conferred by these two SNPs was largely restricted to the NTG group. This is compatible with the notion that non-IOP-related factors are probably more important in the pathophysiology of NTG than of HTG.[3 5] The T allele at IVS8+4 led to a twofold increased risk of NTG, and, although the IVS8+32 SNP on its own was not a risk factor, compound genotype analysis suggested a synergistic influence with the IVS8+4 SNP and identified CT/TT as the high-risk compound genotype.

To confirm our initial findings, we performed a more rigorous logistic regression analysis to control for the possible influence of other variables that might affect the risk of developing glaucoma, thereby minimising the chance of identifying a spurious association. The OR for the CT/TT compound genotype remained highly significant, and was associated with a 30-fold increased risk of NTG, independent of age, gender, maximum pre-treatment IOP and mtDNA haplogroup. However, the CT/TT compound genotype was not associated with markers of disease severity, either higher pre-treatment IOPs or worse optic disc cupping, supporting the conclusions of a previous report.[20] MtDNA haplogroup J was also over-represented among the NTG group compared with controls, although this became non-significant with Bonferroni correction. Nevertheless, this is an interesting observation given that the mtDNA background is thought to exert a direct effect on the assembly of the mitochondrial respiratory chain complexes,[21] and haplogroup J specifically has been linked with an increased risk of visual loss among Caucasian LHON mutation carriers,[22] the classic example of an inherited mitochondrial optic neuropathy.

We performed a literature review to identify all previous *OPA1* glaucoma association studies, including unpublished meeting abstracts, and there is a consistent lack of association between the IVS8+4 and IVS+32 SNPs and HTG (table 5). A high-risk compound genotype for developing NTG was found in two studies involving British Caucasian subjects[11 13] and one Japanese study,[23] with the latter reporting a weaker association. However, no association was identified in other populations of Asian[14 15 24] and African extraction,[25 26] possibly indicating that the influence of *OPA1* polymorphisms on NTG is limited to certain ethnic groups or it has a smaller effect (OR <1.5), not detectable by the sample size (<100) used in most of these studies. In this respect, it is worth noting that the control groups in these studies indicate a marked variation in the frequency of

Table 4 Allele and genotype frequencies for the c.473A→G *OPA1* single-nucleotide polymorphism

		Allele			Genotype			
	N	A	G	p Value	AA	AG	GG	p Value*
Whole group	137	128 (46.7%)	146 (53.3%)		26 (19.0%)	76 (55.5%)	35 (25.5%)	
Controls	75	75 (50.0%)	75 (50.0%)	0.543	19 (25.3%)	37 (49.3%)	19 (25.3%)	0.531
HTG	67	65 (48.5%)	69 (51.5%)		13 (19.4%)	39 (58.2%)	15 (22.4%)	
Controls	75	75 (50.0%)	75 (50.0%)	0.813	19 (25.3%)	37 (49.3%)	19 (25.3%)	0.548
NTG	70	63 (45.0%)	77 (55.0%)		13 (18.6%)	37 (52.9%)	20 (28.6%)	
Controls	75	75 (50.0%)	75 (50.0%)	0.818	19 (25.3%)	37 (49.3%)	19 (25.3%)	0.613

*χ^2 analysis of all three possible genotypes at c.473A→G.

Table 5 Summary of previous studies investigating the role of *OPA1* polymorphisms in POAG

		Significant association				High-risk compound genotype (NTG)		
Study*	**Population**	**HTG**	**N**	**NTG**	**N**	**IVS8+4/+32**	**Odds ratio†**	**95% CI**
[11,12]	Caucasian	No	90	Yes	163	CT/TC	6.25	2.67 to 14.59
[13]	Caucasian	N/A	–	Yes	61	CC/CC	2.71	1.31 to 5.57
[14]	Japanese	N/A	–	No	337	–	–	–
[15]	Korean	N/A	–	No	65	–	–	–
[24]	Indian	N/A	–	No	50	–	–	–
[24]	Chinese	N/A	–	No	53	–	–	–
[24]	Japanese	N/A	–	No	42	–	–	–
[25]	African-Caribbean	No	48	No	61	–	–	–
[23]	Japanese	No	191	Yes	194	CC/TC	2.14	1.32 to 3.45
[26]	Caucasian	No	279	N/A	–	–	–	–
[26]	African-American	No	193	N/A	–	–	–	–
[26]	African	No	170	N/A	–	–	–	–

*Studies in chronological order.
†ORs were derived by χ^2 analysis using published figures and additional unpublished data provided by Dr Vincent Raymond (Personal communication) for study [14].
N/A, not assessed; N, number of patients analysed; POAG, primary open angle glaucoma.

the minor T allele at IVS8+4c→t in different populations: Caucasian (7–18%), African (2–5%) and Asian (1–2%). Of note, the three other studies that have found a significant association between *OPA1* and NTG have all identified different high-risk compound genotypes from the one identified in our study. As case–control studies are open to several sources of bias which can be difficult to control, this could be due to a spurious population stratification effect. Alternatively, association with different alleles in the same gene can occur when the actual susceptibility allele is in linkage disequilibrium with the SNPs under investigation.

What are the possible explanations for the increased risk of NTG in individuals harbouring the CT/TT compound genotype? The majority of pathogenic *OPA1* mutations are truncative (>70%), and the reduction in protein concentration implicates haploinsufficiency as the underlying process leading to optic nerve degeneration in DOA.[27] Opa1 is a multi-functional protein and its crucial pro-fusion properties contribute to the maintenance of a highly interconnected mitochondrial network within cells.[10] It is therefore not surprising that mitochondrial fragmentation is a prominent feature in fibroblasts cultured from patients with DOA, with the release of cytochrome *c* from the mitochondrial compartment precipitating the onset of apoptotic cell death.[28 29] A recent study has also found murine RGCs to be more sensitive to the downstream events of mitochondrial fragmentation and pro-apoptotic stimuli than other neuronal populations.[30] As the IVS8+4 SNP is located within the donor splice site region, the CT/TT compound genotype may exert an effect, albeit unproven, on mRNA transcript concentrations, which would then potentiate RGC loss by disrupting the delicate balance between mitochondrial fusion and fission. However, the more pronounced effect seen in NTG compared to HTG clearly implicates other mechanisms, and additional investigations are required.

Unlike other association studies, we also sequenced the whole *OPA1* coding region, firstly to exclude the possibility of pathogenic mutations because DOA is quite often misdiagnosed as NTG in clinical practice,[31] and secondly to explore the possibility that IVS8+4 and IVS8+32 are actually tagging SNPs in linkage disequilibrium with another functional *OPA1* variant. Except for one NTG patient, all individuals carrying the CT/TT compound genotype shared the same *OPA1* haplotype, with homozygosity at both the c.473A→G (p.N158S) and c.2109C→T (p.A703A) SNPs, suggesting a common ancestral event. Subsequent analysis of our entire cohort did not identify any significant difference in allele or genotype frequency at the poorly conserved, non-synonymous c.473A→G SNP in exon 4 (figure 1B). However, our study has not excluded the possibility that the IVS8+4 and IVS8+32 SNPs are in linkage disequilibrium with another causative gene in the vicinity of *OPA1* or the presence of *OPA1* intronic variants regulating mRNA splicing or transcriptional activity.

The finding of a significant association between the specific combination of *OPA1* polymorphisms and NTG does not imply causation, and, although biologically plausible, our results require additional functional confirmation, for example by comparing the bioenergetics and mitochondrial network morphology of fibroblasts obtained from patients with and without the high-risk CT/TT compound genotype. With a rapidly ageing population, glaucoma will remain an important cause of visual morbidity, and a greater understanding of the complex genetic influences that lead to RGC loss will have important implications both for the identification and screening of high-risk groups and in identifying pathophysiological pathways that could be amenable to therapeutic intervention.

Key points

- Primary open angle glaucoma (POAG) is the second leading cause of blindness in developed countries, and on the basis of their pre-treatment intraocular pressures (IOPs), patients are classified as having either high-tension glaucoma (HTG, IOP >21.0 mm Hg) or normal-tension glaucoma (NTG, IOP ≤21.0 mm Hg).
- Although POAG is a late-onset acquired optic neuropathy, it has a major genetic basis and it shares striking clinical and pathological overlap with autosomal dominant optic atrophy (DOA), which is the result of mutations in the *OPA1* gene.
- In this study, we demonstrate a strong association between two specific *OPA1* SNPs (IVS8+4c→t and IVS8+32t→c) and the risk of developing NTG but not HTG. The high-risk CT/TT compound genotype conferred a 30-fold increased risk of disease, supporting a possible role of the Opa1 protein in the pathophysiology of NTG.

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