The phenotype of normal tension glaucoma patients with and without OPA1 polymorphisms


Glaucoma, the leading cause of irreversible blindness worldwide,\(^1,2\) is typified by progressive loss of optic nerve axons and visual field damage. Normal tension glaucoma (NTG) is an important subtype of glaucoma in which intraocular pressures (IOP) are within the statistically normal population range, and accounts for approximately a third of all primary open angle glaucoma cases.\(^3,4\) Although there is evidence for the role of genetic factors in NTG,\(^2,5\) the molecular mechanisms underlying NTG are unknown. The discovery of optineurin as a causative gene suggests that one mechanism producing NTG may involve apoptosis of retinal and optic nerve ganglion cells.\(^6\)

Autosomal dominant optic atrophy (ADOA) is another condition with slowly progressive optic nerve damage.\(^7-10\) In ADOA patients, excavation of the optic nerve may develop, and such patients are occasionally misdiagnosed as having NTG.\(^11\) Mutations in OPA1 (MIM No 605290), the gene responsible for ADOA, were recently found to result in primary degeneration of retinal ganglion cells.\(^12\) The similarities between glaucoma and ADOA (in terms of the cell type affected and the phenotype) make OPA1 a good candidate gene for glaucoma, particularly NTG.

A recent study found an association between polymorphisms in the OPA1 gene and NTG.\(^13\) Approximately 20% of NTG subjects were found to carry one single nucleotide polymorphisms (SNPs) on intervening sequence (IVS) eight of the OPA1 gene (IVS 8 +4 C/T; +32 T/C), compared to only 3.7% of control subjects (\(X^2 = 22.04, p = 0.00001\)), indicating that this genotype is strongly associated with NTG, and may represent a diagnostic marker for the disease.\(^14\) This observation raises the possibility that different subgroups of NTG exist, one of which is distinguished by genetic variations in OPA1. The aim of this study was to compare clinical features of NTG patients with and without such polymorphisms in order to determine whether OPA1 polymorphisms impart a characteristic phenotype in NTG patients.

METHODS

A retrospective analysis was performed of 108 white NTG patients who had been previously genotyped for OPA1 variations. There were 25 NTG patients (group 1) with, and 83 NTG patients (group 2) without the at-risk OPA1 genotype IVS 8 +4 C/T; +32 T/C. These patients attended a tertiary referral glaucoma clinic and had undergone various investigations including automated perimetry and Heidelberg retina tomography (HRT, Heidelberg Engineering, Heidelberg, Germany). NTG cases were defined by the following strict criteria: the presence of typical glaucomatous optic neuropathy with compatible visual field loss; mean IOP without treatment that was consistently equal to or less than 21 mm Hg on diurnal testing, open drainage angles on gonioscopy, and absence of a secondary cause for glaucomatous optic neuropathy, such as a previously raised IOP following trauma, a period of steroid administration or uveitis. Only one eye from each patient was included. For bilateral cases, the right eye was analysed. The study had the approval of the Moorfield’s Eye Hospital ethics committee and was performed in accordance with the Helsinki Declaration.

Patients’ hospital records were reviewed and the following data collected: demographic characteristics including sex and age at diagnosis; family history of glaucoma; history of ischaemic heart disease and smoking; history of vasospasm such as migraine and cold hands and feet; the presenting and
highest recorded diurnal intraocular pressure (IOP); cup-disc (CD) ratio at presentation; and interocular symmetry of glaucoma.

Visual field analysis
Subjects underwent static automated white on white threshold perimetry (program 24-2, model 640, Humphrey Instruments, Dublin, CA, USA). The first visual field test for all subjects was discarded from the analyses to allow for learning effects, and the subsequent first reliable visual field was used as the baseline. The global indices such as mean deviation (MD), pattern standard deviation (CPSD), and nasal inferior octant (+225 degrees), nasal superior octant (+45 to +90 degrees), temporal superior octant (+90 to +135 degrees), nasal inferior octant (+135 to +225 degrees), nasal superior octant (+45 to +90 degrees), and temporal inferior octant (−90 to −45 degrees). The mean number of progressing locations per subject, the mean slope for the progressing locations as well as the mean slope of the whole visual field per year was evaluated.

Optic disc analysis
The Heidelberg retina tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany) was used to image the optic disc and the baseline optic disc parameters were analysed. The mean topography of three images was generated in the 10 × 10 degree frame and the disc edge delineated on the mean image by a single trained observer (DP), using a drawn contour line. Images with significant movement artefact were rejected. Global and segmental disc and cup areas were analysed directly by means of HRT software (version 2.01b) using the standard reference plane. Rim area was calculated by subtracting the cup area from the disc area. Six predefined segments were used (0 degrees always temporal, 90 degrees always superior): temporal quadrant (−45 to +45 degrees), nasal quadrant (−90 to −45 degrees), nasal inferior quadrant (−135 to −90 degrees), nasal superotemporal quadrant (+45 to +90 degrees), temporal superior quadrant (−90 to −45 degrees), nasal inferior quadrant (−135 to −90 degrees).

Table 1  Demographic features and systemic history

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=25)</th>
<th>Group 2 (n=83)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>21</td>
<td>0.51</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Age of onset &lt;60 years</td>
<td>11</td>
<td>31</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>14</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Family history of glaucoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
<td>28</td>
<td>0.59</td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Ischaemic risk factors</td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>12</td>
<td>33</td>
<td>0.46</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Vasospasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
<td>17</td>
<td>0.41</td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>19</td>
<td>65</td>
<td>0.81</td>
</tr>
<tr>
<td>Unilateral</td>
<td>6</td>
<td>18</td>
<td></td>
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</table>

Table 2  Presenting clinical features

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=25)</th>
<th>Group 2 (n=83)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean presenting IOP (mm Hg)</td>
<td>16.2 (1.8)</td>
<td>17.0 (2.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean highest diurnal IOP (mm Hg)</td>
<td>17.9 (2.3)</td>
<td>18.9 (2.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean presenting cup disc ratio</td>
<td>0.75 (0.1)</td>
<td>0.76 (0.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean presenting MD (dB)</td>
<td>−8.7 (8.4)</td>
<td>−8.0 (6.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean presenting CPSD (dB)</td>
<td>8.5 (4.8)</td>
<td>8.0 (4.3)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure, MD = mean deviation, CPSD = corrected pattern standard deviation.

Table 3  Presenting optic disc parameters, as measured by HRT

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=25)</th>
<th>Group 2 (n=83)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area (mm²)</td>
<td>2.04 (0.41)</td>
<td>2.11 (0.45)</td>
<td>0.77</td>
</tr>
<tr>
<td>Global rim area (mm²)</td>
<td>0.90 (0.31)</td>
<td>0.89 (0.31)</td>
<td>0.88</td>
</tr>
<tr>
<td>Temporal rim area (mm²)</td>
<td>0.13 (0.07)</td>
<td>0.14 (0.07)</td>
<td>0.57</td>
</tr>
<tr>
<td>Temporal superior rim area (mm²)</td>
<td>0.10 (0.04)</td>
<td>0.10 (0.05)</td>
<td>0.80</td>
</tr>
<tr>
<td>Temporal inferior rim area (mm²)</td>
<td>0.10 (0.08)</td>
<td>0.08 (0.06)</td>
<td>0.56</td>
</tr>
<tr>
<td>Nasal rim area (mm²)</td>
<td>0.29 (0.12)</td>
<td>0.30 (0.11)</td>
<td>0.49</td>
</tr>
<tr>
<td>Nasal superior rim area (mm²)</td>
<td>0.13 (0.06)</td>
<td>0.14 (0.05)</td>
<td>0.63</td>
</tr>
<tr>
<td>Nasal inferior rim area (mm²)</td>
<td>0.16 (0.06)</td>
<td>0.13 (0.06)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

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DISECUSSION
This study did not detect a significant difference in a range of phenotypic features in normal tension glaucoma patients with and without the OPA1 polymorphisms IVS 8 +4 C/T; +32 T/C. This suggests that these specific genetic variations in OPA1 do not underlie any major phenotypic diversity in NTG, although the possibility of more subtle phenotypic differences, such as variable rates of response to treatment cannot be excluded. The mean presenting IOP and the highest diurnal IOP appeared to be lower in NTG patients with the OPA1 polymorphisms (almost reaching significance for the latter), which may indicate that the glaucoma in such patients is less IOP dependent. If this were to be the case, it would suggest that NTG patients have different IOP thresholds for glaucomatous damage to occur, and that those with OPA1 polymorphisms may be at risk of glaucoma at lower IOP levels.

Polymorphisms are associated with a variety of other diseases including Alzheimer's dementia,20 age related macular degeneration,21 diabetes mellitus,22 and schizophrenia.23 Although intronic polymorphisms, of which OPA1 (IVS 8 +4 C/T and +32 T/C) is an example, are associated with conditions like intracerebral haemorrhages and cerebral aneurysms,24 little is known about how intronic polymorphisms influence disease phenotype. Possible mechanisms include regulation of transcription,25 26 effects on protein function, or indirectly by conferring susceptibility in patients to other factor(s) that mediate disease.27

The biochemical mechanisms by which OPA1 may influence NTG remain obscure. The pathogenic characteristics of OPA1 resemble those of Leber hereditary optic neuropathy, which occur in the highly energy demanding neurons of the optic nerve, notably the papillomacular bundle, this implicating hypotension,28 29 systemic hypotension,30 31 and an abnormal coagulability profile.32–36 A strong genetic component is likely to be significant in NTG.

It is hypothesised that several interacting genes contribute to the development of disease, with the putative role of each polymorphic sequence variation influenced by an individual's genetic and environmental background. However the number and identity of genes contributing to NTG has yet to be fully determined. Much remains to be learned about the phenotypic effects of specific genes and alleles in this condition. It is hoped that further research efforts will be directed towards investigating the association of OPA1 polymorphisms found in a substantial proportion of NTG patients, as it may lead to greater understanding of the factors underlying this important cause of blindness.

Table 4 Visual field progression of subjects with at least 5 years of follow up at and at least 10 visual fields performed during this time

<table>
<thead>
<tr>
<th>Subgroup 1 (n=18)</th>
<th>Subgroup 2 (n=70)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with progressing locations</td>
<td>16 (88.9%)</td>
<td>54 (77.1%)</td>
</tr>
<tr>
<td>Mean number of progressing locations per subject (dB/year)</td>
<td>7.89 (14.67)</td>
<td>7.28 (7.77)</td>
</tr>
<tr>
<td>Mean slope of progressing locations per year (dB/year)</td>
<td>-0.51 (0.91)</td>
<td>-0.37 (0.56)</td>
</tr>
<tr>
<td>Mean slope of whole visual field per year (dB/year)</td>
<td>-1.99 (1.62)</td>
<td>-1.92 (1.13)</td>
</tr>
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</table>

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T Aung and K Okada contributed equally to the paper and are joint first authors.

Authors’ affiliations
T Aung, S S Bhattacharya, S S Bhattacharya, Institute of Ophthalmology, University College London, London, UK
T Aung, Singapore National Eye Centre, Singapore
K Okada, Department of Ophthalmology, Hiroshima University Faculty of Medicine, Hiroshima, Japan
G Brice, A H Child, St George’s Hospital Medical School, London, UK
Correspondence to: Dr Tin Aung, Department of Molecular Genetics, Institute of Ophthalmology, Bath Street, London EC1V 9EL, UK; aung_tin@yahoo.co.uk

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