# Genetic Findings in a Large Cohort of Retinal Dystrophy Patients: Implications for Treatments and Clinical Trials

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## Introduction

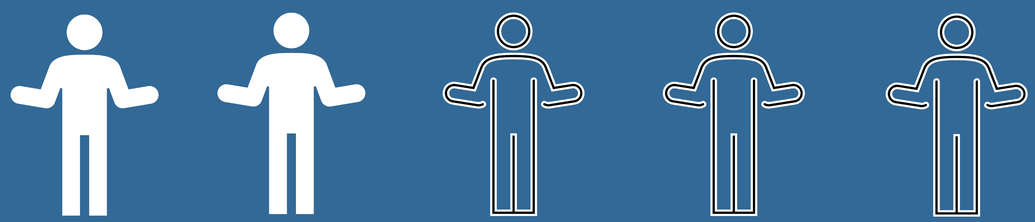
- Vision loss secondary to inherited retinal disease (IRD) was long considered 'incurable.' However, progress in both gene therapy and the molecular characterization of IRDs has led to a rapid increase in the number of gene-specific treatments as well as interventional clinical trials for ocular disease.
- In this study, we evaluate how often NGS-based panel testing in a large cohort of patients with IRD, identifies individuals who are potentially eligible for treatments and clinical trials specific to their molecular diagnosis.

## Methods

- This was a retrospective analysis of test results from 18,026 deidentified patients who were tested consecutively with an IRD-related panel at Blueprint Genetics (Table 1). All patients had a suspected or confirmed IRD diagnosis per the information provided on the test requisition.
- Testing included both sequencing and copy number variant (CNV) analysis.
- A diagnostic test result was defined by the identification of a pathogenic (P) or likely pathogenic (LP) variant(s) (classified using a modified ACMG/AMP variant classification scheme) that were consistent with the patient's reported phenotype and known disease inheritance.

| Panel Name | #of Patients Tested (% total cohort) | # of Genes Tested |
|---|---|---|
| Retinal Dystrophy | 16,768 (93.0%) | 181-325 |
| Retinitis Pigmentosa | 563 (3.1%) | 80-116 |
| Macular Dystrophy | 325 (1.8%) | 26-28 |
| Cone Rod Dystrophy | 109 (0.6%) | 42-44 |
| Usher Syndrome | 104 (0.6%) | 15-21 |
| Congenital Stationary Night Blindness | 53 (0.3%) | 18-20 |
| Leber Congenital Amaurosis | 40 (0.2%) | 26-28 |
| Achromatopsia | 34 (0.2%) | 8 |
| Flecked Retina Disorders | 30 (0.2%) | 12 |

**Table 1. IRD-related panels and number of patients tested.**



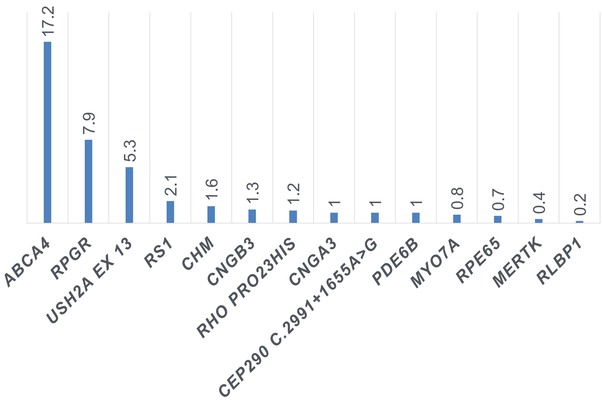
**2 in 5** patients with IRD with a molecular diagnosis identified through NGS panel testing were found to have a diagnostic finding that may allow them to **access a gene/specific variant treatment or clinical trial**

Variants in *ABCA4* (17.2%), *RPGR* (7.9%) and *USH2A* exon 13 (5.3%) were the most common of these diagnostic findings

## Results

- Males made up 48.4% (n=8,730) of the cohort while females made up 51.1% (n=9,203). Sex was not specified in 0.5% (n=93) patients. The median age at testing was 46 years.
- A diagnostic (sequence or copy number variant) was identified in 50.8% (n=9,156) patients in the cohort. In addition, 5.4% (n=973) patients had a variant of uncertain significance (VUS) favoring pathogenic.
- Molecular diagnoses were made in 214 genes; 14 of these are associated with a gene-specific therapy or clinical trial.
- A total of 41.7% molecular made in these 14 genes; the most common were in *ABCA4* (17.2%), *RPGR* (7.9%), and in exon 13 of *USH2A* (5.3%) (Figure 1.)

**Figure 1. Diagnostic Findings (%) by Gene/Targeted Region**




## Conclusions

- Approximately half of the patients In this large cohort received a molecular diagnosis for their IRD through NGS panel testing.
- For every 5 patients who received molecular findings that help diagnose for their IRD in this cohort, 2 have findings involving a gene/specific variant that may allow them to access treatment or a clinical trial.
- This work demonstrates that a significant number of patients with IRD who undergo genetic testing may be eligible for personalized treatment/trial options; these discussions can be an important component of both pre-and post-test genetic counselling

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

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