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The Prevalence and Natural History of Dominant Optic Atrophy due to *OPA1* Mutations

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Abstract

Purpose—Autosomal dominant optic atrophy (DOA) is a major cause of visual impairment in young adults and it is characterized by selective retinal ganglion cell loss. In order to define the prevalence and natural history of this optic nerve disorder, we performed a population-based epidemiological and molecular study of presumed DOA cases in the north of England.

Design—Case series

Participants—Seventy-six affected probands with a clinical diagnosis of DOA were identified from our neuro-ophthalmology and neurogenetics database.

Methods—*OPA1* genetic testing was performed using a PCR-based sequencing strategy. *OPA1* negative cases were then screened for large-scale *OPA1* re-arrangements and *OPA3* mutations. Additional affected family members identified through contact tracing were examined and longitudinal visual data was analyzed.

Main Outcome Measures—The prevalence and molecular characteristics of DOA in the north of England. Visual function and disease progression among patients with *OPA1* positive mutations.

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Results—The detection rate of *OPA1* mutations was 57.6% among probands with a positive family history of optic atrophy (19/33) and 14.0% among singleton cases (6/43). About two-thirds of our DOA families harbored *OPA1* mutations (14/22, 63.6%), and five novel *OPA1* mutations were identified. Only one family carried a large-scale *OPA1* rearrangement and no *OPA3* mutations were found in our optic atrophy cohort. The minimum point prevalence of DOA in the north of England was 2.87 per 100,000 (95% CI 2.54-3.20), or 2.09 per 100,000 (95% CI 1.95-2.23) when only *OPA1* positive cases were considered. Snellen visual acuity varied markedly between *OPA1* positive cases with a mean of 20/173 (Range 20/20-hand movement), and visual function worsened in 67.4% of patients during follow-up. The mean rate of visual loss was 0.032 LogMAR/years but some patients experienced much faster visual decline (Range = 0–0.171 LogMAR/years). *OPA1* missense mutations were associated with a significantly worse visual outcome compared to other mutational subtypes ($P = 0.0001$).

Conclusions—DOA causes significant visual morbidity and affects at least 1 in 35,000 of the general population.

Keywords

Dominant optic atrophy; epidemiology; mitochondrial DNA; optic neuropathy; *OPA1*; prevalence

Introduction

Autosomal dominant optic atrophy (DOA) is an important cause of inherited visual failure and the primary pathological process selectively targets retinal ganglion cells (RGCs) resulting in optic nerve degeneration. The majority of DOA families harbor pathogenic mutations in the *OPA1* gene (3q28-q29, OMIM 165500) and the characteristic features observed in this condition are an insidious onset in early childhood, reduced colour vision, central field defects and a marked inter- and intra-familial variation in disease severity.^{1, 2} Over 200 different *OPA1* mutations have been reported including single nucleotide changes within the coding regions (44%), splice site variants (27%) and small exonic deletions and duplications (29%).³ In a recent study using a multiplex ligation probe amplification (MLPA) assay, large scale *OPA1* rearrangements were identified in 8/42 (19%) probands with no previously identified *OPA1* mutations by conventional screening methods.⁴ Heterozygous mutations in the *OPA3* gene (19q13.2-q13.3, OMIM 165300) have also been implicated in two French families segregating bilateral optic atrophy in association with premature cataracts,⁵ a more benign phenotype compared to the generalised neurodegenerative process seen in the autosomal recessive form of the disease, 3-methylglutaconic aciduria type III or Costeff's syndrome (OMIM 258501).^{6, 7} Interestingly, both *Opa1* and *Opa3* are inner mitochondrial membrane proteins and pathogenic mutations exert their deleterious effects on RGC survival via several, likely interacting, mechanisms, namely impairment of mitochondrial oxidative phosphorylation, disruption of the delicate balance regulating mitochondrial fusion and fission, and an increased susceptibility to apoptotic cell death.^{8, 9}

Although the mutational spectrum and natural history of DOA have been described in several case series,^{3, 10-15} there are currently no robust prevalence figures of molecularly confirmed cases in the general population, so the true impact of this disorder is not known.

The latter reflects the methodological limitations of these studies which were performed by specialist research centers with often wide and overlapping patient catchment areas. We therefore performed an extensive clinical and molecular study of DOA in the north of England, both to address these important epidemiological issues and to clarify the burden of *OPA1* and *OPA3* mutations in this patient group.

Patients and Methods

Study Population

The north of England has been relatively stable in terms of migratory flux and based upon the mid-2007 United Kingdom (UK) national census, it consists of a predominantly white, Caucasian population of 3,061,400 individuals. As a result of historical clinical links and the nature of healthcare provision in our region, patients with unexplained visual failure and/or possible inherited optic neuropathies are referred to the neuro-ophthalmology (PYWM, MPC and PGG) and neurogenetics (RH and PFC) services in Newcastle upon Tyne for further assessment. This includes molecular testing provided by the Mitochondrial Diagnostic Laboratory since 1990 and with UK National Commissioning Group status for “Rare Mitochondrial Diseases” since 2007 (<http://www.mitochondrialnecg.nhs.uk/>, Accessed 10-12-09). Over the past two decades, these referral patterns have enabled us to establish a comprehensive research database of patients with a likely genetic basis for their optic atrophy, both in the north of England and from outside the region. This study had the relevant institutional approval from the County Durham and Tees Valley 1 Research Ethics Committee and complied with the Declaration of Helsinki.

Optic Atrophy Cohort

We identified 76 affected probands with clinical features suggestive of DOA in our database and these were initially screened for possible *OPA1* mutations as part of their diagnostic work-up. All affected individuals had previously been investigated to exclude compressive, inflammatory and infiltrative causes for their bilateral optic neuropathy, and a complete ophthalmological examination had also been performed including: (i) intraocular pressure (IOP) measurement by applanation tonometry, (ii) visual field assessment by confrontation, static (Humphrey) and/or kinetic (Goldmann) perimetry, (iii) colour discrimination with the Ishihara pseudochromatic plates, (iv) dilated slit lamp biomicroscopy, (v) measurement of the peripapillary retinal nerve fibre layer (RNFL) thickness by optical coherence tomography (OCT), and (vi) visual electrophysiology when appropriate. Genomic DNA samples were extracted from peripheral blood leukocytes using established methods.

Visual Acuity

For the purpose of longitudinal analysis, additional clinical information and visual acuity data were obtained from archived records held in the patients' local ophthalmology units (PWS, LG, DAK). In the majority of cases, best corrected visual acuity (BCVA) was measured using the Snellen chart and for the purpose of statistical analysis, Snellen ratios were converted to LogMAR (Logarithm of the minimum angle of resolution) decimal values. A LogMAR value of 0 is equivalent to 20/20 Snellen vision and a value of 1.0 is equivalent to 20/200 Snellen vision, the largest optotype on standard Snellen charts. Patients

with visual acuities reduced to counting fingers (CF) were assigned a LogMAR value of 2.0, whilst those with only hand movement (HM) perception were given a LogMAR value of 2.3.^{16, 17}

Molecular Genetics

The entire coding region of the *OPA1* and *OPA3* genes was amplified by the polymerase chain reaction (PCR) (Primer oligodeoxynucleotide sequences are available on request) and sequenced with BigDye™ terminator cycle chemistries on an ABI3100 Genetic Analyzer (Applied Biosystems). Sequence chromatograms were directly compared with the appropriate Genbank reference sequence using SeqScape™ software v2.1 (Applied Biosystems): *OPA1* accession number AB011139 according to mRNA transcript variant 1, NM_011560, and *OPA3* accession numbers NM_001017989.2 (Transcript 1) and NM_025136.2 (Transcript 2).

OPA1 Sequence Variants

All genetic variants were confirmed by reverse sequencing and checked against the eOPA1 database (<http://lbbma.univ-angers.fr/eOPA1/>, Accessed 10-12-09) to determine whether they had been described in previous mutational reports. Bioinformatic analysis and the functional significance of intronic *OPA1* nucleotide changes were determined using the publicly available Fruitfly predictor software (http://www.fruitfly.org/seq_tools/splice.html and http://www.fruitfly.org/seq_tools/promoter.html, Accessed 10-12-09). Novel *OPA1* mutations were also screened in a panel of 186 age-matched, white Caucasian controls from the north of England using a multiplex primer extension assay and product analysis with matrix-associated laser desorption/ionization time of flight mass spectrometry (MALDI-TOF) (Sequenom, San Diego, CA).

MLPA Assay

All optic atrophy patients with a family history suggesting an autosomal dominant pattern of inheritance, which was defined as affected family members in two or more generations, and no pathogenic *OPA1* mutations with direct sequencing were subsequently screened for possible large scale *OPA1* rearrangements using a previously described MLPA kit (MRC-Holland).⁴

Statistical Analysis

Statistical analysis was performed using GraphPad™ v.4 statistical software (San Diego, CA). Fisher's exact test, χ^2 analysis, independent sample t-test, and one-way ANOVA were used for group comparisons, as required.

Results

Frequency of *OPA1* Mutations

In our initial molecular screen, *OPA1* mutations were identified in 25/76 probands (32.9%), 17 families were from the north of England and 8 families were from outside the region. The detection rate was significantly higher among those referred by ophthalmologists (19/37,

51.4%) compared to referrals from neurologists and geneticists (6/39, 15.4%) (Odds ratio (OR) = 5.8, 95% confidence interval (CI) = 2.0-17.2, $P = 0.0013$). Similarly, there was a greater likelihood of identifying an *OPA1* mutation among probands with a positive family history of optic atrophy (19/33, 57.6%) compared to singleton cases (6/43, 14.0%) (OR = 8.4, 95% CI = 2.8–25.3, $P < 0.0001$). For the remainder of this epidemiological study, the 8 *OPA1* positive families that were referred from outside the region were not included.

North of England Cohort

OPA1 positive families from the north of England harbored 13 different pathogenic mutations: missense (2/13, 15.4%), nonsense (2/13, 15.4%), splice site (5/13, 38.4%) and deletions (4/13, 30.8%) (Table 1, Figure 1). Of these, 5 were novel variants not present among 186 normal controls: c.636_637delAG in exon 6, c.876-878delTGT and c.889C>T in exon 9, c.1198C>T in exon 12, and c.2818+5g>a in intron 27. The c.636_637delAG, c.876-878delTGT and c.889C>T mutations are predicted to result in premature termination codons. The c.1198C>T mutation in exon 12 was identified in a singleton case (OA-17) with typical ophthalmological features of DOA, but it was not found in his unaffected father and two unaffected siblings (Figure 2). The mother was not thought to be visually affected but no DNA sample was available for analysis. The C to T substitution at nucleotide position 1198 is predicted to change a highly conserved amino acid proline to serine (p.P400S) in the critical GTPase domain of the Opa1 protein. The c.2818+5g>a splice site mutation in intron 27 segregated with affected status in a three-generation family (OA-6), all affected family members sharing the same disease haplotype. Previous pathogenic mutations have been described at positions +2 and +6 (<http://lbbma.univ-angers.fr/eOPA1/>, Accessed 10-12-09) and the c.2818+5g>a substitution is predicted to completely abolish the functionality score of the splice donor site from 0.88 to 0.00, supporting the pathogenic status of this intronic variant.

Haplotype Analysis

Affected family members within pedigrees OA-3, OA-4 and OA-5 (c.876-878delTGT) harbored the same *OPA1* disease haplotype, suggesting a shared common ancestor (Table 2). Haplotype analysis of pedigrees OA8, OA-9 and OA-10 also revealed a similar combination of non-pathogenic *OPA1* single nucleotide polymorphisms (SNPs) in combination with the c.2713C>T mutation, again indicating a likely founder event (Table 3).

OPA1 Rearrangements

Family OA-18 is a large three-generation family showing clear paternal transmission of early onset, bilateral optic atrophy. The clinical diagnosis of DOA was robust and when *OPA1* sequencing failed to identify a pathogenic change, DNA samples were sent for further linkage analysis at the Institute for Ophthalmic Research in Tübingen, Germany. A deletion encompassing exons 1 to 5b was subsequently identified in family OA-18⁴ and we therefore wished to determine the frequency of large scale *OPA1* re-arrangements in other DOA families in the north of England without *OPA1* mutations using our PCR-based sequencing protocol (N = 8). No additional rearrangements were found with the same MLPA kit (MRC-

Holland) used by *Fuhrmann and colleagues*,⁴ giving an overall frequency of 11.1% (1/9) in this particular subgroup.

OPA3 Screen

OPA3 sequencing was finally performed in the remaining 50 probands in our optic atrophy cohort with no confirmed molecular diagnosis, a heterogeneous group consisting of families with affected individuals in two or more generations ($N = 11$), more than one affected individual but in only one generation ($N=2$), and singleton cases ($N=37$), none of whom had a history of premature cataracts. No *OPA3* mutations were identified and 18 probands harbored a previously reported c.231T>C SNP in exon 2.¹⁸ A previously reported⁶ intronic c.1-38g>a SNP in the 5' untranslated region was found in 3 probands but with no predicted effect on splicing at the acceptor site or on putative transcriptional promoters upstream of the start codon.

Prevalence Data

Our molecular investigations have established 14 genetically distinct *OPA1* positive pedigrees in the north of England, with 64 living affected family members resident in the region at the time of contact tracing (Mean age = 39.5 years, standard deviation (SD) = 17.8 years, range 6.0– 78.0 years) (Table 1). There was no gender bias among affected individuals with a male to female ratio of 1.06:1. An additional 8 families (8/22, 36.4%) with a total of 24 affected family members had an autosomal dominant pattern of inheritance but no *OPA1* or *OPA3* mutations (*OPA1* negative group) (Mean age = 40.1 years, SD = 16.6 years, range 12.0– 72.0 years). Including these *OPA1* negative cases with a positive family history, the minimum point prevalence of DOA in the north of England was therefore estimated at 2.87 per 100,000 (95% CI 2.54–3.20), about 1 in 35,000 of the general population. The minimum point prevalence of patients with visual failure secondary to a confirmed *OPA1* mutation was 2.09 per 100,000 (95% CI 1.95–2.23).

Fundal Appearance

The appearance of the optic nerve head was abnormal in all carriers with an *OPA1* mutation, with total disc pallor observed in 32/82 (39.0%) eyes and a prominent temporal wedge of pallor in the remaining 50/82 (61.0%) eyes (Figure 2B). Other morphological changes were noted: (i) tilted discs (6/82, 7.3%), (ii) peripapillary optic atrophy (16/82, 19.5%), and (iii) cup to disc ratios > 0.5 (10/82, 12.2%) which was symmetrical between the 2 eyes, with normal IOPs and no family history of glaucoma. No significant macular or peripheral pigmentary changes were noted in all *OPA1* cases.

Visual Function

The mean age of onset of visual failure among *OPA1* positive patients was 7.0 years (SD = 3.9 years, range 1.0–16.0 years) and 80% of affected individuals were symptomatic before the age of 10 years (Table 1, Figure 3). These figures do not include a small minority of patients (5/45, 11.1%) who were subjectively asymptomatic but were found to have mild reduction in visual acuity and subclinical optic neuropathy during contact tracing. Colour vision was abnormal in all but one patient, the daughter of proband OA-2, who had full

Ishihara colour discrimination with 20/30 Snellen vision (OU) and only mild temporal disc pallor. Reliable Goldmann field perimetry was possible in 29 patients and 20/29 (69.0%) had a demonstrable field defect, a central scotoma in 15/29 cases (51.7%) and a centro-caecal scotoma in 5/29 cases (17.2%).

At the time of their last ophthalmological assessment, the mean visual acuity for our north of England cohort was as follows: (i) all DOA cases; 0.94 LogMAR, 20/173 Snellen (N = 65), (ii) *OPA1* positive group; 1.02 LogMAR, 20/207 Snellen (N = 45), and (iii) *OPA1* negative group; 0.76 LogMAR, 20/117 Snellen (N = 20) (Table 1, Figure 4A). There was no significant difference in mean LogMAR visual acuity between these 3 groups ($P = 0.1133$), and there was a wide range in visual acuities (20/20-HM) both within and between families. Visual acuity was symmetrical between both eyes in the majority of patients (52/65, 80.0%), there was a difference of ≥ 2 LogMAR lines in 8/65 (12.3%) patients, and a difference of > 2 LogMAR lines in 5/65 (7.7%) patients. Among the latter group, 3/5 cases had childhood strabismus and they underwent horizontal recti surgery to improve ocular alignment.

There was a significant difference in visual outcome between *OPA1* mutational subtypes (Figure 5, $P = 0.0018$), with the mean LogMAR visual acuity for patients with missense mutations (Mean = 1.83, SD = 0.19) being worse compared to those harboring deletions, nonsense, and splice site mutations (Mean = 0.93, SD = 0.07, $P = 0.0001$). However, there was no significant difference in LogMAR visual acuity between *OPA1* mutations when grouped according to their locations within the main functional gene domains ($P = 0.6161$).

Disease Progression

OPA1 positive patients > 40 years old had worse LogMAR visual acuities (Mean = 1.27, SD = 0.72) compared to those who were ≤ 40 years old (Mean = 0.73, SD = 0.48, $P = 0.0001$) (Figures 4B and 4C). Longitudinal visual acuity data was also available for 43 *OPA1* positive patients with a mean follow-up duration of 18.0 years (SD = 14.7 years, range 1.2–53.0 years). BCVA worsened in 29/43 (67.4%) patients, with a reduction of ≥ 2 LogMAR lines (0.2 decimal value) in 4/43 (9.3%) patients and > 2 LogMAR lines in 25/43 (58.1%) patients. The mean rate of visual loss was 0.032 LogMAR/years (SD = 0.045 LogMAR/years), but some patients experienced much faster visual decline (Range = 0–0.171 LogMAR/years). There was also a significant overall reduction in LogMAR visual acuities with disease duration when comparing baseline values (Mean = 0.68, SD = 0.53) with the patients' most recent measurements (Mean = 1.06, SD = 0.67, $P = 0.0001$) (Figure 4D).

Discussion

This is the first population-based epidemiological study of DOA and in the north of England the minimum point prevalence of DOA was 2.87 per 100,000, about 1 in 35,000. About two-thirds of our families harbored *OPA1* mutations (14/22, 63.6%) which is consistent with the average figure of 60% found in previous case series,² and if only these molecularly-confirmed cases are considered, the minimum point prevalence of visual failure secondary to *OPA1* mutations was 2.09 per 100,000. However, it must be emphasised that for the remaining families with no molecular diagnosis, the possibility of pathogenic variants within the *OPA1* gene promoter and intronic regions has not been excluded, with putative roles in

the regulation of *OPA1* mRNA splicing or transcriptional activity. The prevalence of DOA is often quoted in the literature as 1 in 50,000 but this is only an estimate based upon one author's personal views on the relative prevalence of DOA in comparison to other genetic ocular disorders.¹⁹ A higher figure of 1 in 12,000 in Denmark was derived from the Register of Hereditary Eye Diseases held at the National Eye Clinic in Hellerup, but this was based upon a clinical diagnosis of DOA in the pre-molecular era.²⁰ Furthermore, the mutational spectrum of DOA in Denmark is more limited with about 42% of Danish pedigrees harboring the c.2708_2711delTTAG deletion in exon 27.²¹ This significant allelic overrepresentation has been attributed to an ancestral mutational event and this probably also accounts for the higher prevalence of DOA in this specific population. The prevalence of DOA in this study is comparable to that of Leber hereditary optic neuropathy (LHON) which was previously estimated at 3.22 per 100,000 (95% CI 2.47-3.97) in the north of England,²² further confirming the clinical impression that DOA and LHON are the two most common inherited optic nerve disorders in the general population. Unlike LHON, there is no gender bias in DOA and no cases of non-penetrance were identified in our cohort. The proportion of *OPA1* carriers not manifesting optic nerve dysfunction varies between 0–57% in the literature,^{11, 12, 23} and this variation is likely due to a combination of factors such as the methods of case ascertainment, the clinical criteria used to define non-penetrance, and whether ancillary tests such as OCT and visual electrophysiology have been employed in the patient's investigations.

As expected, the majority of *OPA1* mutations were located in the GTPase, dynamin central region and terminal effector domains, and we have described 5 novel pathogenic variants extending the mutational spectrum of this highly polymorphic gene (Figure 1).^{3, 15} Although large scale *OPA1* rearrangements should be ruled out when there is a high index of clinical suspicion supported by a positive family history, this mutational subtype probably accounts for only 10-20% of DOA cases found to be *OPA1* negative with conventional PCR-based screening methods.⁴ *OPA3* mutations have also been reported in two French families segregating both DOA and premature cataracts in an autosomal dominant mode of inheritance.⁵ However, no *OPA3* mutations were identified in our study which suggests that these are likely rare causes of inherited optic atrophy especially in the absence of early-onset lenticular abnormalities.

Our clinical observations stress the importance of considering DOA in the differential diagnosis of patients with progressive onset of visual failure in early childhood, especially in the presence of prominent temporal optic disc pallor. The latter is a characteristic morphological feature seen in DOA and it was observed in 61% of our *OPA1* positive cases, similar to other case series (41-52%).^{23, 24} It can be better appreciated with dilated, stereoscopic slit lamp biomicroscopy, reflecting the much higher *OPA1* hit rate among cases referred by ophthalmologists (51.4%) compared to other specialties (15.4%). Although a positive family history of optic atrophy increases the diagnostic yield, in practice this can be difficult to ascertain and it is further compounded by the possibility of subtle visual deficits in asymptomatic family members.^{14, 25, 26} For example, the proband of OA-15 was initially thought to be a singleton case but examination of both her asymptomatic son and daughter revealed that they had subtle but definite temporal optic disc pallor, with visual acuities of

20/20 and 20/30 OU respectively, and abnormal visual electrophysiology. In one study, about half of all diagnosed *OPA1* cases were “sporadic”, with the only caveat that this was conducted in a diagnostic center with no active contact tracing of other family members.^{3, 10-15} Nevertheless, *OPA1* sequencing should be advocated in all cases presenting with clinical and ophthalmological features suggestive of DOA even in the absence of any apparent family history.

Our DOA cohort has confirmed the salient clinical features in this condition, with the majority of patients experiencing visual loss in early childhood, and a marked inter- and intra-familial variability in disease severity. The legal definition of severe visual impairment in the UK is a BCVA < 10/200 Snellen (1.30 LogMAR) (http://www.dh.gov.uk/en/Healthcare/Primarycare/Optical/DH_4074843, Accessed 10-12-09), and registered individuals are entitled to a range of social care and financial benefits. It is therefore significant that patients with *OPA1* missense mutations were much more likely to fall within this disability category compared to other mutational subtypes (OR = 12.4, 95% CI = 2.3-67.2, P = 0.0023). This has important clinical implications and although additional confirmatory studies are needed, it is tempting to speculate that missense *OPA1* mutations are having a greater detrimental effect on RGC survival via a possible dominant-negative effect.

During follow-up, visual acuity worsened in two-thirds of patients and the rate of visual decline varied widely, being much faster in a subgroup of patients. In previous reports, including pre-molecular case series, 19-50% of patients experienced progressive,^{10, 13, 14, 27, 28} albeit slow, visual deterioration and 13-46% were registered legally blind.^{20, 23, 29} Although DOA has a relatively better visual prognosis compared to LHON,³⁰ the majority of patients will still suffer a decline in visual function and some caution is therefore recommended when counselling *OPA1* positive patients and their families. In conclusion, this study has defined the mutational spectrum and natural history of DOA in the north of England and our epidemiological data indicate similar prevalence figures for DOA and LHON in our region. However, these two mitochondrial optic neuropathies exhibit distinct clinical and ophthalmological features which can be helpful to clinicians in directing appropriate molecular investigations and subsequent genetic counselling. There is currently no proven treatment for LHON or DOA and given the central role played by mitochondrial dysfunction in the pathophysiology of both these disorders, future mechanistic studies will hopefully reveal disease pathways amenable to therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

A

B

C

D

Patient	GLQRMVLVDLSGVINTVTSGM
H.sapiens	GLQRMVLVDLPGVINTVTSGM
P.troglodytes	GLQRMVLVDLPGVINTVTSGM
M.musculus	GLQRMVLVDLPGVINTVTSGM
G.gallus	GLQRMVLVDLPGVISTVTSGM
D.rerio	GIQRMVLVDLPGVISTVTTGM
D.melanogaster	GLQRMVLVDLPGIISTMTVDM
A.gambiae	GLQRMVLVDLPGIISTQTVDM
C.elegans	NLPRMVLVDLPGVISTVTADM
S.cerevisiae	RVPDLSLVDLPGYIQVEAADQ

Figure 3.

Figure 4.

Figure 5.

Table 1
Molecular and Clinical Characteristics of *OPA1* Positive Pedigrees Identified in the North of England

Pedigree	cDNA Change	Consequence	Affected N =	Examined N =	Age of Onset (Yrs)		Snellen BCVA	
					Mean	Range	Mean	Range
OA-1	c.1212+3a>t	Splicing defect	3	3	4.7	4.0-5.0	20/417	20/160-CF
OA-2	c.870+5g>a	Splicing defect	4	3	10.0	8.0-12.0	20/210	20/30 - CF
OA-3 ^{b, c}	c.876-878delTGT*	p.V294fsX667	3	1	5.0	N/A	CF	N/A
OA-4 ^{b, c}	c.876-878delTGT*	p.V294fsX667	10	6	6.0	4.0-11.0	20/167	20/40 - CF
OA-5 ^{b, c}	c.876-878delTGT*	p.V294fsX667	7	3	5.0	5.0	20/197	20/200 - 20/400
OA-6	c.2818+5g>a*	Splicing defect	4	3	5.3	5.0-6.0	20/93	20/40 - 20/200
OA-7	c.2708_2711delTTAG	p.V903fsX3	2	1	5.0	N/A	20/200	N/A
OA-8 ^{b, c}	c.2713C>T	p.R905X	3	3	14.0	11.0-16.0	20/273	20/60 - CF
OA-9 ^{b, c}	c.2713C>T	p.R905X	2	1	5.0	N/A	20/80	N/A
OA-10 ^{b, c}	c.2713C>T	p.R905X	3	2	5.0	5.0	20/200	20/200
OA-11	c.2613+1g>a	Splicing defect	3	3	7.0	3.0-10.0	20/160	20/120 - CF
OA-12	c.1516+1g>t	Splicing defect	4	3	15.0	15.0	20/53	20/20 - 20/200
OA-13	c.794_797delTTGA	p.I265fsX42	3	1	15.0	N/A	20/40	N/A
OA-14	c.636_637delAG*	p.K214fsX2	3	1	8.0	N/A	20/40	N/A
OA-15	c.889C>T*	p.Q297X	3	3	5.0	5.0	20/107	20/20 - CF
OA-16	c.1635C>G	p.S545R	3	3	3.7	1.0-5.0	20/1170	20/200 - HM
OA-17	c.1198C>T*	p.P400S	1	1	2.0	N/A	HM	N/A
OA-18	Exons 1 -5b deletion*	p.M1fsX208	3	4	7.3	5.0-9.0	20/130	20/60 - 20/200
Entire Study Cohort			64	45	7.0	1.0-16.0	20/207	20/20 - HM

BCVA: Best corrected visual acuity, CF: Counting fingers, HM: Hand movement, N/A: Not applicable, Yrs: Years.

^a Affected individuals resident in the north of England,

^{b, c} Shared *OPA1* haplotype,

* Novel *OPA1* mutations,

Table 2
Haplotype Analysis of Pedigrees OA-3, OA-4 and OA-5

Location	OA-3, III-3	OA-4, III-1	OA-4, III-2	OA-5, I-1	OA-5, II-3	OA-5, III-1	Haplotype
Exon 4	c.473A>G	c.473A>G	c.473A>G	c.473A>G	c.473A>G	c.473A>G	c.473A>G
Intron 4	c.557-19t>c				c.557-19t>c	c.557-19t>c	
Exon 5				c.575C>T			
Intron 8	c.870+4c>t	c.870+4c>t	c.870+4c>t	c.870+4c>t	c.870+4c>t	c.870+4c>t	c.870+4c>t
Intron 8	c.870+32t>c				c.870+32t>c	c.870+32t>c	
Exon 9	c.876-878delTGT						
Intron 11					c.1141-55t>a		
Intron 14						c.1443+23g>a	
Exon 17				c.1608A>C			
Intron 18	c.1770+16t>g				c.1770+16t>g		
Intron 18	c.1770+51t>g				c.1770+51t>g	c.1770+51t>g	
Exon 21	c.2109C>T	c.2109C>T	c.2109C>T	c.2109C>T	c.2109C>T	c.2109C>T	c.2109C>T
Intron 26	c.2707+25t>a				c.2707+25t>a	c.2707+25t>a	

Homozygous *OPA1* SNPs are highlighted in blue and *OPA1* mutations are highlighted in red.

Table 3
Haplotype Analysis of Pedigrees OA-8, OA-9 and OA-10

Location	OA-8, II-1	OA-8, III-1	OA-8, III-2	OA-9, II-1	OA-IO, II-1	OA-IO, II-2	Haplotype
Exon 4	c.473A>G				c.473A>G		
Intron 4	c.557-19t>c	c.557-19t>c	c.557-19t>c	c.557-19t>c	c.557-19t>c	c.557-19t>c	c.557-19t>c
Intron 8	c.870+32t>c	c.870+32t>c	c.870+32t>c	c.870+32t>c	c.870+32t>c	c.870+32t>c	c.870+32t>c
Intron 18	c.1770+16t>g	c.1770+16t>g	c.1770+16t>g	c.1770+16t>g	c.1770+16t>g	c.1770+16t>g	c.1770+16t>g
Intron 18	c.1770+51t>g	c.1770+51t>g	c.1770+51t>g	c.1770+51t>g	c.1770+51t>g	c.1770+51t>g	c.1770+51t>g
Exon 21	c.2109C>T				c.2109C>T	c.2109C>T	
Intron 26	c.2707+25t>a	c.2707+25t>a	c.2707+25t>a	c.2707+25t>a	c.2707+25t>a	c.2707+25t>a	c.2707+25t>a
Exon 27	c.2713C>T						

Homozygous *OPA1* SNPs are highlighted in blue and *OPA1* mutations are highlighted in red.