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# Retinal Dystrophy in a Japanese Boy Harboring the Mitochondrial DNA T8993G Mutation

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**Background:** Patients with the mitochondrial (mt) DNA T8993G mutation reportedly have variable neurologic manifestations. In these patients, retinal dystrophies progress from salt-and-pepper appearance to severe diffuse pigmentary retinopathy.

**Case:** A Japanese boy harboring the mtDNA T8993G mutation had hypotonia, ataxia, and developmental delay. His lactate values in serum and cerebrospinal fluid were elevated. Magnetic resonance imaging showed symmetrical areas of T2-weighted hyperintensity in the putamen and caudate.

**Observations:** In ophthalmological examinations, his pupils reacted sluggishly to light. The patient had mottling of the retina without pigmentation and subnormal electroretinographic responses in both fundi. No ophthalmoparesis or nystagmus was observed.

**Conclusion:** Retinal dystrophy without pigmentation was found in a Japanese boy diagnosed with the mtDNA T8993G mutation. This is believed to be the first report of retinal manifestations in Japanese patients with this mutation. **Jpn J Ophthalmol 2002;46:460–462** 

**Key Words:** Japanese patient, mitochondrial DNA, retinal dystrophy.

## Introduction

The T-to-G substitution at nucleotide position 8993 in the mitochondrial DNA (mtDNA) has been found in patients with developmental delay, ataxia, psychomotor regression, seizures, peripheral neuropathy, and ocular manifestations (Leigh syndrome), or with neurologic weakness, ataxia, and retinitis pigmentosa (NARP syndrome).[1–6] Patients with mtDNA T8993G mutation have had variable retinal and neurologic changes.[4] To our knowledge, retinal manifestations in Japanese patients with this mutation have not been described previously. We report here retinal lesions in a Japanese boy found to have the mtDNA T8993G mutation.

## Case Report

The proband was a boy born after a full-term pregnancy to healthy unrelated parents in February 1999. His family history for neurologic or ophthalmic diseases was unremarkable. Although he appeared healthy at birth, his development was delayed at the age of 1 year. At 16 months, he showed hypotonia, ataxia, and loss of motor and cognitive milestones. Lactate values in serum and cerebrospinal fluid were elevated (26.7 and 57.9 mg/dL; normal, 0.6–1.8 and 3.3–14.9 mg/dL, respectively). Magnetic resonance imaging (MRI) showed symmetrical areas of T2-weighted hyperintensity in the putamen and caudate. After informed consent was obtained from his parents, analysis of leukocyte mtDNA was performed in the Department of Pediatrics of another university hospital. A heteroplasmic point mutation (T to G mutation) at nucleotide position 8993 was identified. The percentage of abnormal mtDNA was not determined.

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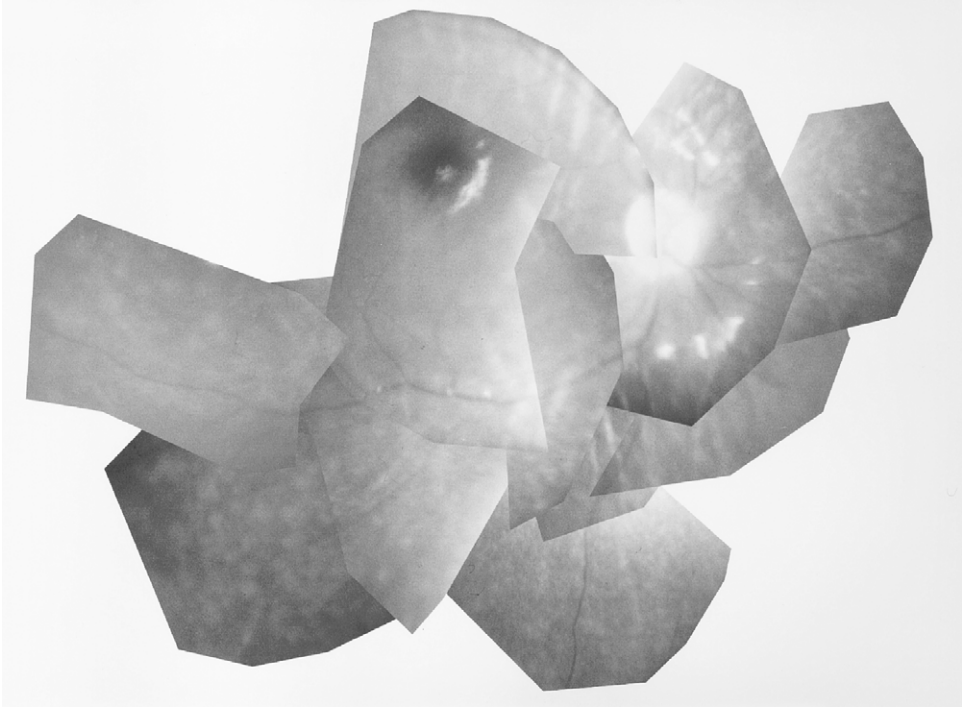

**Figure 1.** The right fundus of a young Japanese boy harboring mitochondrial DNA T8993G mutation shows mottling of the retinal pigment epithelium and slightly pale optic disc at 20 months of age.

Ophthalmologic examination in our department at age 20 months showed that the boy's pupils reacted sluggishly to light. The corneas, lenses, and vitreous appeared normal. Mottling of the retina with a slightly pale disc was found ophthalmoscopically in both fundi (Figure 1). No pigmentation was seen in the fundi. A bright white flash electroretinogram after 30 minutes of dark adaptation revealed decreased a- and b-wave amplitudes in both eyes (Figure 2). No ophthalmoplegia, nystagmus, or blepharoptosis was observed. Visual acuity and visual fields could not be examined because of the patient's age.

The proband's mother, a 30-year-old woman, had good visual acuity (1.0) and normal fundi with normal electroretinographic responses in both eyes. No neurologic abnormality was noted. After informed consent was obtained, analysis of leukocyte mtDNA was carried out. No mutation at nucleotide position 8993 was found in the mother.

## Discussion

Our patient had hypotonia, ataxia, developmental delay, lactic acidemia, symmetrical hyperintensity in


**Figure 2.** Single bright flash electroretinogram reveals decreased a- and b-wave amplitudes in both eyes.

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putamen and caudate in a T2-weighted MRI scan, and mtDNA T8993G mutation. These findings were consistent with those of Leigh syndrome or NARP syndrome.[1–3] The patient's mother had no mutation at nucleotide position 8993 in mtDNA analysis. It is possible that the de novo mutation developed in the patient.

Ortiz and associates[4] showed varying degrees of retinal pigmentary change ranging from salt-and-pepper retinopathy to severe diffuse pigmentary retinopathy in American patients with mtDNA T8993G mutation. Chowers et al[5] demonstrated cone and rod dysfunction in Israeli patients with NARP syndrome. Kerrison and co-workers[6] showed that salt-and-pepper retinopathy progressed into bone spicule pigment formation in an American patient with NARP syndrome associated with mtDNA T8993G mutation.

Our Japanese patient with Leigh syndrome associated with mtDNA T8993G mutation had retinal dystrophy without pigmentation, similar to the early stage of retinitis pigmentosa.

## References

1. Holt IJ, Harding AE, Petty RKH, Morgan-Hughes JA. A new mitochondrial disease associated with mitochondrial DNA heteroplasmy. Am J Hum Genet 1990;46:428–433.
2. Tatuch Y, Christodoulou J, Feigenbaum A, et al. Heteroplasmic mtDNA mutation (T→G) at 8993 can cause Leigh disease when the percentage of abnormal mtDNA is high. Am J Hum Genet 1992;50:852–858.
3. Santorelli FM, Shanske S, Macaya A, DeVivo DC, DiMauro S. The mutation at nt 8993 of mitochondrial DNA is a common cause of Leigh's syndrome. Ann Neurol 1993;34:827–834.
4. Ortiz RG, Newman NJ, Shoffner JM, Kaufman AE, Koontz DA, Wallace DC. Variable retinal and neurologic manifestations in patients harboring the mitochondrial DNA 8993 mutation. Arch Ophthalmol 1993;111:1525–1530.
5. Chowers I, Lerman-Sagie T, Elpeleg ON, et al. Cone and rod dysfunction in the NARP syndrome. Br J Ophthalmol 1999;83:190–193.
6. Kerrison JB, Biousse V, Newman NJ. Retinopathy of NARP syndrome. Arch Ophthalmol 2000;118:298–299.