# Characterization of copy number variants (CNVs) identified by genetic testing of inherited retinal disorders

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## Introduction

Retinal dystrophies (RDs) are a heterogeneous group of syndromic and non-syndromic diseases that damage the photoreceptor (PR) of the retina. The prevalence of these disorders is ~1:3000 worldwide and the most common disorder is Retinitis pigmentosa (~25% of vision loss in adults). A comprehensive genetic testing for a prompt diagnosis of RD enables accurate estimation of genetic risk, management of symptoms and selection of the appropriate targeted treatment such as gene-replacement therapy. Studies of relatively small cohorts or RDs patients have shown a role of copy number variants in these diseases. We estimated the prevalence and characteristics of CNVs in a large cohort of patients referred for genetic testing of RDs.

## Methods

In collaboration with Foundation Fighting Blindness (FFB), a total of 128 patients from a large cohort of 2754 patients referred for testing using the RD panel between May 2017 and October 2018 were included in the study. The DNA was sequenced by targeted OS-Seq using the Illumina NextSeq500 sequencing platform or the IDT xGEN Exome Research Panel using the Illumina NovaSeq platform. The sensitivity for one-exon CNV is 92.3% and the sensitivity for two exons CNV is 100%, while specificity is >99.9% for both. The average coverage was 231.5 and >99.9% of the panel's regions were covered at least at 20X. Smaller CNV were confirmed using a quantitative-PCR assay.

## Results

One hundred and twenty-eight CNVs in a total of 47 genes were reported as a primary finding in 127 out of 2754 (4.6%) cases. Of the identified CNVs, 63 (49.2%) were partial gene deletions, 16 (12.5%) whole gene deletions, 32 (25%) one exon deletions, and 2 (1.6%) were a partial exon deletion. In addition, ten (7.8%) partial gene duplications, three (2.3%) whole gene duplications, one (0.8%) whole gene gain (CN>3), and one (0.8%) partial gene gain (CN>3) were identified (Figure 1).

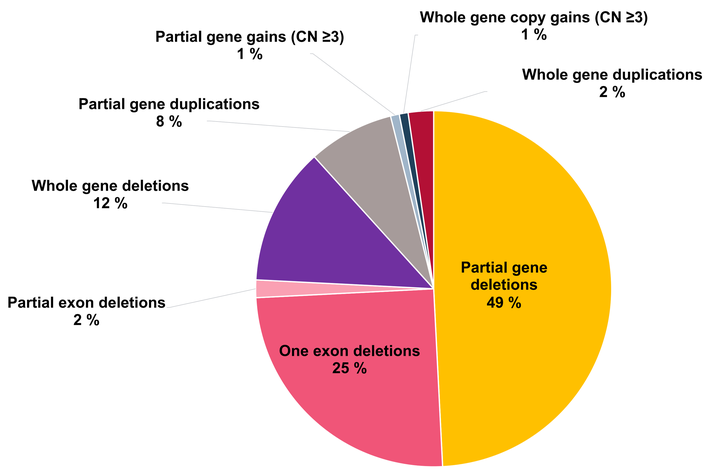


Figure 1. distribution of CNVs in the sample set.

## Conclusions

- **CNVs** were identified **in 4.6% of analyzed cases.**
- **Intragenic CNVs** were the **most common** type of CNVs.
- **25%** of CNVs were **one exon level** deletions.
- ***USH2A***, ***PRPF31*** and ***EYS*** genes were **enriched in CNVs.**
- **71.9%** of the identified CNVs were **diagnostic**.
- **High resolution del/dup analysis** is recommended in addition to sequencing analysis for the **diagnosis of RDs**.

## CNV findings

The genes most commonly bearing CNVs were *USH2A* (n=27), *EYS* and *PRPF31* (n=13). These were followed by *CHM* (n=6), *MERTK* and *CLN3* (n=5), RP2 (n=4), *KCNV2*, *ADGRV1*, *CRX* and *TRPM1* (n=3), *PDE6B*, *RHO*, *POC1B*, *BBS1*, *RPE65*, *ABCA4* and *CACNA2D4* (n=2). On the other hand, one distinct CNV was identified in 29 genes. Notably, CNVs were identified also in genes in which CNVs are not commonly reported, such as *ABCA4* and *RPE65* (Figure 2).

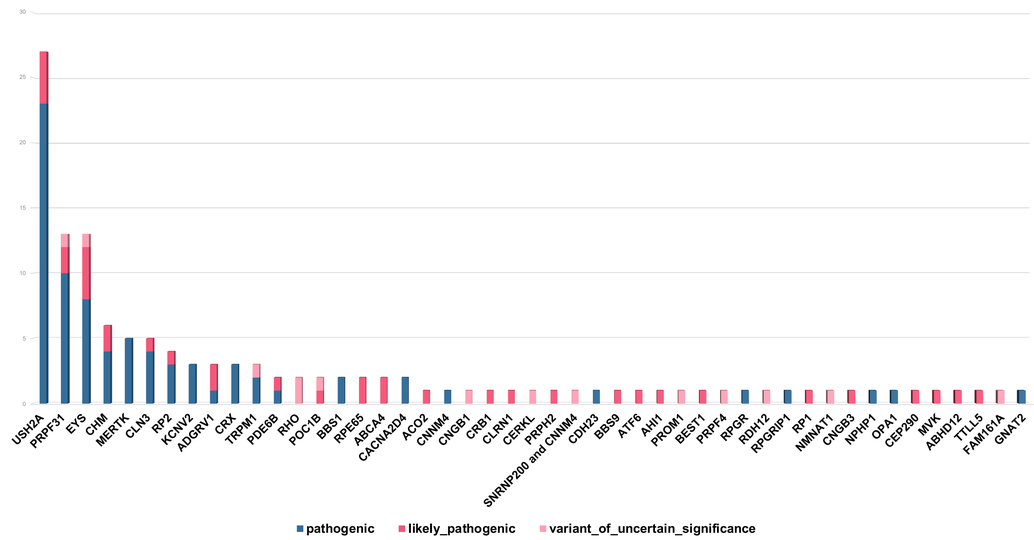


Figure 2. Distribution of CNVs by gene.

Recurrent CNVs were identified in *USH2A*, *PRPF31*, *MERTK*, *CLN3*, *EYS*, *CRX*, *CHM*, *TRPM1*, *RHO* and *KCNV2*, and the top three recurrent alterations were *USH2A* exon 27 deletion, *PRPF3* whole gene deletion and *CLN3* exon 8-9 deletion which is a known founder alteration (Figure 3).

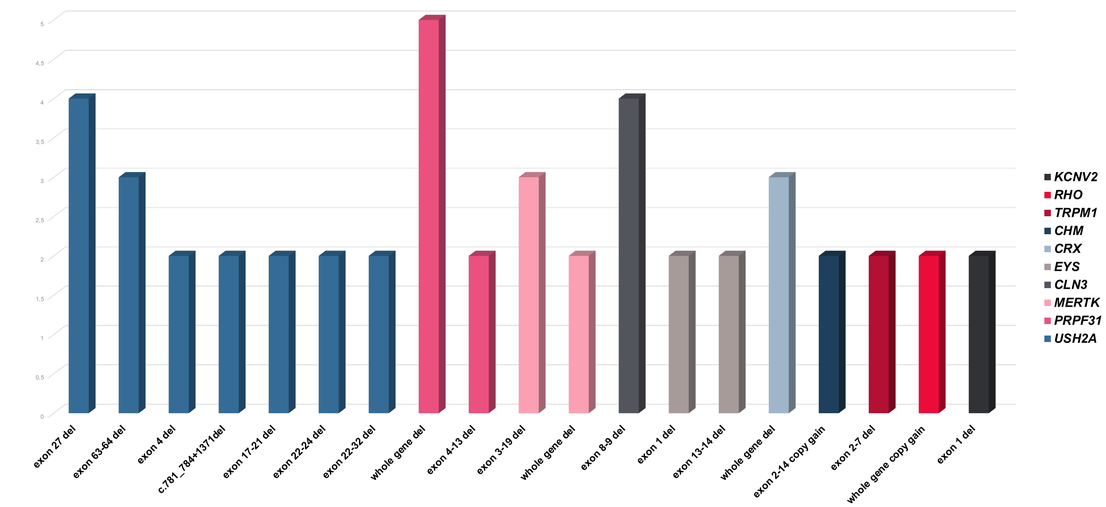


Figure 3. Recurrent CNVs by gene.

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