

LETTER TO THE EDITOR

Reply: Sensorineural hearing loss in *OPA1*-linked disorders

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Sir, Autosomal dominant optic atrophy (DOA) is the most common inherited optic neuropathy seen in clinical practice, and in >60% of cases, the underlying genetic defect is a pathogenic mutation within the *OPA1* gene (Ferre *et al.*, 2009; Yu-Wai-Man *et al.*, 2010a). The pathological hallmark of this disorder is the preferential loss of retinal ganglion cells and patients typically present with bilateral symmetrical visual loss, which progresses insidiously from early childhood onwards (Fraser *et al.*, 2010; Yu-Wai-Man *et al.*, 2011b). Although optic atrophy remains the defining feature of DOA, recent reports published in *Brain* have highlighted the much broader phenotypic manifestations that can result from pathogenic *OPA1* mutations (Amati-Bonneau *et al.*, 2008; Hudson *et al.*, 2008). In a multi-centre study of 104 patients from 45 independent *OPA1*-positive families, we found that up to 20% of mutation carriers developed significant neurological deficits in addition to visual failure (Yu-Wai-Man *et al.*, 2010b). A striking observation in this clinical subgroup was the high prevalence of sensorineural deafness, which affected nearly two-thirds of all patients with DOA phenotypes. In their Letter to the Editor, Leruez *et al.* (2012) have provided confirmatory information on the interesting association between *OPA1* mutations and sensorineural deafness by reviewing the case records of 1380 patients with suspected inherited optic neuropathy referred to their laboratory services for molecular genetic testing. Out of 327 patients found to harbour a pathogenic *OPA1* mutation, 21 (6.4%) suffered from significant hearing impairment, a higher prevalence figure when compared with an age-matched normal population cohort. The causal link between *OPA1* mutations and hearing loss has also been strengthened further by the findings of an article currently in press in *Brain*, describing a new mouse model of DOA harbouring the *OPA1*delTTAG mutation (Sarzi *et al.*, 2012).

Heterozygous mutant mice exhibited a progressive and severe form of deafness that became apparent at the relatively early age of 5 months.

According to Leruez *et al.* (2012), among those patients who could pinpoint the actual onset of their visual symptoms, 54% of them became aware of their hearing problems before the occurrence of visual loss. However, a slight note of caution is required when drawing conclusions about the chronology of these clinical features, especially when relying on retrospective patient account. A few points need to be considered, namely (i) the inherent difficulties in reliably ascribing a definite age of onset, for example, affected individuals with only mildly reduced visual acuities are not infrequently asymptomatic; (ii) the application of high-resolution optical coherence tomography imaging can reveal subclinical retinal ganglion cell loss among carriers thought to be non-penetrant because of normal visual parameters (Barboni *et al.*, 2011; Yu-Wai-Man *et al.*, 2011a); and (iii) there is some evidence that the size of the optic disc is smaller among patients harbouring *OPA1* mutations compared with controls, this structural difference being possibly related to apoptotic retinal ganglion cell death *in utero* (Barboni *et al.*, 2010; Milea *et al.*, 2010). The evidence so far therefore points to an ongoing process of accelerated retinal ganglion cell loss starting in early embryonic development and several years before the subjective appreciation of subnormal visual function.

Leruez *et al.* (2012) raise an important practical point whether all *OPA1* carriers should undergo a formal hearing assessment. Based on the prevalence of hearing impairment in their unselected patient cohort and our own experience, such an approach is neither likely to be cost-effective nor is it clinically justified in the absence of overt hearing difficulties. As part of genetic

counselling, *OPA1* carriers should be informed about the possible development of extra-ocular neurological complications, including sensorineural deafness, and clinicians overseeing their care need to be vigilant about the need for timely investigations. Although the evidence is limited to a handful of cases, patients with hearing loss secondary to *OPA1* mutations do seem to benefit from cochlear implants, the electrical stimulation of the proximal myelinated portions of auditory nerve proving sufficient to restore hearing potential (Huang *et al.*, 2009).

What further molecular insight can we gain from the data set provided by Leruez *et al.* (2013)? Similar to our own earlier observation (Yu-Wai-Man *et al.*, 2010b), their study has confirmed an intriguing predilection of the c.1334G>A (p.Arg445His) mutation for the inner ear and the unmyelinated portion of the auditory nerve. In their case series, this specific *OPA1* variant accounted for 10 of 21 (47%) patients with sensorineural deafness. It is also revealing that the majority of *OPA1* mutations associated with hearing loss, including c.1334G>A (p.Arg445His), were missense mutations affecting the GTPase domain of the protein. This specific genotype effectively conferred a 3-fold increased risk compared with other mutation subgroups (Leruez *et al.*, 2012). Although the disease mechanisms underpinning this excess attributable risk remain to be clarified, the most attractive hypothesis is a dominant negative effect linked to an aberrantly modified protein structure within the critical catalytic GTPase domain.

It is now abundantly clear that *OPA1* mutations need to be considered by neurologists and ophthalmologists for a more heterogeneous category of clinical presentations, rather than just 'autosomal DOA'. The broad intra- and inter-familial variability observed in *OPA1* disease only serves to encapsulate several fundamental questions relating to tissue specificity, secondary genetic modifiers and possible environmental influences—all of which need to be addressed if we are to make significant therapeutic inroads, not only for DOA, but for other multi-systemic nuclear mitochondrial disorders.

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