Clinical Features and Course of Patients with Glaucoma with the E50K Mutation in the Optineurin Gene

Tin Aung,[1,2,3] *Tayebeh Rezaie,*[4] *Koji Okada,*[1,5] *Ananth C. Viswanathan,*[1] *Anne H. Child,*[6] *Glen Brice,*[6] *Shomi S. Bhattacharya,*[3] *Ordan J. Lehmann,*[1,3,7] *Mansoor Sarfarazi,*[4] *and Roger A. Hitchings*[1]

Purpose. To investigate the clinical features of subjects with glaucoma with the E50K mutation in the optineurin (*OPTN*) gene and to compare the onset, severity, and clinical course of these patients with a control group of subjects with glaucoma without this mutation.

Methods. The phenotype of well-characterized subjects from Moorfields Eye Hospital, London, who had been identified as carrying the *OPTN* E50K mutation was examined. A wide range of structural, psychophysical, and demographic factors were then compared with those in a control group of subjects with glaucoma without this mutation.

Results. Eleven subjects with glaucoma with the E50K mutation (nine in two families and two sporadic cases) were studied. All 11 subjects had normal tension glaucoma (NTG), with presenting and highest IOP of 15.3 ± 3.0 and 16.5 ± 2.5 mm Hg (±SD) on diurnal testing. Compared with 87 NTG control subjects who did not have this mutation, subjects with E50K presented at a younger age (40.8 ± 15 years, $P = 0.0001$) and had more advanced optic disc cupping (mean cup-disc ratio ± SD 0.86 ± 0.1, $P = 0.001$) and smaller neuroretinal rim area (±SD; 0.5 ± 0.28 mm^2, $P = 0.001$) at diagnosis. The rate of filtration surgery performed for progressive visual field loss in those with and without the E50K mutation was 72.7% and 25.3%, respectively ($P = 0.003$), and all subjects with E50K were found to have progressing visual fields. In addition, seven E50K mutation-carrying individuals in two families (age range, 23–58 years) presented with normal optic discs and visual fields and, as yet, no signs of glaucoma.

Conclusions. In this study, subjects with glaucoma who had the *OPTN* E50K mutation were found to have NTG that appeared to be more severe than that in a control group of subjects with NTG without this mutation. The findings emphasize the importance of early detection and treatment of glaucoma in such individuals, to minimize visual loss. (*Invest Ophthalmol Vis Sci.* 2005;46:2816–2822) DOI:10.1167/iovs.04-1133

Glaucoma, the leading cause of irreversible blindness worldwide affecting approximately 70 million people,[1,2] is typified by progressive loss of optic nerve axons and visual field damage. Because it is insidious, the disease is frequently detected only when patients have advanced irreversible visual impairment. Primary open-angle glaucoma (POAG) is the most common form of glaucoma worldwide and accounts for most of the glaucoma in white and Afro-Caribbean populations.[3–6] The prevalence of POAG increases with age, and intraocular pressure (IOP) is a major risk factor for glaucomatous optic nerve damage.[4,7]

Glaucoma is thought to have a substantial heritable basis, as illustrated by the numerous linked loci, number of genes identified to date, and a significant proportion of patients with glaucoma who show a positive family history.[8–11] In 1997, myocilin (*MYOC*, MIM 601652; Mendelian Inheritance in Man; National Center for Biotechnology Information, Bethesda, MD) mapping to the 1q24.3 region,[12] was the first gene found to be mutated in patients with POAG.[13] Subsequent studies found that *MYOC* mutations account for fewer than 5% of all cases of juvenile- and adult-onset POAG.[13–17] Recently, Rezaie et al.[18] identified a second POAG gene, optineurin (*OPTN*; MIM 602432) from within the *GLC1E* interval on 10p13,[19] and showed that variations in this gene predominantly result in normal tension glaucoma (NTG), a major subtype of POAG, in which IOPs are constantly within the statistically normal population range. The most common *OPTN* mutation, Glu^{50}→Lys (E50K) was found to be a significant cause of glaucoma identified in 13.5% of families studied.[18,20]

Knowledge of the clinical behavior of specific mutations is helpful in disease management by providing patients and clinicians with useful information regarding the course and prognosis of the disease. This is illustrated in POAG with the finding that the Ile477Asn and Tyr437His mutations in the *MYOC* gene are associated with a more severe form of glaucoma with an early age of onset, high IOP, and resistance to medical treatment,[14,21] whereas the Gln368STOP *MYOC* mutation causes a much less virulent form of disease.[14,22–24] The purpose of this study was to investigate the clinical features of subjects with the *OPTN* E50K mutation to determine whether this mutation imparts a characteristic phenotype in patients with glaucoma. The onset, severity, and clinical course of these patients were then compared with those in a group of patients with glaucoma who did not have the *OPTN* E50K mutation.

Methods

The clinical features of all patients attending glaucoma clinics at Moorfields Eye Hospital, London, who had been identified as having the E50K mutation in the *OPTN* gene, were examined. The study had the approval of the Moorfields Eye Hospital ethics committee and was

From the [1]Moorfields Eye Hospital, London, United Kingdom; [2]Singapore National Eye Centre, Singapore; [3]Institute of Ophthalmology, University College London, London, United Kingdom; the [4]University of Connecticut Health Center, Farmington, Connecticut; [5]Hiroshima University Faculty of Medicine, Hiroshima, Japan; [6]St. George's Hospital Medical School, London, United Kingdom; and the [7]University of Alberta, Edmonton, Alberta, Canada.

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Corresponding author: Tin Aung, Consultant, Glaucoma Service, Singapore National Eye Centre, 11, Third Hospital Avenue, Singapore 168751; tin11@pacific.net.sg.

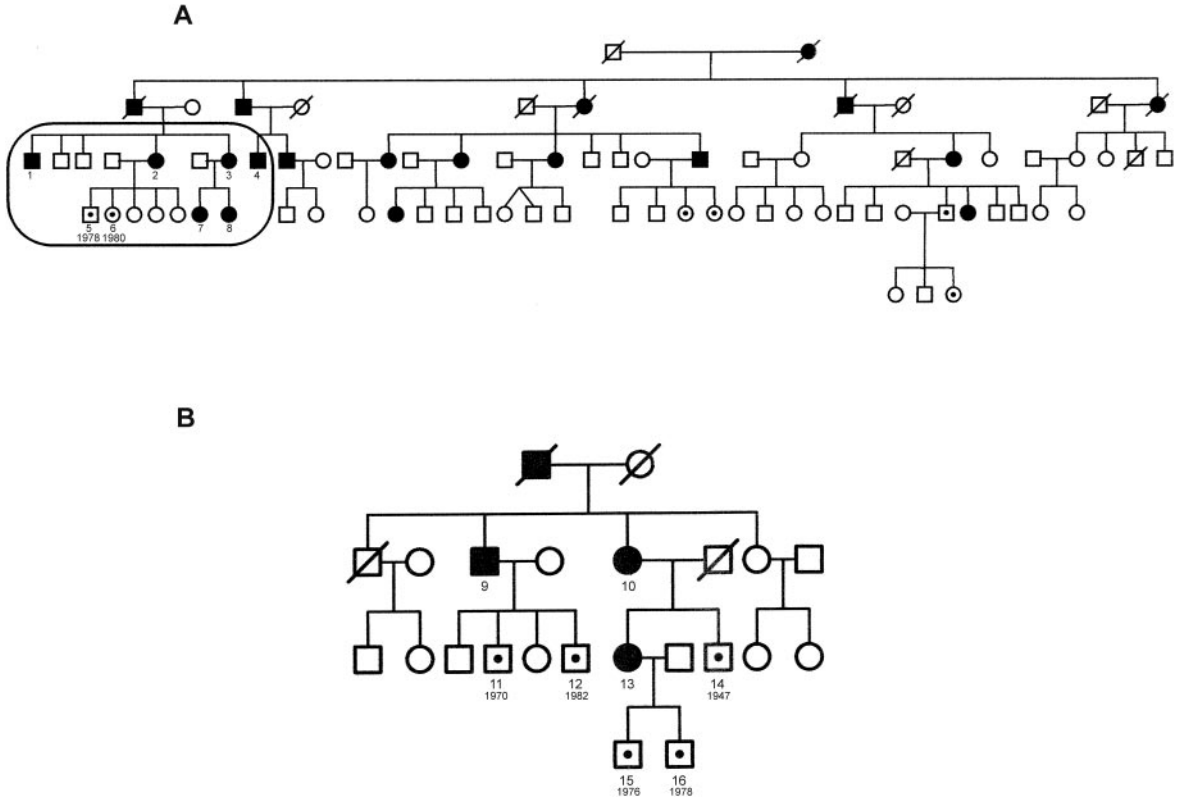

FIGURE 1. Complete pedigree structures for two families with the *OPTN* E50K mutation. (**A**) Pedigree 1, the original *GLC1E*-linked family. The six affected subjects included in this study are shown within a *circle*. (**B**) Pedigree 2. Phenotype information is included on the pedigrees: POAG with E50K mutation (*filled symbols*), asymptomatic mutation carriers (*dotted symbols*), normal individuals without mutation (*unfilled symbols*). *Diagonal line* through a symbol identifies the deceased individuals. Individuals' pedigree number and year of birth (only for the seven asymptomatic mutation carriers included in this study) are shown.

performed in accordance with the Helsinki Declaration. These subjects had been included in four separate genetic studies, the methodologies of which have been described elsewhere[18–20,25] and are summarized as follows. In one study, 54 POAG families were selected from a national database of families with glaucoma, because at least one member of each family had NTG.[18] Seven families were found to have the E50K mutation, of which two families were examined at this hospital, as they lived in the London area. In another study, the possibility of the E50K mutation as a founder effect in the same seven families was excluded.[20] In a more recent study, 315 unrelated persons, cases of sporadic POAG, were screened for the *OPTN* E50K mutation only (but not the entire *OPTN* gene), of which 2 subjects were found to have the mutation.[25]

POAG was defined according to the following diagnostic criteria: the presence of typical glaucomatous optic neuropathy with compatible visual field loss; open drainage angles on gonioscopy; and the absence of a secondary cause for glaucomatous optic neuropathy, such as previous trauma, a period of steroid administration, or uveitis. Patients with POAG who had mean IOP without treatment that was consistently ≤21 mm Hg on diurnal testing were classified as having NTG.

The following data were collected: demographic characteristics including gender and age at diagnosis of glaucoma; family history of glaucoma; history of ischemic risk factors such as hypertension, diabetes mellitus, ischemic heart disease, and smoking; history of vasospasm such as migraine and cold hands and feet; the presenting and highest recorded diurnal IOP as measured by applanation tonometry; cup-disc (CD) ratio at presentation; and interocular symmetry of glaucoma. The treatment administered and history of filtration surgery was also recorded.

Subjects underwent static automated white-on-white threshold perimetry (program 24-2, Humphrey perimeter, model 640; Carl Zeiss Meditec, Dublin, CA). The first two visual field tests for all subjects were discarded from the analyses to allow for learning effects, and the subsequent first reliable visual field was used as the baseline. The global indices, mean deviation (MD), and corrected pattern SD (CPSD) of the baseline visual fields were analyzed. The visual fields of a subgroup of subjects who had at least 5 years of follow-up were also analyzed on computer for progression by point-wise linear regression (Progressor for Windows software; OBF Labs. Ltd., Malmesbury, UK).[26] Progression was defined as the presence of a significant regression slope ($P < 0.01$) showing 1 dB per year or more of sensitivity loss at the same test location with the addition of two of three successive field tests to the series. The mean number of progressing locations, the mean slope for the progressing locations, and the mean slope of the whole visual field per year were evaluated.

The Heidelberg retina tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) was used to image the optic disc, and the baseline optic disc parameters were analyzed. The mean topography of three images was generated in the 10° × 10° frame, and the disc edge was delineated on the mean image by a single trained observer. Images with significant movement artifact were rejected. Global and segmental disc and cup areas were analyzed directly by means of the HRT software (ver. 2.01b) using the standard reference plane.

Control Group

A control group of 87 NTG subjects who did not carry the *OPTN* E50K mutation[25] was selected for comparison, using identical study methodology and data collection. Only those who had undergone repeated automated perimetry (with at least 5 years of follow-up), as well as imaging of the optic disc with the HRT, were eligible for selection as control subjects.

Statistical Analysis

Only one eye of each patient was analyzed. This was randomly selected in bilateral cases, and the affected eye was selected in unilateral cases.

Statistical analysis was performed on computer (Statistical Package for Social Sciences, ver. 9.0; SPSS Inc., Chicago, IL). Parametric and nonparametric tests of significance were performed when appropriate. Comparisons between groups were performed with Mann-Whitney tests for continuous variables that were not normally distributed. The χ^2 analysis was used for comparison of proportions. Statistical significance was assumed at $P < 0.05$, and significant statistical associations were corrected by the Bonferroni test for multiple comparisons (20 comparisons made).

Results

Eleven white subjects with glaucoma treated at Moorfields Eye Hospital had been found to have the *OPTN* E50K mutation.[18,25] Six of the subjects were from one family (circled individuals in pedigree 1; Fig. 1A), which was actually part of an original *GLC1E* pedigree (consisting of 15 living affected individuals) described in three previous publications.[18–20] Although studies had shown that all 15 living affected subjects and 6 asymptomatic members of this family carried the *OPTN* E50K mutation,[18,20] only those examined at Moorfields Eye Hospital were included in the study, and the clinical features of the other subjects from this pedigree were not included. Another three subjects with glaucoma were from a second family (pedigree 2; Fig. 1B).[18,20] The glaucoma phenotype in both pedigrees segregated as an autosomal dominant condition (Fig. 1), and every glaucoma-affected person carried the E50K mutation.[18,20] Two unrelated sporadic NTG cases were also identified with this mutation in a separate study.[25]

Table 1 lists the age, sex, age at diagnosis, laterality, presenting CD ratio, presenting MD and CPSD, and surgical treatment of the 11 patients with the *OPTN* E50K mutation. All 11 subjects were classified as having NTG, with presentation of highest IOP (on diurnal testing) of 15.3 ± 3.0 mm Hg (mean ± SD; range, 12–20) and 16.5 ± 2.5 mm Hg (range, 12–21 Hg), respectively. One subject (individual 2 in pedigree 1; Fig. 1A) had one previous IOP reading of 23 mm Hg (measured by an optician), though IOP was consistently less than 21 mm Hg when measured subsequently in the hospital during diurnal testing. The mean (±SD) corneal thickness was 543 ± 10.6 μm (range, 533–558). The mean age at diagnosis was 40.8 ± 15 years (range, 24–59) with only 2 of 11 subjects diagnosed when older than 50 years. All but one subject had bilateral disease. This 56-year-old (individual 1 in pedigree 1; Fig. 1A) had a cup-disc ratio of 0.8 and visual field defects in one eye, but the other eye had a cup-disc ratio of 0.6 with normal visual fields and HRT tests. The glaucomatous eye had a few signs of pigment dispersion syndrome, but IOP was consistently within the normal range.

Most of the subjects with NTG presented with relatively advanced disease: the mean CD ratio at the time of diagnosis was 0.86 ± 0.1, and all but one subject had a CD ratio ≥0.8. Visual field status was also severe at the time of diagnosis: 8 of 11 subjects had presenting MD < −15.0 dB, and 7 of 11 subjects had presenting CPSD >10.0 dB. One subject was already blind at the time of diagnosis, with bilateral central visual fields of <20°. Eight of the 11 subjects with glaucoma had undergone filtration surgery for progressive visual field loss.

Comparison with the Control Group

The clinical features of the 11 NTG subjects with the *OPTN* E50K mutation were compared with those of 87 NTG subjects without this mutation. There was no significant difference in the two groups with respect to gender, history of ischemic risk factors or vasospasm, or laterality of glaucoma (Table 2). Patients with NTG who had the *OPTN* E50K mutation, however,

Table 1. Clinical Features of Patients with Glaucoma Affected with the *OPTN* E50K Mutation

Pedigree (Fig. 1)	Patient Number	Sex	Age	Age at Diagnosis	Presenting IOP	Highest IOP Recorded on Diurnal Testing	Laterality	Presenting Cup-Disc Ratio	Presenting MD (dB) on Humphrey Perimetry	Presenting CPSD (dB) on Humphrey Perimetry	Filtering Surgery
1	1	Male	56	50	18	18	Unilateral	0.8	−8.1	13.5	+
1	2	Female	53	38	12	14	Bilateral	0.9	−15.6	14.5	+
1	3	Female	64	52	12	14	Bilateral	0.9	−19.6	14.7	+
1	4	Male	60	43	17	19	Bilateral	0.7	−6.5	4.4	+
1	7	Female	33	31	16	17	Bilateral	0.8	−1.2	2.0	−
1	8	Female	31	24	13	12	Bilateral	0.9	−16.7	16.6	−
2	9	Male	63	42	15	15	Bilateral	0.95	−23.5	11.6	+
2	10	Female	82	45	18	16	Bilateral	0.9	−32.2	3.4	+
2	13	Female	60	25	14	18	Bilateral	0.9	−25.1	10.6	+
Sporadic	S1	Female	59	40	12	18	Bilateral	0.8	−21.4	11.8	+
Sporadic	S2	Female	71	59	20	21	Bilateral	0.9	−22.3	8.3	−
(Mean ± SD)			57.0 ± 15.0	40.8 ± 15	15.3 ± 3.0	16.5 ± 2.5		0.86 ± 0.1	−16.0 ± 9.5	9.7 ± 4.7	

TABLE 2. Comparison between Patients with NTG, with and without the *OPTN* E50K Mutation

	Group 1 (n = 11)	Group 2 (n = 87)	P	Corrected P
Sex			> 0.99	
Male	3 (27.3)	23 (26.4)		
Female	8 (72.7)	64 (73.6)		
Age at diagnosis (y)			< 0.0001	0.0003
<60 years	11 (100)	33 (37.9)		
≥60 years	0 (0)	54 (62.1)		
Mean age at diagnosis (y)	40.8 ± 11.0	61.7 ± 10.1	0.0001	0.002
Ischemic risk factors			0.74	
Positive	3 (27.3)	33 (37.9)		
Negative	8 (72.7)	54 (62.1)		
Vasospasm			0.24	
Positive	4 (36.4)	17 (19.5)		
Negative	7 (63.6)	70 (80.5)		
Laterality			0.68	
Bilateral	10 (90.9)	70 (80.5)		
Unilateral	1 (9.1)	17 (19.5)		

Data, showing demographic features, are n, with the percentage of the total group in parentheses, unless noted otherwise.

were younger when first diagnosed (P = 0.0001; Bonferroni-adjusted P = 0.002). The comparisons of IOP, CD ratio, visual field global indices, MD and CPSD, and rate of surgery in the two groups are summarized in Table 3. Patients with NTG who had the *OPTN* E50K mutation had lower mean peak IOP on diurnal testing (P = 0.01; Bonferroni-adjusted P = 0.2), and lower mean presenting IOP, which approached significance (P = 0.06). These patients also had worse initial cup-disc ratio (P = 0.001; Bonferroni-adjusted P = 0.02) and higher mean presenting MD of initial visual fields (P = 0.006; Bonferroni-adjusted P = 0.12). However, there was no significant difference in the initial CPSD. Eight (72.7%) patients with the *OPTN* E50K mutation underwent filtration surgery for progression of visual field loss, compared with 22 (25.3%) of 87 patients without this mutation (P = 0.003; Bonferroni-adjusted P = 0.06).

The presenting optic disc parameters (as measured by HRT) are summarized in Table 4. There was no difference in the mean optic disc area. However, optic discs of nine patients with the *OPTN* E50K mutation (HRT scans of two subjects were not interpretable due to poor quality of images) had smaller mean neuroretinal rim areas (global, nasal, and temporal) than did the control subjects. The difference was more marked in the nasal neuroretinal rim, for both superior and inferior nasal rim areas. Comparing the visual fields of the subgroup of subjects who had at least 5 years of follow-up, all 8 (100%) subjects with the *OPTN* E50K mutation were found to have progressing locations, compared with 71 (81.6%) of 87 of those without this mutation (P = 0.34). There was no difference in the mean number of progressing locations per subject, the mean slope of the progressing locations, or the mean slope for the whole visual field (Table 5).

Asymptomatic Gene Carriers

In addition, in an earlier study, we reported seven E50K mutation-carrying individuals from the two pedigrees (Fig. 1A, 1B) who had normal optic discs and visual fields and as yet showed no signs of glaucoma.[18,20] Their ages ranged from 23 to 58 years (their years of birth are shown under subject symbols in Fig. 1).

DISCUSSION

In this study, all subjects with glaucoma with the E50K mutation in the *OPTN* gene were found to have NTG, with IOP usually below 16 mm Hg (mean, 15.3 mm Hg). The highest measured IOP on diurnal testing was found to be significantly lower (mean, 16.5 mm Hg) than in a control group of other NTG subjects without the mutation. The corneal thickness in these individuals was in the normal range (533–558 μm), which suggests that IOP was not influenced by an abnormal corneal thickness and contrasts with the finding of thinner corneas in other NTG subjects.[27–30] Unfortunately, corneal thickness data were not available in the control group of NTG subjects.

NTG has been reported to be more common in patients identified through population screening than among patients with glaucoma diagnosed in routine clinical practice.[31] As patients are usually asymptomatic and as the condition is difficult to diagnose, patients with NTG often have marked irre-

TABLE 3. Comparison of Clinical Features between Patients with NTG, with and without the *OPTN* E50K Mutation

	Group 1 (n = 11)	Group 2 (n = 87)	P	Corrected P
Mean presenting IOP (mm Hg)	15.3 ± 3.0	17.0 ± 2.7	0.06	
Mean highest diurnal IOP (mm Hg)	16.5 ± 2.5	18.8 ± 2.6	0.01	0.2
Mean presenting cup-disc ratio	0.86 ± 0.1	0.76 ± 0.1	0.001	0.02
Mean presenting MD (dB)	−16.0 ± 9.5	−7.8 ± 6.8	0.006	0.12
Mean presenting CPSD (dB)	9.7 ± 4.7	8.1 ± 4.4	0.25	
Number who underwent filtration surgery for visual field progression, n (%)	8 (72.7)	22 (25.3)	0.003	0.06

TABLE 4. Comparison between Patients with NTG, with and without the *OPTN* E50K Mutation, of Presenting Optic Disc Parameters, as Measured by HRT

	Group 1 (n = 9)	Group 2 (n = 87)	P	Corrected P
Disc area (mm^2)	1.95 ± 0.53	2.09 ± 0.47	0.26	
Global neuroretinal rim area (mm^2)	0.50 ± 0.28	0.89 ± 0.31	0.001	0.02
Temporal rim area (mm^2)	0.08 ± 0.04	0.13 ± 0.08	0.02	0.40
Superior	0.07 ± 0.05	0.10 ± 0.05	0.09	
Inferior	0.05 ± 0.03	0.08 ± 0.07	0.13	
Nasal rim area (mm^2)	0.14 ± 0.11	0.30 ± 0.11	0.0004	0.008
Superior	0.08 ± 0.04	0.14 ± 0.06	0.006	
Inferior	0.08 ± 0.06	0.14 ± 0.06	0.01	

Data are expressed in square millimeters ± SD.

versible visual damage at the time of diagnosis. Subjects with the E50K mutation in this study were found to have advanced optic disc cupping, neuroretinal rim thinning, and visual field damage when first examined. The degree of glaucomatous damage at the time of diagnosis exceeded that of other subjects with NTG without the mutation, despite the fact that some of the subjects in the two pedigrees had been screened for glaucoma at a younger age, because they had a positive family history. This was noteworthy, as one would expect subjects diagnosed earlier because of an ascertainment bias to have less severe optic nerve damage. The findings emphasize the importance of early detection of glaucoma in individuals at risk, such as those with a family member affected by this mutation.

The glaucomatous disease process caused by the E50K mutation is also characterized by a progressive course (Fig. 2), with visual field progression detected in all subjects (over 5 years), as opposed to 81% of control subjects with and 77% in a previously reported series of subjects with NTG.[32] Filtration surgery for visual field progression was performed in 72% of NTG cases with E50K mutation compared with only 25% in those without this mutation. All patients were under the care of the Moorfields Eye Hospital NTG clinic under the supervision of a senior ophthalmologist (RAH), and the indication for surgery was primarily for progressive visual field loss. Follow-up was at least 5 years in all cases. The therapeutic implications of this finding are that close monitoring and earlier intervention may be necessary in these subjects, to minimize visual loss. Treatment in such cases could involve lowering of IOP by 20% or more, as this has been found to alter the course of visual field progression favorably in some patients with NTG.[33–39] However, with starting IOPs in the 12- to 18-mm Hg range, this may be difficult to achieve except by means of filtration surgery, possibly augmented by antiproliferative drugs.[39]

Although there is likely to be some bias toward earlier diagnosis because of a positive family history, the E50K mutation seems to predispose individuals to an early age of onset in young adulthood (mean age at diagnosis, 40 years), which is approximately two decades earlier than most persons with NTG, and all subjects (including the two with sporadic cases) were diagnosed before the age of 60. There was, however, some variation in the age of onset of disease. There were two individuals with the mutation who were diagnosed in their 20s, whereas others were diagnosed in their 50s. We found seven E50K mutation-carrying individuals (age range, 23–58 years) who had normal optic discs and visual fields and as yet showed no signs of glaucoma.[18,20] It was not possible to ascertain the penetrance of E50K, as most asymptomatic carriers were young, and in them, glaucoma may develop by the time they reach the ages of the affected individuals in the study.

The mechanism by which the E50K mutation causes disease is unknown. Vittitow and Borras[40] studied the effect of glaucomatous insults on the expression of *OPTN* in human eyes maintained in organ culture. Sustained elevated IOP, TNF-α exposure, and prolonged dexamethasone treatment all significantly upregulated *OPTN* expression, suggesting a protective role of *OPTN* in the trabecular meshwork.[40] The recurrent E50K mutation is located within a putative bZIP motif, conserved in the mouse, bovine, and macaque genomes, and it was hypothesized that visual loss and optic neuropathy may be the result of a dominant negative effect.[18,20] It remains to be seen if there are other molecular mechanisms or factors mediating NTG that interact with this gene.

Although all subjects with glaucoma with the E50K mutation in this study were found to have NTG and a predominant NTG phenotype associated with E50K has also been documented,[19–20] affected individuals with high IOPs have been reported. For example, three members of the extended family of pedigree 1 were observed to have IOPs of 23 to 25 mm Hg,[19,20] and 18% of individuals among the seven families identified with the E50K mutation had a high IOP.[18,20] Although such high IOPs may reflect diurnal fluctuations,[41,42] it is possible that there is some phenotypic variability in IOP. Other mutations in *OPTN* have also been reported in cases of juvenile glaucoma that are not specifically associated with low IOP.[43]

It is inevitable that investigations of temporal changes in phenotype associated with mutations in newly identified glaucoma-causing genes will initially use retrospective data. To minimize the potential effects of bias that stem from such analysis, we relied on objective measurements in patients attending a single tertiary referral center. This subset of patients had detailed and accurate documentation of their clinical features *at presentation* as well as a minimum of 5-year longitudinal data (HRT and fields). We believe this approach offers distinct advantages, although we accept that patients with more complex disease may have been overrepresented. A major limitation of this study is that our findings and conclu-

TABLE 5. Comparison between Patients with NTG, with and without the *OPTN* E50K Mutation, of Visual Field Progression with at Least 5 Years of Follow-up

	Subgroup 1 (n = 8)	Subgroup 2 (n = 87)	P
Patients with progressing locations, n (%)	8 (100)	71 (81.6)	0.34
Progressing locations per subject (n)	8.63 ± 8.68	7.95 ± 9.6	0.66
Mean slope of progressing locations per year (dB/y)	−2.02 ± 0.75	−1.97 ± 1.22	0.45
Mean slope for whole visual field per year (dB/y)	−0.57 ± 0.36	−0.43 ± 0.66	0.15

Data are expressed as the mean ± SD, unless otherwise noted.

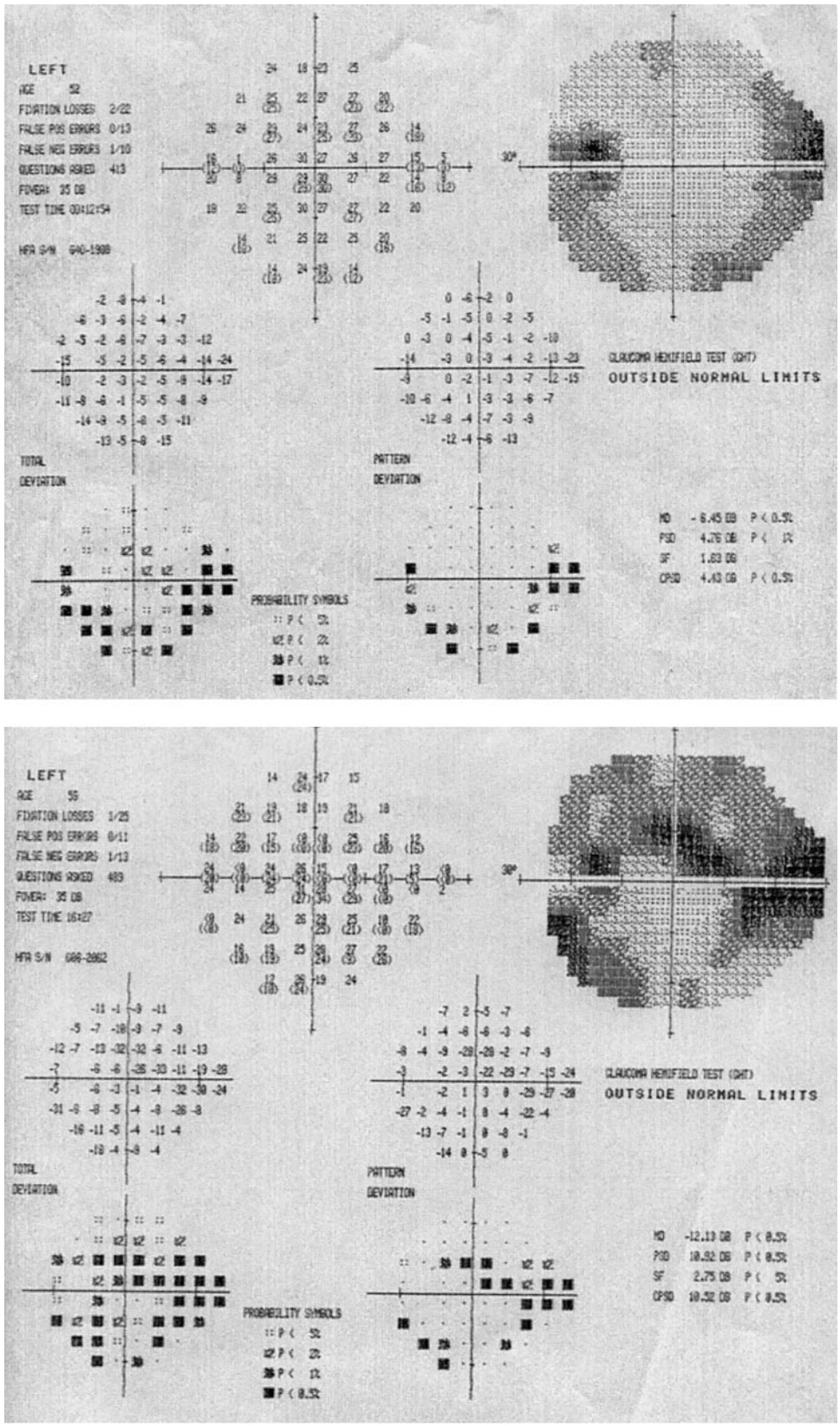

FIGURE 2. Visual fields of individual 4 (pedigree 1A) showing progressive visual field damage. (**A**) Initial visual fields results in the left eye and (**B**) the left eye after 5 years.

sions may be altered if data of other members of the pedigrees not examined at our center, such as those previously found to have high-tension glaucoma,[18–20] were included in the analysis. It remains to be seen if other specific features distinguishing those with the mutation will become apparent, as may be the case when more patients are found to carry the mutation. We believe that this study provides important information about the clinical behavior associated with the *OPTN* E50K mutation and highlights the benefits that accrue from rigorous phenotyping.

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