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Dominant Optic Atrophy – Novel *OPA1* Mutations and Revised Prevalence Estimates

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Autosomal dominant optic atrophy (DOA) is the most common form of inherited optic neuropathy seen in clinical practice.¹ So far, two causative genes have been identified in patients with DOA; *OPA1*, which accounts for 50-60% of cases, and *OPA3*, which is relatively rare having been identified in only isolated families in association with premature cataracts.^{2, 3} *OPA1* mutations have a high penetrance rate (80-90%), but the disease phenotype is characterised by marked intra- and inter-familial variability. Patients classically present with increasing visual difficulties in early childhood and there is a high rate of progression to blind registration. As a result of the selective involvement of the retinal ganglion cells within the papillomacular bundle, the optic disc often has a characteristic temporal wedge of pallor. Although optic nerve involvement is a cardinal feature of *OPA1* disease, extraocular manifestations are being increasingly recognised and the term DOA plus (DOA+) has been coined to describe these more severe syndromal variants. In a major collaborative effort involving diagnostic and research centres in Northern Europe, up to 20% of *OPA1* carriers developed neurological deficits ranging from early-onset sensorineural deafness to peripheral neuropathy, ataxia, myopathy, and late-onset chronic progressive external ophthalmoplegia.⁴ These findings have obvious practical implications for the multidisciplinary care of affected patients and the wider aspects of genetic counselling for familiar carriers.

In a recent study in *Ophthalmology*,¹ we provided for the first time a population-based estimate of the prevalence of DOA and *OPA1* mutations as part of an ongoing epidemiological study of inherited optic neuropathies in the North of England. The

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minimum prevalence of DOA in this defined geographical region was estimated at 2.87 per 100,000 (95% confidence interval [CI], 2.54–3.20), about 1 in 35,000. The minimum prevalence of patients with visual failure secondary to a confirmed pathogenic *OPA1* mutation was 2.09 per 100,000 (95% CI, 1.95–2.23), about 1 in 48,000. In the three years since these results were published, it has become apparent to us that these figures represent underestimates of the true burden of disease in the North of England. Although this in itself is not surprising, and something we expected with the deliberate use of the term “*minimum point prevalence*” in our original report, it does emphasise the limitations of case ascertainment in any epidemiological study, even more so for relatively rare disorders that require access to specialist genetic services for a definite molecular diagnosis to be made.

We have identified an additional eight families with confirmed pathogenic *OPA1* mutations (e-Table 1). Two patients (A and D) who presented in their mid-twenties had no definite family history and the possibility of a genetic aetiology was considered after a comprehensive investigative work-up had excluded other possible acquired causes of an isolated, slowly progressive, bilateral optic neuropathy. Three probands harboured novel heterozygous *OPA1* variants that had not been previously catalogued in the *eOPA1* database (<http://mitodyn.org/home.php>, accessed March 22, 2013). All three mutations were predicted to result in premature termination codons assuming that a viable mRNA transcript is stable enough to be translated and not destroyed by nonsense-mediated decay: (i) c.3G>T in exon 1 (p.Trp2fsX13b); (ii) c.2012_2013del(AA) in exon 21 (p.Lys701fsX4); and c.2294dup(A) in exon 23 (p.Asn765fsX26). The wide mutational spectrum observed in our cohort is entirely consistent with the highly polymorphic nature of the *OPA1* gene. It also confirms the absence of a major mutational founder event in the North of England, as has been described in some populations, for example Denmark, where nearly half of all families harbour the c.2708_2711del(TTAG) deletion in exon 27.5 Finally, in one family (C), two affected carriers developed sensorineural deafness and peripheral neuropathy in addition to bilateral visual failure. Interestingly, the causative *OPA1* missense mutation in this family involves the critical catalytic GTPase domain of the protein, and a dominant-negative effect has been postulated to account for the increased risk of developing DOA+ with this specific mutation subtype.⁴

By including these additional *OPA1*+ve families, our revised estimate for the prevalence of *OPA1* mutations in the North of England is 2.91 per 100,000 (95% CI, 2.58–3.26), about 1 in 34,000. The overall prevalence of DOA was derived by including *OPA1*-ve families with a clear-cut dominant pattern of inheritance; eight families from our original report,¹ and five additional families that have been investigated in the intervening period. Based on this stringent diagnostic criteria, our revised estimate for the prevalence of DOA in the North of England is 4.07 per 100,000 (95% CI, 3.68–4.49), about 1 in 25,000. There are two main reasons to account for this increase in case ascertainment over the past three years. Firstly, access to *OPA1* genetic testing has become more widespread to clinicians in non-academic institutions via the United Kingdom Genetic Testing Network (UKGTN), exemplified by the fact that two families were diagnosed with *OPA1* mutations prior to being referred to us for further assessment. Secondly, we are receiving an increasing number of referrals relating to patients with (presumed) sporadic inherited optic atrophy and without a definite diagnosis for consideration of *OPA1* genetic screening. In that respect, our revised prevalence figure

for DOA is still likely to represent a conservative estimate as it does not include this specific subgroup of sporadic patients who have been found to be *OPA1*-ve on subsequent testing. In an outbred population and in the absence of consanguinity, a good proportion of these *OPA1*-ve cases will eventually be found to harbour as yet unidentified nuclear genes causing DOA. Notwithstanding these caveats, our updated epidemiological data firmly establishes DOA as an important cause of inherited visual failure and the urgent need for effective treatment strategies to help patients with this disabling form of mitochondrial blindness.

Extended Data

eTable 1
Additional *OPA1* +ve families identified in the north of England

Family	cDNA Change	Location	Consequence	Affected ^a
A	c.3G>T [*]	Exon 1	p.Trp2fsX13 ^b	1
B	c.703C>T	Exon 7	p.Arg235X	5
C	c.869G>A	Exon 8	p.Arg290Gln	3
D	c.2012_2013del(AA) [*]	Exon 21	p.Lys701fsX4	1
E	c.2294dup(A) [*]	Exon 23	p.Asn765fsX26	4
F	c.2613+1g>a	Intron 25	Splicing defect	2
G	c.2708_2711del(TTAG)	Exon 27	p.V903fsX3	7
H	c.2713C>T	Exon 27	p.R905X	3

^aNumber of affected individuals resident in the north of England

^bIf a viable mRNA transcript is translated

^{*}Novel previously unreported *OPA1* mutations.

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