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Review

# Meta-analysis of genotype-phenotype analysis of OPA1 mutations in autosomal dominant optic atrophy

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ABSTRACT

Autosomal Dominant Optic Atrophy (ADOA) is a neuro-ophthalmic disease characterized by progressive bilateral vision loss, pallor of the optic disc, central vision loss, and impairment of color vision. Additionally, a small percentage of patients experience hearing loss and ataxia, while recent studies suggest disruption of cardiac and neuromuscular functions. In order to obtain a better understanding of the genotype-phenotype correlation of the various mutations in the optic atrophy 1 (*OPA1)* gene, we obtained both clinical and genetic information of ADOA patients from published reports. We conducted a systematic review of published *OPA1* literature and identified 408 individuals with confirmed *OPA1* mutations, 120 of whom reported extra-ocular (ADOA 'plus') manifestations through their descriptions of visual and multi-systemic symptoms. Our results show that there is a significant variation in frequency of the specific exons involved between the ADOA classic and ADOA 'plus' patients. Classic ADOA groups were more likely to have mutations in exon 8 and 9, while ADOA 'plus' groups were more likely to have mutations in exons 14, 15 and 17. Additional comparisons revealed significant differences between mutation types/domains and specific ADOA 'plus' manifestations. We also found that individuals with maternally inherited *OPA1* mutations were significantly more likely to develop 'plus' manifestations than those with paternally inherited mutations. Overall, this study provides novel information regarding genotype-phenotype correlations of ADOA which warrants additional recommendations added to the current clinical management of ADOA patients.

## 1. Introduction

Autosomal Dominant Optic Atrophy (ADOA) is one of the most common neuro-optic disorders, with an estimated prevalence of 1 in 50,000 in the general population and 1 in 10,000 in Denmark (Thiselton et al., 2002). Other common names of the disorder are Optic Atrophy Type I or Kjer's Optic Neuropathy (OMIM 165500). The main clinical anomalies associated with ADOA are early onset (between ages 4 and 6 years) progressive bilateral visual loss, temporal pallor of the optic disc, central vision loss, and impairment of color vision (Delettre et al., 2001; Lenaers et al., 2012). The latter feature is due to the loss of retinal ganglion axons in the optic nerve whose role is to receive visual information from the retinal photoreceptors (Amati-Bonneau et al., 2009). Approximately 10 to 20% of patients carrying *OPA1* mutations are reported to suffer from extra-ophthalmological (ADOA 'plus') manifestations, such as hearing loss and ataxia in small studies (Santarelli et al., 2015; Amati-Bonneau et al., 2008; Yu-Wai-Man et al., 2010a,b). Similar to the ophthalmological phenotypes, the hearing loss is caused by loss of nerve cells in the vestibule-cochlear nerve (Hayashi et al., 2017; Huang, Santarelli, & Starr, 2009) and begins in late childhood to early adulthood. Ataxia, myopathy, and neuropathy generally manifest in the third decade of life, due to the disruption of mitochondrial function.

The OPA1 gene is located on chromosome 3q28–29 (Davies & Votruba, 2006). The OPA1 gene is comprised of 31 exons and encodes a dynamin-related GTPase protein (Fig. 1). The OPA1 protein is most highly expressed in the retina but is also abundant in the brain and muscle (Alexander et al., 2000). The OPA1 protein serves a variety of roles, which includes fusion of mitochondria, oxidative phosphorylation, membrane potential maintenance, cristae organization, and control of apoptosis (Patten et al., 2014; Amati-Bonneau et al., 2009). Recent studies indicate that OPA1 proteins accumulate in the

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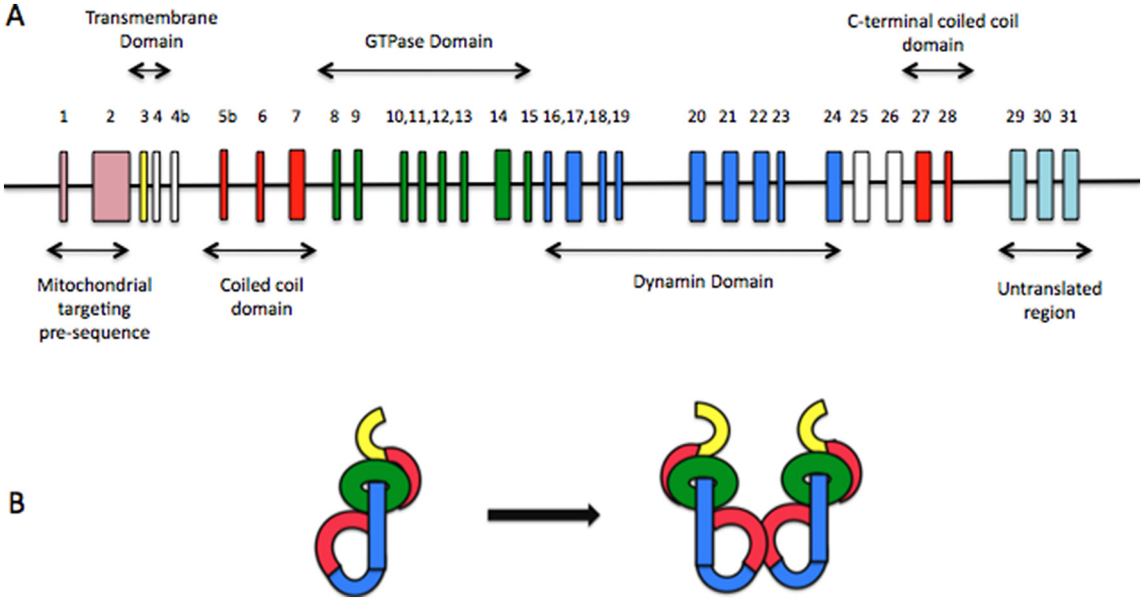


**Fig. 1.** Structure of *OPA1* (color).

mitochondrial inner membrane and serve as anchors for mitochondrial DNA (mtDNA), allowing for mtDNA replication and distribution (Del Dotto et al., 2017; Elachouri et al., 2011). The loss of OPA1 expression prevents normal mitochondrial function due to disruption of oxidative phosphorylation and mtDNA maintenance and replication (Elachouri et al., 2011). Changes in mitochondrial genome stability result in decreased production of ATP, which leads to improper cell function, cell damage, and apoptosis, thus resulting in ADOA. Most of the OPA1 mutations (50%) are nonsense mutations, and are dispersed throughout the GTPase domain (exons 8 through 15), dynamin central domain (exons 16 through 24), and in the 3′ end of the coding region that contains exons 27 and 28 (Baqli et al., 2017; Ahmad, Davis & Sue, 2015; Amati-Bonneau et al., 2008).

Linear structure of *OPA1,* with the mitochondrial targeting sequence in pink, transmembrane domain in yellow, coiled coil domains in red, GTPase domain in green, and dynamin domain in blue.

Genetic counseling is challenging due to the variability in not only with visual prognosis, but also the manifestations of 'plus' phenotypes. The primary goal of this study is to obtain a clearer understanding of the variable expressivity of the mutations in the *OPA1* gene by collecting and analyzing clinical information from published reports. We assessed the severity of manifestations based on the location of the mutation (exon/intron, domain), the type of mutations (missense, nonsense), as well as other factors that may affect severity, such as parent of origin, gender, and familial vs. de novo cases. This study has the potential to improve the health management of ADOA patients by increasing surveillance of other systems that are at risk and may potentially aid in preconception, prenatal, and postnatal genetic counseling sessions.

## 2. Methods

This review was performed according to PRISMA guidelines for conducting systematic reviews. An electronic literature search was conducted in PubMed from data base inception until September 2012. The following search terms were used: OPA1, ADOA, autosomal dominant optic atrophy, optic atrophy plus, extra ophthalmic, or multi systemic. Another database utilized in this study was the eOPA1 database of sequence variations in the gene (http://lbbma.univ-angers.fr/eOPA1/), established by Patrizia Bonneau among other contributors at the Laboratory of Biochemistry and Molecular Biology of Angers in France. The reference lists of articles were also searched to identify additional potentially relevant articles. Only articles in English that were able to be accessed were reviewed. Original authors were not contacted for this study.

A systematic review of literature was conducted, and studies were selected if individuals and families had confirmed *OPA1* mutations. Cases of individuals with compound heterozygous or double heterozygous mutations were excluded. Extracted data such as mutations, age, gender, and visual or multi-systemic phenotypes from selected studies were collected. Statistical analysis was performed using IBM SPSS Statistics v.20 (SPSS Inc., Chicago, IL). Statistical significance was defined as a $p$-value $< 0.05$, or with 95% confidence intervals. Comparisons between subgroups were made using chi-square tests and Fisher's exact tests for categorical variables, and One-way ANOVA for continuous variables. Fisher's exact tests were performed using the College of Saint Benedict & Saint John's University's contingency table found at: http://www.physics.csbsju.edu/stats/exact.html. All comparisons were tested at the 0.05 significance level. The null hypothesis was that there was no difference in ADOA or ADOA plus symptom frequency across mutation types, domain affected, or specific exons. P-values $< 0.05$ indicate statistically significant difference in ADOA or ADOA plus symptom frequency across mutation or exon types and the number of affected systems.

A total of 408 individuals with ADOA were identified in the published reports. Patient information was obtained from the following sources: 47 were obtained from Yu-Wai-Man et al. (2010a,b), 45 from Yu-Wai-Man et al. (2010a,b), 38 from Cécile Delettre et al. (2000), 27 from Fuhrmann et al. (2009), 25 from Pesch et al. (2001), 22 from Nakamura et al. (2006); Puomila et al. (2005) respectively, 21 from Baris et al. (2003), 15 from Delettre et al. (2001), 14 from Payne et al. (2004), 10 from Almind et al. (2011), 9 each from Chen et al. (2000); Yen et al. (2010), 8 from Amati-Bonneau et al. (2008), 7 each from Alexander et al. (2000); Hudson et al. (2008); Schimpf et al. (2006); Stewart et al. (2008), 6 each from Cardaioli et al. (2006); Han et al. (2006), 5 each from Hamahata et al. (2012); Li et al. (2005); Shimizu et al. (2003); Spinazzi et al. (2008), 4 each from Amati-Bonneau et al. (2005); Puomila et al. (2005); Yamada (2003), 3 each from Pretegiani et al. (2011); Shimizu et al. (2002); Yu-Wai-Man et al., 2016a,b), 2 each from Hayashi, Gekka, Omoto, Takeuchi, & Kitahara (2005); Huang, Santarelli, & Starr (2009); Liguori et al. (2008), and one each from Amati-Bonneau & Pasquier (2003); Ban, Yoshida, Kawasaki, & Mochida

**Table 1**
Demographic information of ADOA patients by ADOA classic and 'plus' category.

| | All Patients | ADOA classic | ADOA 'plus' |
|---|---|---|---|
| | N | N | N |
| | 408 | 288 | 120 |
| **Gender** | | | |
| Total | 273 | 157 | 119 |
| Male | 137 | 83 | 55 |
| Female | 136 | 74 | 64 |
| Male: Female | 1:01 | 1.1: 1 | 0.86: 1 |
| **Age of onset** | | | |
| Total | 121 | 92 | 29 |
| 0 to 9 | 76 | 58 | 18 |
| 10 to 19 | 28 | 21 | 7 |
| 20 to 29 | 7 | 4 | 3 |
| 30 to 39 | 10 | 9 | 1 |
| **Visual defects*** | | | |
| Total | 380 | 280 | 100 |
| Optic nerve atrophy | 219 | 137 | 82 |
| Atrophy of optic discs | 17 | 15 | 2 |
| Pallor of optic discs | 83 | 77 | 6 |
| Central scotoma | 56 | 50 | 6 |
| Dyschromatopia | 33 | 29 | 4 |
| Tritanopia | 24 | 24 | – |
| Deuteranopia | 1 | 1 | – |
| Cataracts | 2 | 1 | 1 |
| Glaucoma | 1 | 1 | – |
| Peripheral concentric narrowing | 2 | 1 | 1 |
| Duane retraction syndrome | 1 | – | 1 |

* Specific visual defects were documented in 380 of the 408 patients.

(2007); Magnin, Allibert, Berger, Dollfus, & Rumbach (2012); Mizutari et al. (2010); Ranieri et al. (2012); Yu-Wai-Man et al. (2011).

## 3. Results

Patients were grouped into two categories: classic ADOA (with symptoms relating only to vision) and ADOA 'plus' (presence of extra-ocular manifestations); 71% of patients had classic ADOA ($n$ = 288), and 29% had ADOA 'plus' ($n$ = 120) (Table 1).

The mean age of our population was 38 years (SD = 18.7 years) with the mean age being 34 years (SD = 19.0 years) in the classic ADOA cohort and 42 years (SD = 17.8 years) in the ADOA 'plus' cohort. Age ranges were between 3 and 77 years of age. The age of onset in 63% of cases of ADOA classic and 62% of cases of ADOA plus cohort occurred between 0 and 9 years of age. The mean age of onset however was 13 years (n = 67) in the ADOA classic cohort and 10 years (n = 32) in the ADOA plus because of the wide spectrum ranging from congenital to 54 years of age.

Across all individuals with an *OPA1* mutation, 93.8% experienced phenotypes affecting vision (n = 219), such as optic nerve atrophy, atrophy of optic discs, pallor of optic discs, central scotoma (diminished central vision), dyschromatopia (color vision defect), tritanopia (blue/yellow colorblindness), deuteranoia (inability to detect green color), cataracts, and glaucoma.

**Table 2**
Frequencies of mutation types and domains affected in different ADOA types.

| | All patients | ADOA classic | ADOA 'plus' | p-value* |
|---|---|---|---|---|
| | N % | N % | N % | |
| | 408 | 288 | 120 | |
| **Mutation type** | | | | < 0.001 |
| Missense | 137 (31) | 55 (19) | 82 (68) | |
| Nonsense | 64 (16) | 50 (17) | 14 (12) | |
| Splicing defect | 72 (18) | 58 (20) | 17 (14) | |
| Deletion | 122 (30) | 115 (40) | 7 (6) | |
| Insertion | 6 (1) | 6 (2) | – | |
| Duplication | 4 (1) | 4 (1) | – | |
| **Domain affected** | | | | < 0.001 |
| Total | 401 | 285 | 117 | |
| GTPase | 213 (53) | 132 (46) | 81 (70) | |
| C-terminal coiled coil | 78 (19) | 65 (23) | 13 (11) | |
| Dynamin | 65 (16) | 51 (18) | 14 (12) | |
| Mitochondrial | 23 (6) | 15 (5) | 8 (7) | |
| Exons 25 to 26 | 22 (5) | 22 (8) | 1 (1) | |

* Fisher's exact test with null hypothesis (no difference in ADOA or ADOA plus symptom frequency across mutation types or domains affected) and alternative hypothesis (statistically significant difference in ADOA or ADOA plus symptom frequency across mutation types or domains affected). $p < 0.001$ led to rejection of null hypothesis.

### 3.1. Description of mutations (Table 2, Fig. 2)

There was a statistically significant difference in frequency of mutation types between the ADOA classic and ADOA plus groups

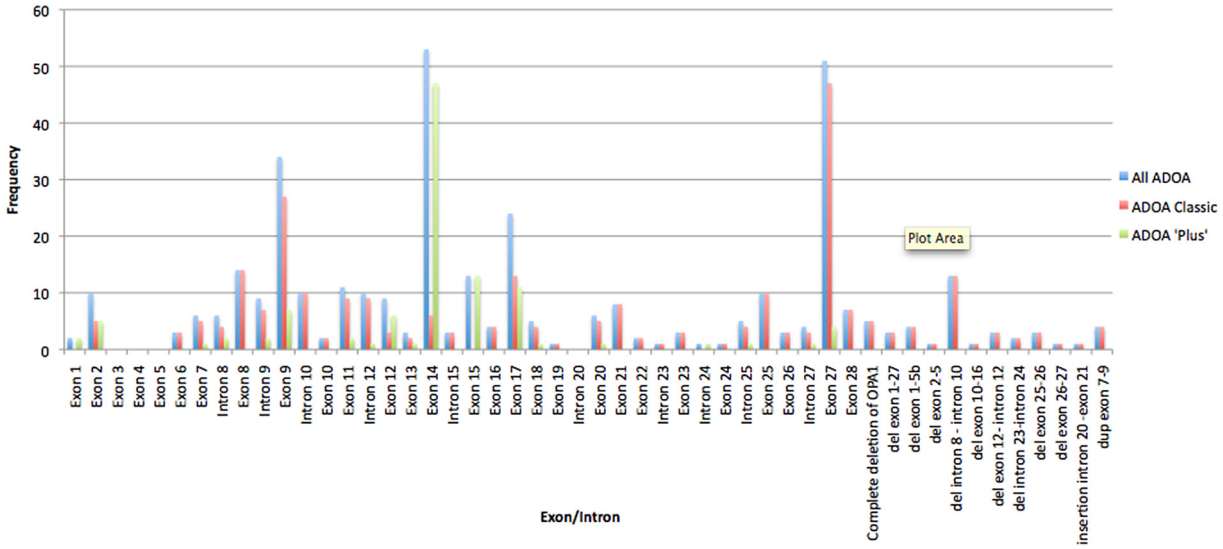


**Fig. 2.** Exon/intron mutation frequencies in all ADOA patients (blue), ADOA classic (red), and ADOA 'plus' (green) patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 3**
Frequency of associated ADOA 'plus' phenotypes within musculoskeletal, neurological, audiological, brain imaging, and other systems.*

| | N (%) |
|---|---|
| **Musculoskeletal** | |
| Total | 65 |
| Ophthalmoplegia | 36 (30) |
| Myopathy | 28 (23) |
| Ptosis | 23 (19) |
| Gait difficulties | 17 (14) |
| Fatigue | 4 (3) |
| Diffuse Myalgia | 3 (3) |
| Muscle wasting | 3 (3) |
| Winging Scapulae | 2 (2) |
| Developmental delays/hypotonia | 1 (1) |
| Feeding difficulties | 1 (1) |
| Dysphagia | 1 (1) |
| Facial Weakness | 1 (1) |
| **Neurological** | |
| Total | 60 |
| Axonal sensory motor/peripheral neuropathy | 46 (38) |
| Ataxia | 30 (25) |
| Migraine | 6 (5) |
| Multiple Sclerosis like | 5 (4) |
| Nystagmus | 5 (4) |
| Hereditary Spastic Paraplegia | 4 (3) |
| Arreflexia | 3 (3) |
| Positive Romberg-sensory ataxia | 3 (3) |
| Epilepsy | 2 (2) |
| Spasticity | 2 (2) |
| Cognitive impairment | 1 (1) |
| Dementia | 1 (1) |
| Hemiparesis | 1 (1) |
| **Audiological** | |
| Total | 74 |
| Sensorineural hearing loss | 74 (62) |
| **Brain Imaging** | |
| Total | 5 |
| Cerebellar atrophy | 3 (3) |
| brainstem atrophy | 2 (2) |
| Frontal and temporal white matter lesions/ focal ischemic lesions | 2 (2) |
| Calcification of basal ganglia | 1 (1) |
| atrophy of corpus callosum | 1 (1) |
| Atrophy of optic chiasm | 1 (1) |
| Unspecific white matter FLAIR hypersignal | 1 (1) |
| Periventricular white matter lesions | 1 (1) |
| **Other** | |
| Total | 9 |
| **Endocrine** | |
| Diabetes | 3 (3) |
| Hypothyroidism | 1 (1) |
| Hypogonadism | 1 (1) |
| **Skeletal** | |
| Pes cavus | 2 (2) |
| **Cancer** | 1 (1) |
| **Gastrointestinal** | |
| Colic Occlusion | 1 (1) |
| Irritable Bowel Syndrome | 1 (1) |
| **Psychiatric** | |
| Acute paranoid delusions and hallucinations | 1 (1) |
| **Hematologic** | |
| Macrocytic anemia | 1 (1) |

* Percentages in this table will total > 100%, due to individuals with multiple symptoms.

($p < 0.001$). In the ADOA classic group, deletions were the most common mutation seen in 40% of cases, while in the ADOA plus group the most common mutations seen in 70% of the individuals were missense mutations. In both groups mutations were most frequently in the GTPase domain of the *OPA1* gene. The common exons involved in the classic ADOA group were exon 27 (n = 49 of 288, 17%), exon 9 (n = 28, 10%), exon 8 (n = 16, 6%), and exon 17 (n = 14, 5%). In contrast, the common exons mutated in the ADOA 'plus' group were exons 14 (n = 47 of 120, 40%), exon 15 (n = 13, 11%), and exon 17 (n = 11, 9%) (Fig. 2).

### 3.2. ADOA 'plus' phenotypes

Of the 408 patients, 120 had the ADOA 'plus' phenotype. The most reported affected systems were musculoskeletal such as ophthalmoplegia, ptosis, myopathy, and gait difficulties (n = 65, 54%), neurological such as ataxia as well as motor and sensory neuropathies (n = 60, 50%), and auditory (n = 74, 64%) (Table 3).

### 3.3. Genotype-phenotype analysis of ADOA 'plus' (Table 4)

We observed the frequency of ADOA 'plus' manifestations across various mutation types, domain, and exons. ADOA 'plus' patients with missense mutations experienced a higher incidence of neurological (n = 41 of 82, 50%), musculoskeletal (n = 51 of 82, 62%), and hearing loss manifestations (n = 60 of 82, 73%) versus nonsense mutations associated with neurological manifestations (n = 5 of 14, 36%) and hearing loss (n = 6 of 14, 43%) ($p < 0.001$). Of those with splicing defects, 35% had musculoskeletal (n = 6 of 17) and 71% neurological manifestations (n = 12 of 17) ($p < 0.007$). Interestingly all seven ADOA 'plus' individuals with deletions exhibited hearing loss while fewer had neurological or neuromuscular symptoms, although the group was too small to draw any conclusions.

We also observed differences in the frequency of musculoskeletal, neurological, and hearing loss manifestations for each domain affected. A greater proportion of individuals with a mutation in the GTPase domain demonstrated musculoskeletal manifestations (63%), neurological manifestations (53%), and hearing loss (68%) ($p < 0.001$). Interestingly, 63% of patients exhibiting ataxia symptoms (n = 19 of 30) had mutations in the GTPase domain of their *OPA1* gene. Of those with mutations in the dynamin domain, 43% exhibited musculoskeletal and neurological manifestations (n = 6 of 14). 31% of patients with an affected C-terminal coiled coil domain experienced an onset of musculoskeletal manifestations (n = 4 of 13), and 69% exhibited hearing loss (n = 9) ($p < 0.001$).

We observed the frequency of manifestations across exons 14, 15, and 17 in individuals with ADOA 'plus', and found that higher incidence of hearing loss (81%, n = 38) was associated with exon 14 ($p < 0.001$), higher incidence of musculoskeletal (83%) and neurological manifestations (92%) ($p < 0.001$) was associated with exon 17, and higher incidence of musculoskeletal manifestations (92%) was associated with exon 15.

### 3.4. Factors affecting severity of ADOA

Next we observed the severity of ADOA patients by comparing the number of affected bodily systems. Details of frequencies including p-values are provided in Table 5. There were manifestations within the systems, which included vision, musculoskeletal, neurological, hearing, gastrointestinal, psychiatric, endocrine, hematologic, and cancer. Missense mutations affected the GTPase domain of the OPA1 gene, in particular involving exon 14 and 15, and led to highest frequencies of 3+ affected systems (81% missense, 69% GTPase domain, 55% exon 14 and 15).

### 3.5. Influence of maternal versus paternal inheritance

When comparing the frequency of maternally and paternally inherited cases across classic ADOA and ADOA 'plus' groups, 61% of ADOA 'plus' individuals had maternally inherited mutations (n = 31 of 51) versus 40% of the ADOA classic group (n = 36 of 92) who inherited their mutations maternally ($p = 0.015$).

**Table 4**
Frequency of symptoms across various mutation types, domains, and common exons.

| | ADOA 'plus'** | Musculoskeletal | Neurological | Hearing loss | p-value* |
|---|---|---|---|---|---|
| | N | N % | N % | N % | |
| | 120 | 65 (54) | 60 (50) | 74 (62) | |
| **Mutation type*** ** | | | | | |
| Missense | 82 | 51 (62) | 41 (50) | 60 (73) | < 0.001 |
| Nonsense | 14 | 3 (21) | 5 (36) | 6 (43) | < 0.001 |
| Splicing defect | 17 | 6 (35) | 12 (70) | 1 (6) | 0.007 |
| Deletion | 7 | 4 (57) | 2 (29) | 7 (100) | < 0.001 |
| **Domain affected** | | | | | |
| GTPase | 81 | 51 (63) | 43 (53) | 55 (68) | < 0.001 |
| Dynamin | 14 | 6 (43) | 6 (43) | 7 (50) | < 0.001 |
| C-terminal coiled coil | 13 | 4 (31) | 2 (15) | 9 (69) | < 0.001 |
| Mitochondrial | 8 | 2 (25) | 4 (50) | 4 (50) | 0.071 |
| Exons 25 to 26 | 1 | 1 (100) | 1 (100) | 0 (0) | – |
| **Common exons** | | | | | |
| Exon 14 | 47 | 26 (55) | 17 (36) | 38 (81) | < 0.001 |
| Exon 15 | 13 | 12 (92) | 9 (69) | 6 (46) | < 0.001 |
| Exon 17 | 12 | 10 (83) | 11 (92) | 6 (55) | < 0.001 |

* Fisher's exact test with null hypothesis (no difference in extra-ocular symptom frequency across mutation types, domains affected, or exon types) and alternative hypothesis (statistically significant difference in extra-ocular symptom frequency across mutation types, domains affected, or exon types) p-value < 0.001 led to rejection of null hypothesis.

** Rows and columns will not add up to 100% due to the presence of individuals with multiple symptoms.

*** Insertions, duplications were not included due to sample size 0.

**Table 5**
Number of affected bodily systems across mutation types, affected domains, and exons.

| | Total | Number of affected systems | | | p-value* |
|---|---|---|---|---|---|
| | | 0 or 1 | 2 | 3 or more | |
| | N % | N % | N % | N % | |
| **Mutation type** | 405 | 288 | 62 | 55 | < 0.001 |
| Missense | 137 (33) | 55 (19) | 37 (60) | 45 (81) | |
| Nonsense | 64 (16) | 50 (17) | 12 (19) | 2 (4) | |
| Splicing defect | 72 (18) | 58 (20) | 7 (11) | 7 (13) | |
| Deletion | 122 (30) | 115 (40) | 6 (10) | 1 (2) | |
| Insertion | 6 (2) | 6 (2) | – | – | |
| Duplication | 4 (1) | 4 (1) | – | – | |
| **Domain affected** | 401 | 285 | 62 | 54 | < 0.001 |
| GTPase | 213 (53) | 132 (46) | 44 (71) | 37 (69) | |
| Dynamin | 65 (16) | 51 (18) | 3 (5) | 11 (20) | |
| C-terminal coiled coil | 78 (19) | 65 (23) | 12 (19) | 1 (2) | |
| Others | 45 (11) | 37 (13) | 3 (5) | 5 (9) | |
| **Common exons** | 401 | 285 | 62 | 54 | < 0.001 |
| Exon 8 and 9 | 54 (9) | 47 (16) | 3 (5) | 1 (2) | |
| Exon 14, Exon 15 | 73 (18) | 13 (5) | 30 (51) | 30 (55) | |
| Exon 17 | 25 (6) | 14 (5) | 1 (2) | 11 (20) | |
| Exon 27 and Exon 28 | 73 (18) | 61 (22) | 7 (12) | 1 (2) | |

* Fisher's exact test with null hypothesis (no difference in number of affected systems across mutation types, domains affected, or exon types) and alternative hypothesis (statistically significant difference in number of affected systems across mutation types, domains affected, or exon types). p-value < 0.001 led to rejection of null hypothesis. The other group includes exons 4,4b,5b, coiled-coil domain, exon 25 and 26, and exons 29–31.

### 3.6. Differences in gender

No statistically significant differences were noted for age of onset, presence of 'plus' manifestations, or number of affected systems between male and female patients (p = 0.067, p = 0.385, p = 0.678 respectively).

### 3.7. Affected individuals within familial ADOA

During our literature search of all ADOA patients, 93 individuals in twenty-one families were reported to have at least one individual with ADOA 'plus' manifestations. 88% of these family members (n = 82) experienced classic vision loss symptom. The most common ADOA 'plus' manifestations experienced were auditory (n = 49, 53%), neurological (n = 42, 45%), and muscular (n = 33, 35%) manifestations.

## 4. Discussion

In our analysis, 63% of cases of ADOA classic and 62% of cases of ADOA plus were younger than 9 years of age; 85% of cases of ADOA classic were younger than 20 years of age and 86% of cases of ADOA plus were younger than 20 years of age.

In previous reports, the average age of onset was early childhood between the ages of 4 and 8 years (Kjer et al., 1996; Yu-Wai-Man et al., 2010a,b). In our study, the average age of onset was 13 years (n = 67) in the ADOA classic cohort and 10 years (n = 32) in the ADOA plus due to the wide spectrum of age ranging from congenital to 54 years. It is important to note that the precise age of onset was only available in a few individuals. For some, age of onset was described generally, for example, as "infantile," "childhood," etc. There was no significant difference by gender across all ADOA patients.

Previous studies have suggested a possible sex-influenced phenotype in which males present a more severely affected vision (Chen et al., 2000; Huang et al., 2006). Our study did not find a difference in frequency of affected individuals between genders, with a male to female ratio of 1:1. Moreover, we found no difference in the mean number of affected systems (1.7) between males and females.

### 4.1. ADOA plus manifestations

The systems that were affected in the ADOA 'plus' population were primarily musculoskeletal, neurological, and auditory.

Of the musculoskeletal manifestations, ophthalmoplegia, ptosis, myopathy, and gait difficulties were significant. Of the neurological manifestations, ataxia and neuropathy were most common. Sensorineural hearing loss was the only symptom in the auditory system.

### 4.2. Genotype/phenotype correlations

One of the aims in our analysis was to look for genotype-phenotype correlations within the ADOA population. Of classic ADOA patients, mutations were most commonly located in exon 8 and 9 of the GTPase domain, exon 17 of the dynamin domain, and exon 28 of the C-terminal coiled coil domain. In the ADOA 'plus' group, mutations were commonly located in exon 14 and 15 of the GTPase domain and exon 17 of the dynamin domain (Fig. 2).

Missense mutations made up 33% of all cases in this analysis, and were predominantly located in the GTPase domain as noted in previous studies (Kushnareva et al., 2016; Delettre et al., 2001; Yu-Wai-Man et al., 2010a,b). The GTPase and dynamin domains play an important role in interacting with other mitochondrial membrane proteins and aiding mitochondrial fusion. These areas are also highly conserved regions, where impairment of GTPase activity has been shown to cause instability of the inner mitochondrial membrane structure and decrease in membrane potential due to uncontrolled proton leakage (Olichon, 2002, 2007b). Previous studies have also hypothesized that missense mutations cause a dominant negative affect, and are more likely to develop ADOA 'plus' phenotypes (Amati-Bonneau et al., 2008). However, missense mutations can be observed in a great proportion of classic ADOA patients as well.

We observed that many individuals with three or more affected systems had mutations in exon 17 of the dynamin domain, However, mutations in exon 17 were also prevalent in the classic ADOA population.

Mutations in the C-terminal domain were most predominantly seen in the ADOA classic group. The C-terminal coiled coil domain is not well conserved (Thiselton et al., 2002). The C-terminal domain's main role is to assist with the homopolymerization of the OPA1 proteins, but the C-terminal domain is not the only domain that plays a role in homopolymerization. Exons 5b, 6, and 7 make up another coiled coil domain. Therefore, these insertion mutations may only slightly decrease the production of polymers, since it does not participate in a more critical role like the GTPase and dynamin domain.

In summary, our analysis suggests that although the GTPase domain may be affected in both classic and 'plus' groups, individuals with mutations in exon 9 are more likely to manifest as classic vision loss, whereas individuals with mutations in exons 14 and 15 are more likely to show extra-ocular manifestations. Mutations in the dynamin domain result in a wide spectrum of phenotypes, from having only visual symptoms to having > 3 affected systems. Mutations in the C-terminal coiled coil domain are more likely to remain classic ADOA.

### 4.3. Genotype/phenotype correlations by specific ADOA plus manifestations

Additional genotype/phenotype correlations were found by observing the frequency of specific ADOA 'plus' manifestations among various mutation types, domains, and exons. Overall, audiological manifestations (sensorineural hearing loss) were the most common ADOA plus symptom across all variations, followed by musculoskeletal manifestations and neurological manifestations.

Due to the variability of phenotype in ADOA patients, our study examined parental inheritance as a possible factor that may influence disease manifestation in these individuals. This was based on the idea that if *OPA1* plays an important role in mitochondrial function and fusion, a defect in the gene may increase the frequency of mitochondrial DNA mutations. Since mitochondrial DNA is maternally inherited, an individual who inherits both an *OPA1* mutation along with any coexisting mitochondrial DNA mutations may experience a more severe phenotype. Overall, we observed that individuals with maternally inherited *OPA1* mutations (61%) were more likely to develop 'plus' phenotypes whereas those who paternally inherited *OPA1* mutations were more likely to develop ADOA classic type (61%).

Variable expressivity and reduced penetrance were observed within families. Only 88% of 93 ADOA family members (n = 82) had vision defects, indicating that additional factors, such as genetic heterogeneity, environmental, or epigenetic factors may also play a role in phenotype. Most did not develop additional 'plus' features that a family member was reported to exhibit. However, it is important to note that younger individuals in this cohort may have not been given sufficient time to develop visual or 'plus' phenotypes and may develop them in the future.

In addition, while 30% (n = 36 of 120) of the ADOA 'plus' cohort in our analysis had a c.1334G < A mutation located in exon 14 of the GTPase domain, 2% (n = 6 of 288) of classic ADOA patients also had this same mutation. This suggests that extra-ocular manifestations of ADOA may be valuable in the early diagnosis and treatment of ADOA in affected individuals, as ADOA 'plus' manifestations may stem from same mutations as ADOA classic manifestations.

We also observed a high incidence of neurological symptoms (71%) in ADOA 'plus' patients with splicing defects. Interestingly, 4% of ADOA 'plus' patients with neurological symptoms exhibited multiple sclerosis-like phenotypes. Yu-Wai-Man et al. (2016a,b) described three patients who harbored OPA1 mutations and who were found to have neuroimaging findings that were consistent with multiple sclerosis. These three patients had splice site mutations. One patient harbored a c.2356-1G > T mutation and the two other patients had c.870 + 5G > A mutations. In the series of patients described in our manuscript, however, neuroimaging studies were not carried out. Oligoclonal bands were detected in three patients whose cerebrospinal fluid was examined supportive of an underlying demyelinating process clinically indistinguishable from multiple sclerosis.

The above information is valuable in future genetic counseling sessions with ADOA patients (Han et al., 2006; Yu-Wai-Man et al., 2010a,b). Knowing and associating ADOA 'plus' manifestations with ADOA 'plus' phenotypes may be helpful in proactively diagnosing and treating ADOA patients for these complications, along with the prediction, early diagnosis, and treatment of ADOA in the future. A targeted and individualized treatment method based on mutation analysis and clinical diagnosis would be available for patients. The variable penetrance of OPA1 mutations, however, makes accurate genetic counseling difficult.

Once the diagnosis of ADOA has been established, an annual assessment of visual acuity, color vision, visual fields, extra-ocular muscles, and hearing evaluation is recommended (Baris et al., 2003). However, there are no recommendations regarding the monitoring of musculoskeletal and neurological manifestations. From our meta-analysis, 16% of the total number of ADOA patients demonstrated musculoskeletal manifestations, 15% demonstrated neurological manifestations and 18% had hearing loss. Therefore, a baseline and routine clinical and neurologic evaluation for these manifestations is recommended. It may also be valuable for patients to be evaluated by a metabolic specialist familiar with mitochondrial disorders. In 2011, the FDA approved an emergency protocol for EPI-743, a therapeutic agent designed to treat mitochondrial disorders, such as Leber's Hereditary Optic Neuropathy (LHON) a mitochondrial optic neuropathic disorder that disrupts the function of complex-1 in the respiratory chain. After a one-year treatment trial, four of the five patients with LHON exhibited improvement and halting of the progression of the disease (Sadun et al., 2012). Although the biochemical mechanism of EPI-743 is unknown, the use of this or other mitochondrial therapeutic agent may possibly be extended to ADOA patients in the future due to the similar involvement of the respiratory chain seen in both disorders (Yu-Wai-Man et al., 2016a,Yu-Wai-Man et al., 2016b).

Limitations in this study include the inconsistency of details provided in the various reports analyzed for this meta-analysis. This created a small sample size when examining factors such as familial vs. sporadic ADOA or parental inheritance, and thus may not accurately reflect the difference between the ADOA and ADOA 'plus' groups. Some studies examined all systems including cardiac, and the presence of

mitochondrial mutations in conjunction to the *OPA1* mutation, whereas other smaller case studies did not. Therefore, whether individuals truly did not demonstrate cardiac or other manifestations is unknown. There are limitations from phenotype categorization in data collection and analysis due to the nature of a meta-analysis, which may limit the generalizability of this study to other similar works in the field. Additionally reported individuals tend to be unique, possibly more severely affected, and not necessarily representative of the entire ADOA population. Identifying additional modifying factors, underlying molecular pathways, and their influence on the clinical manifestation of ADOA may lead to better prediction of phenotypic expression and individualized medical management. Future studies thus may uncover the variable expressivity among individuals with the same *OPA1* mutation. Additionally, specific extra-ocular symptoms, such as multiple sclerosis-like symptoms, in ADOA 'plus' patients warrant further investigation in their involvement in genotype-phenotype analyses.

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