Genetic results in a cohort of 633 patients with optic atrophy

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Purpose

- Variants in both nuclear and mitochondrial (mtDNA) genes cause optic atrophy (OA).
- We investigated the yield of panel testing including nuclear and mtDNA genes, covering disease-associated noncoding variants and copy-number variants (CNVs), in a cohort of patients with OA.
- Among patients with a clinical suspicion of OA, both nuclear and mtDNA genes have not been extensively studied.
- This study aimed to determine the clinical utility of this comprehensive testing approach.

Methods

- Clinical reports of consecutive patients who underwent Optic Atrophy Panel testing at Blueprint Genetics (a CLIA-certified laboratory) were examined.
- All patients were tested for the indication of OA.
- Testing included sequence and CNV analyses of NGS data from a validated whole- or clinical-exome assay performed on blood, saliva or extracted DNA samples.
- Target regions included coding exons (+/-20 bp from the intron/exon boundary) of up to 76 genes associated with OA and up to 6 noncoding variants in these genes, catalogued as disease-associated by HGMD and/or ClinVar.
- CNV analysis was performed bioinformatically from NGS data using two variant-calling algorithms including a proprietary method specific for exon-level deletions.
- Variant interpretation was performed using a framework based on ACMG/AMP guidelines (1).
- A positive result in a nuclear gene was defined as a pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the patient's reported phenotype and associated disease inheritance; a positive result in a mitochondrial gene was defined as a P/LP variant with >5% heteroplasmy consistent with the patient's reported phenotype.
- A variant of uncertain significance trending pathogenic was defined as a variant that could be classified as LP after family segregation studies.
- Chi-square ($\chi 2$) analysis was used to determine statistical significance ($P<0.05$).

Demographic	Total cohort, (%)	Cohort with positive results, (%)	Positive rate, (%)
Female	291/633 (46.0%)	93/170 (54.7%)	93/291 (32.0%)
Male	341/633 (53.9%)	77/170 (45.3%)	77/341 (22.6%)
Pediatric (0-18yrs)	234/633 (37.0%)	62/170 (36.5%)	62/234 (26.5%)
Adult (19-82yrs)	399/633 (63.0%)	108/170 (63.5%)	108/399 (27.1%)

Table 1. Patient demographics.

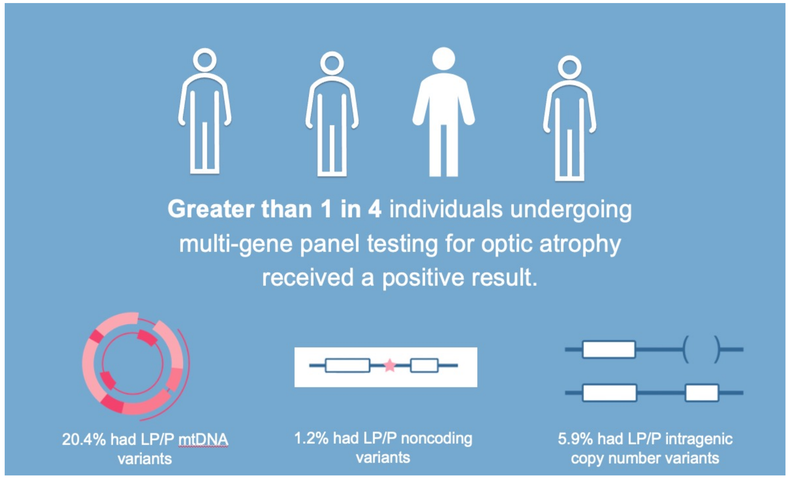
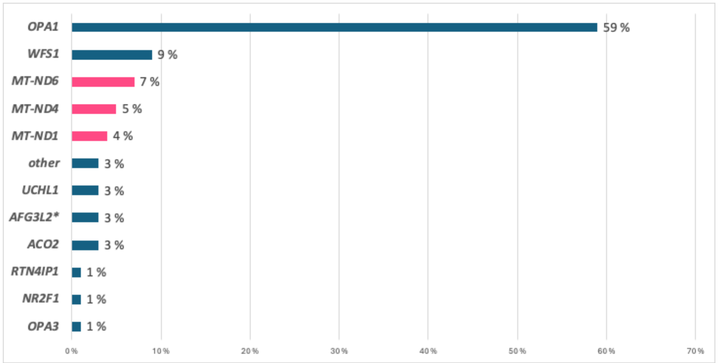


Figure 1. Positive results by gene. MtDNA genes are highlighted with pink. A gene with * is complicated by regions of >90% sequencing homology.



Results

- A total of 633 patient reports were reviewed. The median age at time of testing was 24 years (range: neonatal to 82 years). Children (0-18 years) made up 37.0% (234/633) of those tested. The cohort was 53.9% male (341/633). (Table 1)
- A positive result was reported for 26.9% (170/633) of patients.
- A variant of uncertain significance trending pathogenic was reported in 19 patients (3.0%).
- Those tested in childhood were not significantly more likely to receive a positive result (26.5%, 62/234) than those tested in adulthood (27.1%, 108/399) ($\chi 2=0.025$, $P=0.88$).
- Women (32.0%, 93/291) were significantly more likely to receive a positive result compared to men (22.6%, 77/341) ($\chi 2=7.02$, $P<.05$).
- LP/P variants in 4 genes were responsible for 80% of positive results (*OPA1*, 59%; *WFS1*, 9%; *MT-ND6*, 7%; *MT-ND4*, 5%). (Figure 1)
- LP/P CNVs were responsible for 10 of 170 positive results (5.9%), of which 7 (70.0%) were identified in *OPA1*.
- Two noncoding variants in *OPA1* were responsible for 1.2% (2/170) of the positive results.
- Variants in mtDNA genes accounted for 20.4% of the positive results in the cohort (29/142).

Conclusions

- This study demonstrates the clinical utility of multi-gene panel testing that includes both nuclear and mitochondrial genes, as greater than 25% of individuals with suspected OA in this cohort received a positive result.
- Inclusion of the mitochondrial genome when testing patients for OA is important as variants in mtDNA accounted for over 1 in 5 of the positive results.
- Inclusion of noncoding variants and CNVs should also be considered when testing of individuals with OA, as these variants were responsible for 1 in 14 positive results.

References:

1. Richards et al (2015): Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med.17(5):405-24.

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Conflict of interest statement: All authors are employed by Blueprint Genetics