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A novel mutation producing premature termination codon at the OPA1 gene causes autosomal dominant optic atrophy

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Sirs: Autosomal dominant optic atrophy (ADOA) (MIM #165500) is the most prevalent dominantly inherited optic neuropathy, typically presenting in the first decade of life with progressive loss of visual acuity, abnormal colour discrimination, centrocaecal scotoma and optic nerve pallor. ADOA has variable expression ranging from asymptomatic carriers to legally blind patients, so a high degree of phenotype variation is observed within and between families (Delettre et al. 2002; Pesch et al. 2001; Thiselton et al. 2002; Votruba et al. 1998).

Intriguing clinical and morphological overlaps between ADOA and other optic neuropathies caused by retinal ganglion cell degeneration, such as Leber's optic neuropathy (LHON) (Carelli et al. 2004) and normal-tension glaucoma (NTG) (Alward et al. 2003; Votruba et al. 2003), have recently been reported. ADOA is therefore a genetic disorder that provides insights into common mitochondrial pathophysiological mechanisms leading to optic nerve damage.

Mutations in the *OPA1* gene were recently identified in families that manifest ADOA in an autosomal dominant pattern. The *OPA1* gene contains 30 exons (Delettre et al. 2001), 28 of which encode a 960-amino-acid dynamin-related GTPase. A total of 83 different mutations, mainly family specific, have been reported so far (http://lbbma.univ-angers.fr/eOPA1/). Almost 50 % of the mutations cause premature truncation of the OPA1 protein. Most mutations are in exons 8, 9, 12 and 27, primarily affecting the GTPase domain and the C-terminal coiled-coil domain (Baris et al. 2003). In particular, four mutations are present in exon 9, three being missense mutations and one being a nucleotide deletion.

We recently examined two siblings with bilateral optic neuropathy. The first, a 38-year-old Italian male, had experienced progressive loss of visual acuity since the age of 6 years with a residual bilateral visual acuity of 20/30. Colour vision showed generalized dyschromatopsia. Ophthalmoscopy showed normal cupping and appearance of emerging vessels with slight temporal pallor of both optic nerves. Intra-ocular pressure (IOP) was 21 mm Hg (normal value: 18–20 mmHg) (applanation) in both eyes. Goldmann's visual field charts showed paracentral scotoma. Pattern-reversal visual evoked potentials (VEPs) showed abnormally high P100 latency bilaterally (RE 112 ms, LE 109 ms).

Onset of the disease in the second patient, the 33-year-old sister of the first patient, occurred at 16 years of age. Visual acuity was 20/40 and colour vision (Ishihara) showed red-green dyschromatopsia. Fundoscopy showed a normal cup to disk ratio with normal vessels and bilateral temporal pallor. IOP was 19 mmHg bilaterally (applanation). Goldmann visual field examination showed centrocaecal scotoma. VEPs had abnormally high P100 latency (RE 115 ms, LE 117 ms). The patients' mother (aged 55 years) was without eye disease (visual acuity, fundoscopy and VEPs were normal). Conversely, maternal aunts (65 and 67 years) were reported to have had dyschromatopsia and poor vision since an early age.

After informed consent was obtained, genomic DNA was extracted from peripheral blood leucocytes. A genetic screen of "Leber" mutations at positions 11778, 3460 and 14484 of mtDNA was negative. Exons 8, 9, 12 and 27 of OPA1 gene, including exon-intron junctions, were amplified and sequenced directly using specific primers, as already described (Delettre et al. 2001; Shimizu et al. 2002).

The two patients, their mother and two aunts showed one novel heterozygous nonsense mutation in exon 9, R312X, resulting from a C > T transition at position c.934, i. e. 934 bp from the start codon (cDNA) (Fig. 1), while the father was negative for the mutation. This

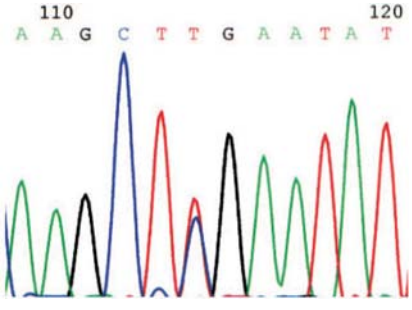

Fig. 1 DNA tracing from segment of exon 9 of OPA1 gene from 38-year-old Italian male with hereditary optic atrophy. Arrows indicate the position of the mutation (c.934 C > T). The sister, mother and two aunts of the patient had the same mutation