Sir,

The Behr syndrome (MIM#210000) is characterized by the association of early-onset optic atrophy with spinocerebellar degeneration resulting in ataxia, pyramidal signs, peripheral neuropathy and developmental delay (Behr, 1909). Although the disorder is believed to be inherited in an autosomal recessive manner, it may be clinically heterogeneous, encompassing several genetic aetiologies and patterns of inheritance. Recently, an adult-onset Behr-like syndrome, including optic atrophy and ataxia, was reported in two brothers carrying a heterozygous mutation in the optic atrophy type 1 gene (OPA1, p.Cys551Tyr) (Marelli et al., 2011). Heterozygous mutations in OPA1, a gene encoding for a dynamin-related GTPase involved in mitochondrial dynamics and mtDNA maintenance, are the main causes of autosomal dominant optic atrophy (DOA). In DOA, the optic neuropathy occurs insidiously in the first decade of life leading to various levels of visual impairment. As many as 20% of patients with DOA exhibit extracocular neuromuscular signs including deafness (Amati-Bonneau et al., 2005), chronic progressive external ophthalmoplegia, ataxia, peripheral neuropathy and mitochondrial myopathy with multiple mtDNA deletions, also called the ‘DOA plus’ phenotype (Amati-Bonneau et al., 2008; Yu-Wai-Man et al., 2010). The ‘DOA plus’ phenotype, which is similar to that observed in multi-systemic mitochondrial disorders (Amati-Bonneau et al., 2005), is often associated with missense mutations in OPA1 (Yu-Wai-Man et al., 2010). Apart from these autosomal dominant forms, only a few syndromic cases have so far been reported with compound heterozygous OPA1 mutations suggestive of either recessive or semi-dominant patterns of inheritance (Pesch et al., 2001; Yu-Wai-Man et al., 2010; Schaaf et al., 2011). However, the clinical spectrum of these emerging double-mutant OPA1-related disorders remains to be characterized. We here report four cases of children affected by the Behr syndrome associated with compound heterozygous OPA1 mutations.

Case 1

This 14-year-old male was the second child born to non-consanguineous parents. His mother had been diagnosed with
Case 3

This 6-year-old female was the first child of non-consanguineous parents without any family history of optic neuropathy. Neither parent had any ophthalmic symptoms. She was born at 36 weeks of gestation following an uncomplicated pregnancy. At birth, her weight was 3390 g, her length 49 cm, and her occipital-frontal circumference 36 cm. The neonatal period was uneventful and the motor and cognitive developmental milestones were normal. She walked unaided at 14 months. At age 3.5 years, she presented with an unsteady gait, poor vision and chronic constipation. Neurological evaluation found mild ataxia and slight tremor without dysmetria or dysarthria. Optic atrophy was diagnosed, with normal ERG but severely altered visual evoked potentials. Brain MRI was normal at age 4 years. Nerve conduction studies and somatosensory evoked potentials evidenced an axonal sensory neuropathy. At age 6 years, her neurological symptoms remained stable, her cognitive functions were normal but she needed support for her visual disability (visual acuity 1/100 in both eyes). The patient had two pathogenic compound heterozygous OPA1 mutations, i.e. the nonsense p.Arg557* mutation due to c.1669C>T in exon 17, and the missense p.Ile382Met mutation due to c.1146A>G in exon 12. Her asymptomatic mother carried the p.Arg557* mutation whereas her asymptomatic father carried the p.Ile382Met mutation.

Case 4

This 16-year-old male was declared legally blind at the age of 3 years. His father had a mild isolated optic neuropathy whereas his mother was asymptomatic. He was born after an uncomplicated pregnancy and the perinatal period had been normal. At birth, his weight was 4380 g, length 52 cm, his occipital-frontal circumference 35 cm, and the Apgar score was 9. He was able to hold up his head at age 6 months and was able to walk unaided at age 13 months. At age 13 years, his visual acuity was 1/40 in both eyes and he was just able to count fingers. The papilla was atrophic at fundoscopy and the visual evoked potentials were altered whereas the ERG was normal. At that age, he had a severe cerebellar syndrome, severe axonal peripheral sensory neuropathy, a mild motor deficit in the lower limbs without amyotrophy or a pyramidal involvement. He was still able to walk unaided but had a clumsy gait and frequent falls. The audiogram, the auditory evoked potentials and the otoacoustic emission tests were all normal. Brain MRI showed hypoplasia of the optic chiasm and both optic nerves (as had already been observed at age 3 years) and moderate cerebellar vermian atrophy. There was no hyperlactataemia but a paradoxical ketonaemia. No deficit of the mitochondrial respiratory chain was evidenced in fibroblasts. The patient had two pathogenic compound heterozygous mutations in OPA1, i.e. the nonsense p.Glu487Lys mutation due to c.1459G>A in exon 15 and the missense p.Ile382Met mutation due to c.1146A>G in exon 12. The father carried the p.Glu487Lys mutation resulting in a mild optic neuropathy. DNA from the asymptomatic mother was not available for testing.
In all the four patients, the direct sequencing of POLG1, MFN2 and WFS1 was normal and large OPA1 rearrangements were excluded by multiplex ligation-dependent probe amplification.

The four unrelated children reported here harbour compound heterozygosity for OPA1 and are affected with a strikingly similar early-onset neurological syndrome: associating severe visual impairment due to optic atrophy (4/4), cerebellar ataxia with cerebellar atrophy evidenced by brain MRI (4/4), peripheral neuropathy (4/4), digestive involvement (2/4) and deafness (1/4) (Table 1). This constellation of neurological signs is characteristic of the Behr syndrome (Behr, 1909).

To date, seven patients from four unrelated families have been reported with two different mutations in OPA1. However, compound heterozygosity for OPA1 has been proven in only three patients from two unrelated families (Table 1). First, Pesch et al. (2001) reported a 30-year-old adult patient harbouring two bi-allelic OPA1 mutations (p.Glu270Lys and p.Arg290Trp). This patient had a far more severe visual loss than her heterozygous parents and sibs, but the report did not mention whether she had any additional neurological signs. Later, Yu-Wai-Man et al. (2010) reported two siblings, 13 and 14 years old, harbouring two distinct mutations in OPA1 (p.Lys212Argfs* and p.Val548Ile), who presented with optic atrophy and deafness without additional neurological involvement. In these cases, however, in the absence of parental DNA samples, compound heterozygosity was not proven. In the same article, Yu-Wai-Man et al. (2010) reported two other cases of adult siblings, 60 and 64 years old, who presented optic atrophy, ataxia, myopathy, neuropathy and spasticity. They both harbour compound heterozygous mutations in OPA1 (p.Ser256Arg and p.Gln285Arg) but again, in the absence of parental DNA samples, compound heterozygosity was not proven.

Finally, Schaan et al. (2011) reported two siblings, 3 and 8 years old, presenting with a severe neonatal-onset disorder associating severe optic atrophy, ataxia, hypotonia, gastrointestinal dysmotility and dysphagia. They both harbour compound heterozygous mutations in OPA1 (p.Val903Glyfs* and p.Leu839Phe). The father, who carried the p.Val903Glyfs* variant, had a mild optic neuropathy associated with a mild hearing loss whereas the mother had normal vision and a mild hearing loss.

The clinical features of these two cases, as described by Schaan et al. (2011), correspond closely to those of the four cases we report here. Thus, in these six cases, compound heterozygosity for OPA1 lead to a severe phenotype strikingly reminiscent of the Behr syndrome. Although all the variants reported in this series (Table 1) are predicted to be pathogenic in the heterozygous state, compound heterozygotes are severely affected whereas simple heterozygotes show mild disease or are asymptomatic, suggesting a recessive or a semi-dominant inheritance with incomplete penetrance in heterozygotes.

Intriguingly, the same variant p.Ile382Met, involving a highly conserved residue in the OPA1 GTPase domain, was recurrently found in five of six patients in this series. Together with Schimpf et al. (2008), we have previously reported this mutation in patients affected with mild isolated optic neuropathy (Ferré et al., 2009). In addition, we have shown that fibroblasts carrying this mutation have 25% lower complex IV activities and ATP/O ratios compared to controls (Chevrollier et al., 2008). Although the p.Ile382Met mutation on its own might have only mild consequences, it may combine with another mutation to induce a severe pathological condition which is consistent with a semi-dominant mode of inheritance. Finally, this report underlines the importance of searching a compound heterozygosity for OPA1 in severe paediatric cases of complicated optic neuropathy.

**Table 1 Clinical features and genotypes of cases with proven compound heterozygosity for OPA1 mutations**

<table>
<thead>
<tr>
<th>Patients (gender, age)</th>
<th>Age of onset</th>
<th>Optic atrophy (age at diagnosis)</th>
<th>Ataxia</th>
<th>Peripheral neuropathy</th>
<th>Deafness</th>
<th>Digestive symptoms</th>
<th>Brain MRI</th>
<th>Genes</th>
<th>Domain</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 (M, 14 years)</td>
<td>18 months</td>
<td>+ (18 months)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Cerebellar atrophy</td>
<td></td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
<tr>
<td>Case 2 (F, 11 years)</td>
<td>1 year</td>
<td>+ (3 years)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Vomiting episodes</td>
<td></td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
<tr>
<td>Case 3 (F, 4 years)</td>
<td>14 months</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Chronic constipation</td>
<td></td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
<tr>
<td>Case 4 (M, 15 years)</td>
<td>3 years</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Verma atrophy, atrophy of optic nerves and chiasm</td>
<td></td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
<tr>
<td>Schaan et al. Case 1</td>
<td>1 year</td>
<td>+ (1 year)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Dyphagia, vomiting episodes, intestinal dysmotility with severe constipation</td>
<td>Mild periventricular leukomalacia</td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
<tr>
<td>Schaan et al. Case 2</td>
<td>6 months</td>
<td>+ (6 months)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Dyphagia, constipation</td>
<td></td>
<td></td>
<td>GPase / Truncative</td>
<td>Schaan et al., 2011</td>
</tr>
</tbody>
</table>

M = male; F = female.

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References


