European Journal of Ophthalmology / Vol. 17 no. 2, 2007 / pp. 253-258

SHORT COMMUNICATION

Dominant optic atrophy in a Japanese family with *OPA1* frameshift mutation (V942fsX966)

T. HAYASHI, T. TAKEUCHI, T. GEKKA, K. KITAHARA

Department of Ophthalmology, Jikei University School of Medicine, Tokyo - Japan

PURPOSE: *The authors report the ophthalmic characteristics of a male proband in a Japanese family with autosomal dominant optic atrophy (DOA) harboring a frameshift mutation in the OPA1 gene.*

METHODS. *Conventional ophthalmologic examinations including static automated perimetry were performed, as well as assessment of the three-generation family history. The peripapillary retinal nerve fiber layer (RNFL) was evaluated using scanning laser polarimetry. Mutation screening of the OPA1 gene was performed with polymerase chain reaction amplification and direct sequencing.*

RESULTS. *A frameshift mutation (p.V942fsX966) was identified in the proband and his mother. In comparison with the adolescent onset of visual loss in the proband and his maternal grandfather, the mother presented with only subtle temporal disc pallor and has never been aware of any visual disturbances. Symmetric thinned peripapillary RNFL was detected in the proband, whose visual field abnormalities were limited to central scotomas and were without mean deviation worsening between 11 to 17 years of age in both eyes. The proband's logMAR visual acuity (0.52 to 0.7) has remained almost unchanged for more than 10 years since initial evaluation at age 10.*

CONCLUSIONS. *The OPA1 mutation may be correlated with slow progression of DOA, and with phenotypic variations within the family. Further study is necessary to determine whether symmetric thinned peripapillary RNFL represents a feature of DOA. (Eur J Ophthalmol 2007; 17: 253-8)*

KEY WORDS. *Hereditary optic neuropathy, Autosomal dominant inheritance, Scanning laser polarimetry, Frameshift mutation*

Accepted: September 28, 2006

INTRODUCTION

Autosomal dominant optic atrophy (DOA), also known as Kjer disease (MIM #165500) (1), is the most common form of the hereditary optic neuropathy. It is characterized by moderate to severe visual acuity loss, color vision defects, and optic disc pallor (2-4). In 2000, disease-causing mutations in the *OPA1* gene were identified in European patients with DOA (5, 6), and approximately 100 *OPA1* mutations have since been reported to the eOPA1 online database (http://lbbma.univ-angers.fr/eOPA1/) (7), mainly in European patients with either DOA or bilateral optic atrophy. A few reports of DOA families with *OPA1* mutations have been in the Japanese population (8, 9). A very recent study has suggested low penetrance and variable expressivity in some Japanese families (10). Red-free funduscopy revealed thinned or absent retinal nerve fiber layer (RNFL) in the temporal region of the optic disc corresponding to the papillomacular

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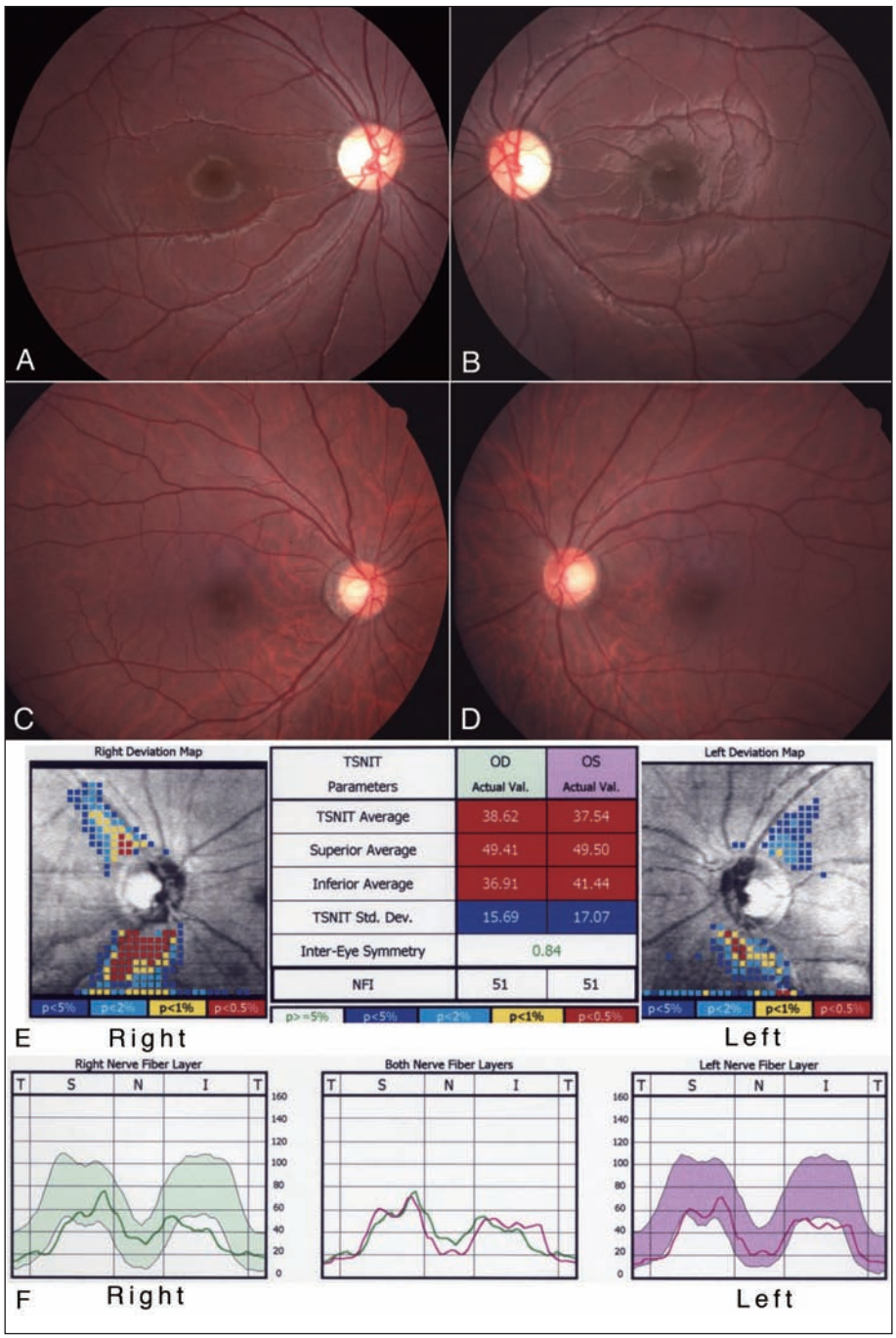

Fig. 1 - *Fundus photographs of the right* **(A)** *and left* **(B)** *eyes of the proband (III-1) at age 12 show diffuse optic disc pallor in each eye. Fundus photographs of the right* **(C)** *and left* **(D)** *eyes of the proband's mother (II-1) show subtle temporal pallor in both optic discs. In scanning laser polarimetry with variable corneal compensation (GDx VCC), the deviation map* **(E)** *and TSNIT (temporal-superior-nasal-inferior-temporal) graph* **(F)** *of the proband at age 20 are shown. See the text for details.*

bundle in all patients with DOA (11, 12). To our knowledge, however, no quantitative measurement of the RNFL in patients with DOA has been reported.

This study was conducted to describe a Japanese family with DOA harboring an *OPA1* frameshift mutation. In the proband, peripapillary RNFL thickness was quantitatively assessed using scanning laser polarimetry.

Case report

A 10-year-old male proband (III-1, JU#0160) was referred to our hospital for evaluation of visual acuity loss. Best-corrected visual acuity (BCVA), determined by using decimal acuity charts, was converted to logarithm of the minimum angle of resolution (logMAR)

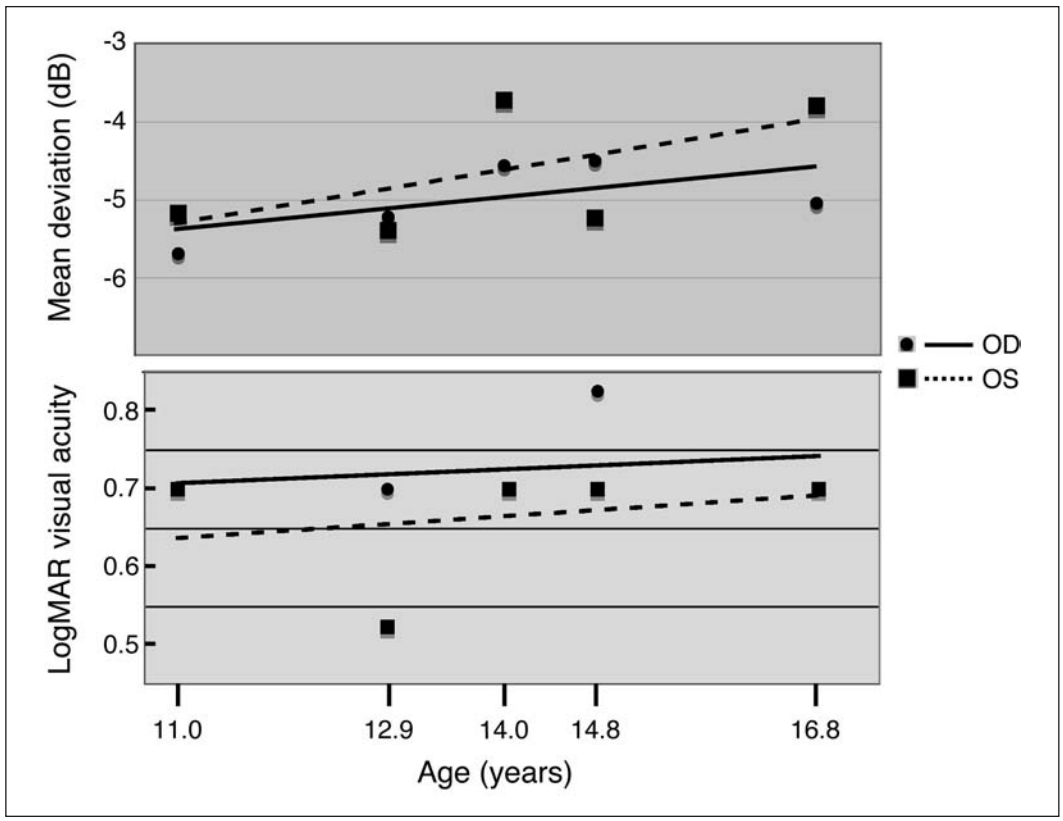

Fig. 2 - *Scatterplots with regression lines for mean deviation values (decibels, dB) and logMAR visual acuity during nearly 6 years of follow-up time since age 11 years of the proband. See the text for details.*

units. His BCVA was 0.52 logMAR units (0.3 decimal acuity) in the right eye (OD) with +1.25 sphere and 0.52 logMAR units in the left eye (OS) with +0.50 sphere. No relative afferent pupillary defect was seen. Funduscopy showed bilateral diffuse optic disc pallor, but no maculopathy or retinopathy was seen (Fig. 1, A and B). Magnetic resonance imaging of the brain and orbit was normal. The proband's maternal grandfather (I-1) had been diagnosed with bilateral optic atrophy with adolescent onset, while his mother (II-1) presented with subtle temporal optic disc pallor in both eyes (Fig. 1, C and D). As her visual acuity was 0.05 logMAR units (0.9 decimal acuity) in both eyes, she has never been aware of visual disturbances. At age 14, color vision tests were performed monocularly. The proband identified only the first plate on the Ishihara test (38-plate edition). The Farnsworth Panel D-15 showed only minor errors. Total error scores in the Farnsworth-Munsell 100-hue tests were 296 (OD) and 280 (OS), and the orientation axes were 7.32 (OD) and 18.08 (OS). These results indicate mixed (red-green plus blue-yellow) color vision defects without a clear axis in either eye, although blue-yellow defects are the most common color vision defects in patients with DOA (3, 4, 9, 13). At age 15, full-field electroretinography was performed, showing normal amplitudes of rod, cone, mixed rod-plus-cone, and 30-Hz flicker ERGs. The proband's visual field defects were assessed using the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA) with the central 30-2 full-threshold program. A total of five HFA tests had been examined at 1- to 2-year intervals for a follow-up of nearly 6 years since 11 years of age. Regression lines were analyzed for the mean deviation values (decibels, dB) and logMAR visual acuity with follow-up time, showing rather weak positive values (OD: 0.14 dB/yr, OS: 0.23 dB/yr) of the mean deviation slopes, and less changeable visual acuity slopes in both eyes (Fig. 2). At his current age of 20, his BCVA has remained 0.7 logMAR units (0.2 decimal acuity) with –3.0 sphere in both eyes. Goldmann perimetry showed 5-degree central scotomas with the I/2c test light in the right eye and I/1e test light in the left eye. Visual fields with I/2e, I/3e, I/4e, and V/4e test lights were normal

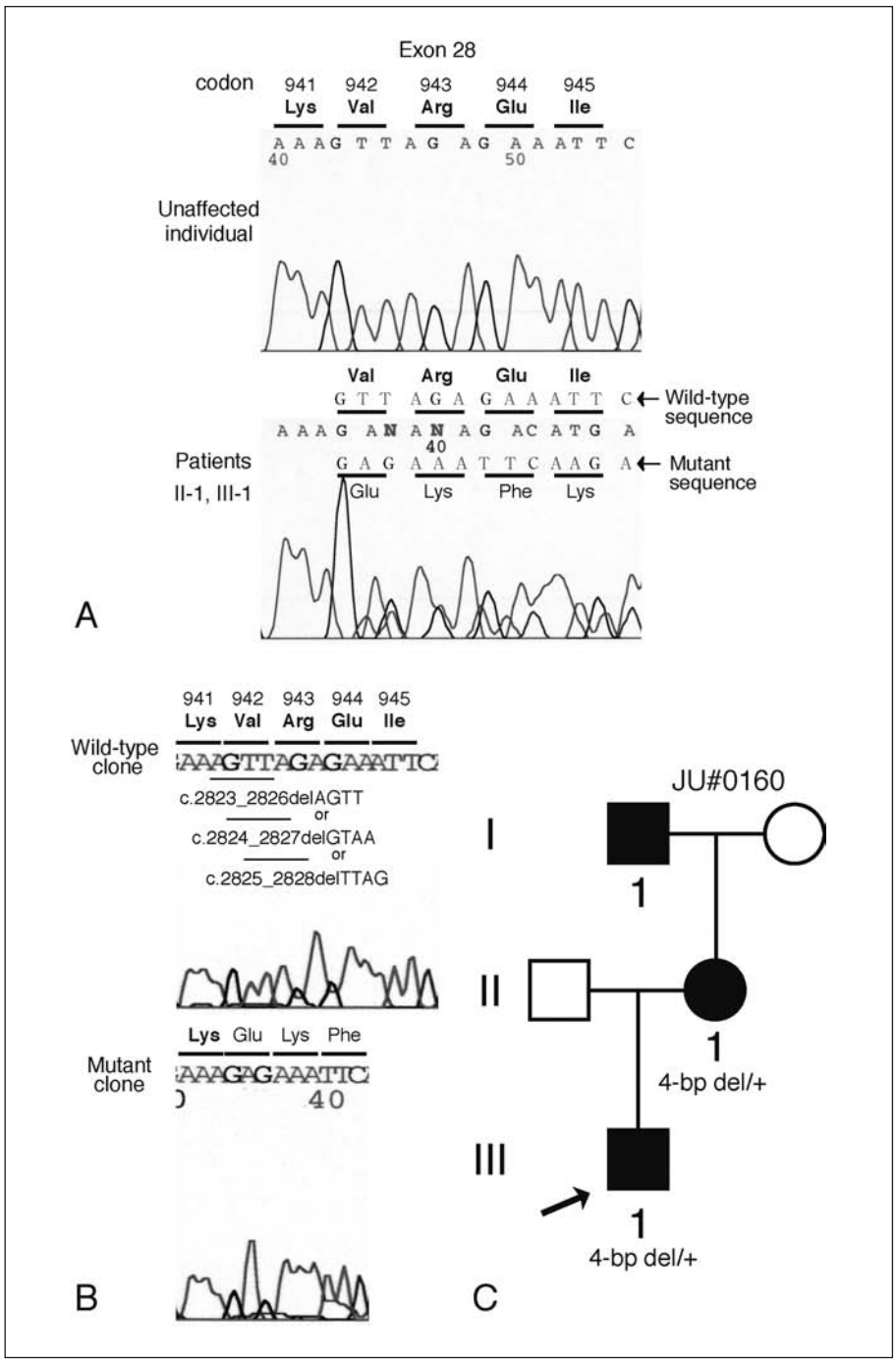

Fig. 3 - *Sequence analysis of the OPA1 gene in the Japanese family (JU#0160). A heterozygous variation is detected in the proband (III-1) and his mother (II-1)* **(A)**. *Plasmid clones with either wild-type or mutated sequences were sequenced. The results show the wild-type and 4-bp deletion mutant (c.2823_2826delAGTT or c.2824_2827delGTTA or c.2825_2828 delTTAG) sequences* **(B)**. *Pedigree of the three-generation family (JU#0160) shows affected family members by a solid circle (female) and squares (males), of whom the proband (III-1) and his mother (II-1) are heterozygotes for the 4-bp deletion (del) mutation* **(C)**.

in each eye. Intraocular pressure was 15 mmHg in both eyes.

In the proband, peripapillary RNFL was assessed using scanning laser polarimetry with variable corneal compensation (GDx VCC; software version 5.3.3; Laser Diagnostic Technologies, Inc., San Diego, CA). In the deviation map (Fig. 1E) and temporal-superior-nasal-inferior-temporal (TSNIT) graph (Fig. 1F), the values of all GDx VCC parameters including TSNIT average, superior average, inferior average, TSNIT standard deviation, and nerve fiber indicator (NFI) were outside the normal limits determined by the normative data-

base for this age and race. This outcome indicates markedly thinned peripapillary RNFL. The value (0.84) for inter-eye symmetry showed good symmetry between the two eyes. RNFL was thinner inferiorly than superiorly in both eyes.

The protocol for the molecular study was approved by the ethics review board of Jikei University School of Medicine, and informed consent was obtained before participation. Venous blood samples for mutation screening of the *OPA1* gene (9) were available only from the proband (III-1) and his mother (II-1). A heterozygous sequence variation was detected in the polymerase chain reaction (PCR) products containing exon 28 in the proband and his mother (Fig. 3A). The PCR products were cloned to plasmid vectors as previously described (9) and then the clones with either wild-type or mutated sequences were analyzed, showing a 4-bp deletion mutation (c.2823_2826delAGTT or c.2824_2827delGTTA or c.2825_2828delTTAG) (Fig. 3B). Each mutation is likely to cause translational frameshifting with the production of nonhomologic 24 amino acids instead of the C-terminal 19 amino acids of the normal OPA1 protein (p.V942 fsX966).

Three major primary mtDNA mutations (at nucleotide positions 3460, 11778, and 14484) associated with Leber's hereditary optic neuropathy were not found.

DISCUSSION

In this study, we investigated the clinical features of members of a Japanese family with DOA harboring a frameshift mutation (p.V942fsX966) in the *OPA1* gene. This mutation has been reported in only one French family (6), but the clinical manifestations in DOA patients with this mutation have not been described.

Wide intrafamilial phenotypic variations in DOA have been reported (3, 4, 14), and our patients' clinical manifestations also indicate phenotypic diversity. With regard to disease progression, the proband's visual acuity has remained largely unchanged since 10 years of age. Mean deviation worsening in the HFA was not observed at least between 11 and 16.8 years (Fig. 2). The outcome suggests that the progression of visual loss has been extremely slow. Therefore, the *OPA1* mutation (p.V942fsX966) may be correlated with slow progression of DOA, and with phenotypic variations within the family.

Previous studies revealed that DOA patients had thinned or absent RNFL in the temporal region of the optic disc corresponding to the papillomacular bundle, resulting in central or cecocentral scotomas (3, 11, 12). The proband also presented with optic disc pallor (Fig. 1, A and B), visual acuity loss, and central scotomas (I/2c or I/1e test lights), suggesting an impaired papillomacular bundle. Unexpectedly, the GDx VCC outcome demonstrated markedly thinned peripapillary RNFL in both eyes (Fig. 1E). Thinned or absent peripapillary RNFL is usually seen in patients with glaucoma and is associated with visual field abnormalities such as the nasal step, paracentral, and Bjerrum scotomas. Thus, the thinned peripapillary RNFL in the proband was compatible with that in patients with glaucoma. On the other hand, inter-eye symmetry value (Fig. 1E) indicated good symmetry between the eyes. This finding seems to be different from glaucoma in which one eye is often more advanced than the fellow eye. In fact, the clinical differentiation of DOA and glaucoma is facilitated by the onset of visual disturbances in the former, usually early in the first 2 decades and the family history of DOA, versus the generally much older age at presentation in the latter. Moreover, central vision in glaucoma is often preserved until advanced stages of the disease. Given limitations in the number of patients, it is necessary to evaluate whether peripapillary RNFL is attenuated in any other patients with DOA.

In conclusion, our study demonstrated intrafamilial phenotypic variations of DOA with the frameshift mutation (p.V942fsX966), and revealed symmetric thinned peripapillary RNFL in the proband, even though the visual field abnormalities were limited to central scotomas only. Mutation analysis of the *OPA1* gene would be useful for differential diagnosis of ambiguous patients or families for DOA.

ACKNOWLEDGEMENTS

Supported by grant #16791073 from the Ministry of Education, Culture, Sports, Science and Technology of Japan (T. Hayashi), and by The Jikei University Research Fund (T. Hayashi).

The authors have no commercial or proprietary interest in this study.

Reprint requests to:
Takaaki Hayashi, MD, PhD
Department of Ophthalmology
Jikei University School of Medicine
3-25-8, Nishi-shinbashi
Minato-ku, Tokyo, 105-8461, Japan
taka@jikei.ac.jp

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