Small CNVs, noncoding, and mitochondrial variants are molecularly diagnostic for ~5% of pediatric patients with inherited retinal disease

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Introduction and Study Aim

- Inherited retinal dystrophies (IRDs) can have extremely heterogeneous molecular and phenotypic presentations.
- Early diagnosis is important for visual rehabilitation, screening for co-morbidities, and identification of at-risk family members. There are now approved therapies and clinical trials for many IRDs, most often contingent on a molecular diagnosis.
- Comprehensive genetic testing is necessary to maximize diagnostic yield, and the impact of including copy number variant (CNV) analysis, mitochondrial genome coverage, and non-coding variation has not yet been characterized.
- Here, we assessed the diagnostic utility of multi-gene panel testing (MGPT) in a pediatric population with IRDs.

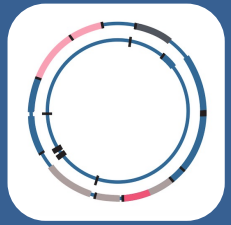
Methods

- We conducted a retrospective review of 1,612 de-identified pediatric patients (ages 0-12 years) tested consecutively at Blueprint Genetics using a MGPT of >300 genes.
- This test targeted all coding exons of nuclear panel genes +/-20 base pairs (bp) from exon-intron boundary, >130 disease-associated non-coding variants, and the mitochondrial genome. CNV analysis included a specific method for calling small, exon-level CNVs.
- Variant interpretation was performed in accordance with ACMG/AMP guidelines.
- A molecular diagnosis was defined as the identification of pathogenic or likely pathogenic variant(s) consistent with the patient's reported phenotype and associated disease inheritance.

Results

- Molecular diagnoses were identified in 56% (906/1612) of patients (Figure 1), involving 114 genes.
- Variants in ABCA4, RS1, CNGB3, RPGR, and CEP290 accounted for 37% of diagnoses (Figure 2).
- Mitochondrial variants were responsible for 3 diagnoses. CNVs contributed to the diagnosis in 4% (71) patients; 39% (28/71) of these patients had small CNVs that were 1 or 2 exons in size. Targeted non-coding variants were identified as the molecular diagnosis for 11% (171) of patients, 26% (45/171) of which were beyond 10 bp from the exon-intron boundary.
- A variant of unknown significance favouring pathogenic was identified in an additional 6% (96) of patients, where family member testing may result in a classification change (Figure 1).

Small CNVs, noncoding, and mitochondrial variants are molecularly diagnostic for ~5% (76/1612) of pediatric patients with inherited retinal disease

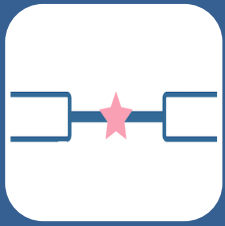


Mitochondrial variants

(n=3)

1-2 exon copy number variants

(n=28)



Disease-associated non-coding variants beyond 10 base pairs from the intron-exon boundary

(n=45)

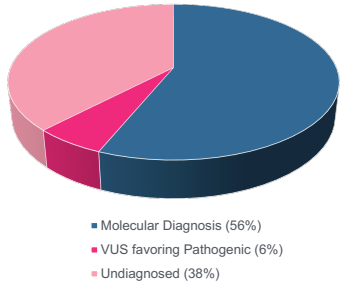


Figure 1: Diagnostic rate. A molecular diagnosis was made in 906 (56%) patients while a variant of unknown significance (VUS) favoring pathogenic was identified in an additional 96 (6.%). The remainder of patient (n= 610; 38%) have not received a molecular diagnosis using this multi-gene panel testing.

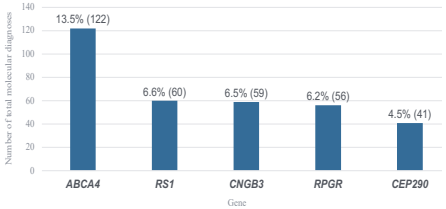


Figure 2: Five most common molecularly diagnostic genes in this cohort. Percentages above bars the frequency of molecular diagnosis due to this gene relative to the total molecular diagnoses. Variants in these five diagnostic genes (ABCA4, RS1, CNGB3, RPGR, and CEP290) accounted for 37.3% of total molecular diagnoses. Numbers in parentheses represent the exact count of molecular diagnoses in this gene.

Conclusion

This study demonstrates the diagnostic utility of multi-gene panel testing in pediatric patients with inherited retinal diseases. Small copy number variants, noncoding (beyond 10 bp from the exon-intron boundary), and mitochondrial variants were the molecular diagnoses for 4.7% of patients, highlighting the importance of a comprehensive testing approach with ability to detect these variant types.

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