LETTER TO THE EDITOR

Early-onset Behr syndrome due to compound heterozygous mutations in OPA1

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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
mild optic atrophy at age 10 years. The boy was born at 41 weeks of gestation following an uncomplicated pregnancy. At birth, his weight was 4200 g, his length 52 cm, his occipital-frontal circumference 37 cm, and his Apgar score was 10 at 1 min and 5 min. His developmental milestones were mildly retarded: head control was acquired at age 4 months, he sat without support at age 6 months and walked unaided at age 18 months. Poor vision was suspected at the end of the first year of life, and optic atrophy was diagnosed at age 18 months. Neurological evaluation at age 3 years found ataxia, dysmetria associated with limb rigidity but no pyramidal involvement. At age 4 years, the electroretinogram (ERG) was normal whereas the visual evoked potentials were altered. Neurological signs worsened with age and he lost the ability to walk at the age of 8 years. At that age, nerve conduction studies evidenced a peripheral axonal sensorineuropathy. At age 14 years, he requires a rolling walker or aid for walking and his visual acuity is 1/100 in both eyes. Brain MRIs performed at ages 5 and 8 years evidenced mild atrophy of the cerebellar vermis and involvement of the white matter, with mild periventricular T1 hypersignals and a focal lesion at the posterior end of the lenticular nucleus. The patient carried two pathogenic compound heterozygous OPA1 mutations, i.e. the nonsense p.Arg824* mutation due to c.2470C>T in exon 24 and the missense p.Ile382Met mutation due to c.1146A>G in exon 12. The mother, who was affected with mild isolated optic atrophy, harboured the p.Arg824* mutation. DNA from the asymptomatic father was not available for testing.

**Case 2**

This 11-year-old female was the first child born to non-consanguineous parents. There was no family history of optic atrophy and neither parent had any ophthalmic symptoms. The girl was born at 41 weeks of gestation after an uncomplicated pregnancy and the neonatal period had been uneventful. The disease started at age 1 year with sudden trunk ataxia, abnormal ocular movement and recurrent vomiting episodes. At that time, fundoscopy, lactate levels in the CSF, and the brain MRI were all normal. The opsomyoclonus syndrome was suspected but treatment with corticosteroids proved ineffective. At age 3 years, she developed an axonal sensoriomotor neuropathy and optic atrophy with decreased vision, confirmed by altered visual evoked potentials and abnormal ERG. Thereafter, she developed cerebellar ataxia without dysmetria and needed support for walking. Her speech was affected by mild dysarthria but she had no cognitive impairment. Cerebellar atrophy, mainly involving the vermis, was revealed by brain MRI at age 5 years, and magnetic resonance spectroscopy evidenced a lactate peak in the vermis. Mitochondrial investigations showed reduced complex I activity in fibroblasts but not in the muscle. The patient had two pathogenic compound heterozygous OPA1 mutations, i.e. the nonsense p.Val903Glyfs* mutation due to c.2708-2711del4 in exon 27, and the missense p.Val402Met mutation due to c.1204G>A in exon 12. The asymptomatic mother harboured the Val903Glyfs* mutation whereas the asymptomatic father harboured the p.Val402Met mutation.

**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 sensorineuropathy. 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, his 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 emissions 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 vermal atrophy. There was no hyperlactacidaemia 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>T in exon 12 and the missense p.Val402Met 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 biallelic OPA1 mutations (p.Glu270Lys and p.Arg290Trp). This patient had a far more severe visual loss than her heterozygous patient had a far more severe visual loss than her heterozygous M = male; F = female.

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>Mutations in OPA1</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>p.Ile382Met</td>
<td>p.Arg824*</td>
<td>GTPase</td>
<td>This study</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>p.Val903Glyfs*</td>
<td>GH79203Glyfs*</td>
<td>Truncative</td>
<td>This study</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>Normal at 4 years</td>
<td>p.Ile382Met</td>
<td>GH79203Glyfs*</td>
<td>Truncative</td>
</tr>
<tr>
<td>Case 4 (M, 15 years)</td>
<td>3 year</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>p.Ile382Met</td>
<td>GH79203Glyfs*</td>
<td>GTPase</td>
</tr>
<tr>
<td>Schaaf et al. Case 1</td>
<td>1 year</td>
<td>+ (1 year)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Dysphagia, vomiting episodes, intestinal dysmotility with severe constipation</td>
<td>Mild periventricular leukomalacia</td>
<td>p.Ile382Met</td>
<td>p.Val903Glyfs*</td>
<td>GTPase</td>
</tr>
<tr>
<td>Case 2 (M, 8 years)</td>
<td>6 months</td>
<td>+ (6 months)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>p.Ile382Met</td>
<td>p.Val903Glyfs*</td>
<td>GTPase / Truncative</td>
</tr>
</tbody>
</table>

The clinical features of these two cases, as described by Schaaf 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 surprisingly 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.

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