neovascularization. Our patient presented with massive subretinal hemorrhage that was not associated with this condition, because choroidal neovascularization was detected neither clinically or angiographically. We postulate that the etiology of the bleeding is the result of spontaneous rupture of the tumorous choroidal capillary mesh. This happened as a result of increased intravascular pressure of choroidal circulation caused by repeated Valsalva maneuvers associated with the patient's competitive swimming. Once the precipitating factor was removed, the patient was confined to bed and underwent corticosteroid therapy to reduce the macula edema; his vision promptly returned to normal.

We have presented a patient with underlying choroidal osteoma, presenting with massive subretinal hemorrhage not associated with choroidal neovascularization. His visual prognosis following resolution of edema and hemorrhage appears to be good, in contrast to subretinal bleed that is secondary to choroidal neovascularization.

REFERENCES

1. Aylward GW, Chang TS, Pautler SE, Gass JDM. A long-term follow-up of choroidal osteoma. Arch Ophthalmol 1998;116: 1337–1341.
2. Gass JDM, Guerry RK, Jack RL, Harris G. Choroidal osteoma. Arch Ophthalmol 1978;96:428–435.
3. Gass JDM. New observations concerning choroidal osteomas. Int Ophthalmol 1979;1:71.

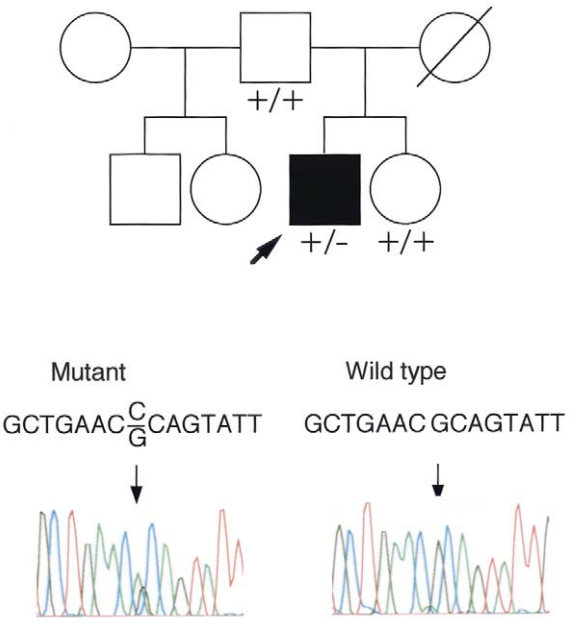

FIGURE 1. (Top) Pedigree of the family with optic atrophy. Affected individual is shown as a filled symbol. Genotypes are shown below the individual symbols, where + represents the wild type and − the mutation. An arrow indicates the proband. No clinical data were available about the proband's mother, who died in her 30s. (Bottom) Electropherograms of *OPA1* sequencing. The mutant position is indicated by arrows.

A Novel Mutation in the *OPA1*Gene in a Japanese Patient With Optic Atrophy

Satoko Shimizu, MD, PhD, Naoki Mori, MD, Mari Kishi, MD, Hirohisa Sugata, MD, Akiko Tsuda, VMD, and Nobue Kubota, MD, PhD

PURPOSE: To report a novel mutation of the *OPA1* gene in a Japanese patient with optic atrophy and to describe the clinical features of the patient.
DESIGN: Observational case report.
METHODS: Genomic DNA was extracted from leukocytes of four unrelated Japanese patients with optic atrophy. All the exons and splice sites of the *OPA1* gene were amplified by polymerase chain reaction and directly sequenced.
RESULTS: One patient with optic atrophy had a heterozygous Arg445His mutation in the *OPA1* gene. The Arg445His mutation was detected neither in 110 control subjects nor in the patient's healthy family members.
CONCLUSIONS: A novel mutation of the *OPA1* gene, similar to those reported in Western countries, was detected in a Japanese patient with optic atrophy. Mutations of the *OPA1* gene may contribute to the development of optic nerve atrophy in Japanese cases of optic atrophy. (Am J Ophthalmol 2003;135:256–257.

Accepted for publication Aug 28, 2002.

From the Department of Ophthalmology, Teikyo University School of Medicine, Tokyo, Japan.
Inquiries to Satoko Shimizu, MD, PhD, Department of Ophthalmology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo, 173-8605 Japan; fax: (+ 81) 3-3963-0303; e-mail: Stkshimi@aol.com

AUTOSOMAL DOMINANT OPTIC ATROPHY IS A DOMInantly inherited optic neuropathy resulting in progressive loss of visual acuity, color vision deficits, a centrocecal scotoma, and optic nerve pallor. Onset is insidious, beginning in the first decade of life. Recently, disease-associated mutations of the *OPA1* gene were identified in families with cases of autosomal dominant optic atrophy.[1]

We studied four unrelated juvenile patients (ranging from 6 to 21 years of age) with bilateral optic atrophy who were seen at Teikyo University Hospital. Two of the four patients had family histories of optic atrophy. Patients with a history of diseases that may cause secondary optic

atrophy were excluded from this study. After informed consent was obtained from all the subjects who participated in this study, genomic DNA was extracted from leukocytes of the peripheral blood. Exons 1 through 28, including exons 4b and 5b, which encode the OPA1 protein, were amplified and directly sequenced as described previously.[2,3] As a result, one patient with no apparent family history of optic atrophy had a heterozygous G to A substitution in the second nucleotide at codon 455 (Arg455His) in the *OPA1* gene (Figure 1). This substitution was detected neither in the 110 control subjects nor in healthy members of the patient's family. Although this substitution may be a rare polymorphism, the lack of substitution among this patient's family members without optic atrophy (Figure 1) and in 220 control chromosomes strongly suggests that this is a disease-causing mutation. The majority of missense mutations in patients with optic atrophy have been detected thus far within the GTPase domain,[1,2,4,5] where the Arg455His missense mutation is located. The position of the Arg455His mutation is consistent with previous reports.[1,2,4,5]

Corrected visual acuity of the patient with the Arg455His mutation was approximately 20/50 in both eyes when he was 10 years old. He was first found to have optic atrophy when he was 17 years old and was referred to our hospital at age 21. His best-corrected visual acuity was 20/200 in both eyes. He had atrophy of the optic disks, central scotoma, and generalized dyschromatopsia bilaterally. Results of complete physical and neurologic examinations were normal except for moderate hearing loss in both ears. At first, he was suspected of having Leber disease; however, he had no mutation at positions 11778, 3460, 14484, 4160, 9438, 9804, and 15257 of mitochondrial DNA, which is a finding in more than 90% of cases of Leber disease. Based on the results of these genetic tests, we determined that the latent disease underlying his optic atrophy was autosomal dominant optic atrophy and was not Leber disease.

The prevalence of *OPA1* gene mutations in autosomal-dominant optic atrophy patients is reported to be 30% to 90%.[2,4,5] The case in our study and a previously reported splicing mutation[3] represent two mutations of the *OPA1* gene that we have found in five unrelated Japanese patients with optic atrophy. These findings suggest that *OPA1* gene mutations are also responsible for the pathogenesis of optic atrophy in a certain percentage of Japanese cases.

REFERENCES

1. Alexander C, Votruba M, Pesch UE, et al. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat Genet 2000; 26:211–215.
2. Delettre C, Griffoin JM, Kaplan J, et al. Mutation spectrum and splicing variants in the OPA1 gene. Hum Genet 2001; 109:584–591.
3. Shimizu S, Mori N, Kishi M, Sugata H, Tsuda A, Kubota N. A novel mutation in the *OPA1* gene in a Japanese patient with optic atrophy. Jpn J Ophthalmol 2002;46:336–340.
4. Pesch UE, Leo-Kottler B, Mayer S, et al. OPA1 mutations in patients with autosomal dominant optic atrophy and evidence for semi-dominant inheritance. Hum Mol Genet 2001;10: 1359–1368.
5. Toomes C, Marchbank NJ, Mackey DA, et al. Spectrum, frequency and penetrance of *OPA1* mutations in dominant optic atrophy. Hum Mol Genet 2001;10:1369–1378.