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LETTER TO THE EDITOR

Reply: Spastic paraplegia in 'dominant optic atrophy plus' phenotype due to *OPA1* mutation

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Sir, Pretegiani *et al*. (2011) describe a 28-year-old female with early-onset optic atrophy who subsequently developed slowly progressive spastic paraplegia. Electrophysiological studies did not suggest a peripheral neuropathy and additional investigations excluded a primary demyelinating process as the cause of her neurological deficits. Interestingly, this patient was eventually found to harbour a previously reported c.2708_2711delTTAG pathogenic deletion in exon 27 of *OPA1*—the causative gene in the majority of patients with autosomal dominant optic atrophy. Based on this isolated observation, it is difficult to conclude that migraine and Duane retraction syndrome are causally related to this specific *OPA1* mutation. In our original study in *Brain*, ~5% of patients with dominant optic atrophy plus (DOA+) suffered from migraine, which is less than the background prevalence in the general population (Yu-Wai-Man *et al*., 2010). Duane retraction syndrome is the most common of the congenital cranial dysinnervation disorders, and the underlying developmental defect is an absent or hypoplastic sixth cranial nerve, with aberrant innervation of the lateral rectus muscle by a branch of the third cranial nerve (Oystreck *et al*., 2011). Multiple chromosomal loci have been implicated and one gene, *CHN1* (MIM 118423), has so far been identified in families with autosomal dominant Duane retraction syndrome.

This report by Pretegiani *et al*. (2011) strengthens the emerging pathophysiological link between *OPA1* mutations and corticospinal tract dysfunction. It also highlights two intriguing features seen in most families manifesting DOA+ phenotypes: incomplete penetrance and the phenotypic variability seen with the same pathogenic *OPA1* mutation. The proband's father and sister were described as asymptomatic mutational carriers, implying non-penetrance for both optic atrophy and spastic paraplegia. It would be interesting to know what actual tests were carried out on these two family members since the criteria for establishing non-penetrance is somewhat linked to how far one decides to investigate. When examined closely, visually asymptomatic *OPA1* carriers will often demonstrate subtle, but definite, impairment in optic nerve function. Furthermore, in borderline cases, optical coherence tomography imaging can prove a useful adjunct, revealing a reduction in peripapillary retinal nerve fibre layer thickness more marked temporally in the distribution of the papillomacular bundle (Yu-Wai-Man *et al*., 2011). In relation to the neurological sequelae seen with *OPA1* disease, rather strikingly, we recently found that one in four mutational carriers with pure dominant optic atrophy (i.e. isolated optic atrophy) had prolonged central motor conduction times with transcranial magnetic stimulation (Baker *et al*., 2010). These findings clearly indicate the presence of subclinical corticospinal tract dysfunction in a sizeable patient subgroup, with those individuals manifesting spastic paraplegia only representing the 'tip of the iceberg'. This phenotypic variability, ranging from true non-penetrance, to subclinical and clinically overt disease, was somewhat to be expected, reflecting the influence of secondary factors on the pathological expression of the *OPA1* mutation. Future studies will hopefully clarify the nature of these modulatory influences and the cellular mechanisms

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underpinning the tissue selectivity observed in DOA+. On a more practical level, patients with unexplained spastic paraplegia should undergo a comprehensive neuro-ophthalmological assessment to specifically look for evidence of optic nerve dysfunction. If present, *OPA1* screening is warranted especially if a muscle biopsy also confirms histochemical and molecular features of mitochondrial dysfunction.

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