

Investigating Missing Heritability in Inherited Retinal Dystrophy

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Introduction: Inherited Retinal Dystrophy (IRD) is a heterogeneous group of degenerative disorders leading to vision loss. Around 300 genes have been associated with IRDs. Despite genetic testing, 15-50% of IRD cases remain undiagnosed and are classified as "gene-elusive."

Methods: Five pedigrees with presumed autosomal/X-linked recessive IRD and inconclusive/negative clinical panel tests underwent ocular examinations, and genome sequencing (GS) was performed on probands. Variants were annotated and validated using filtration pipelines developed at The Center for Applied Genomics, and in the lab. Phenotype driven panel filtering was performed to identify candidate variants, followed by segregation analysis and functional validation. GS analysis was performed as necessary.

Results: Case 1, a 59-year-old male diagnosed with fundus albipunctatus, had 7 variants identified on panel filtering. However, no variants of interest were identified.

Case 2, a 14-month-old male diagnosed with Leber's congenital amaurosis, had 24 variants identified in panel-based filtering, with RPGRIP1 being the only gene with multiple variants. Segregation analysis of RPGRIP1 verified that 3 were maternally inherited (c.3100-229_3238+234dup, c.1468-2A>G and c.491-112G>A), and variant c.906+26T>C

is paternal. Functional validation of the paternal variant is being conducted.

Case 3, an 11-year-old male diagnosed with early onset retinal dystrophy. Two heterozygous variants in the gene CRB1, one exonic (c.906+26T>C) and another intronic (c.849-26A>G) were prioritized. Segregation analysis confirmed them to have been inherited in trans. Minigene confirmed that the intronic variant would result in a splice acceptor loss leading to exon 4 skipping and a premature stop codon (p.[Arg284fs6*]).

Case 4, a 33-year-old male diagnosed with X-linked retinitis pigmentosa, was found to have a large deletion at the 3' untranslated region (UTR) for the gene RPGR. Functional validation is being conducted.

Case 5, a 22-year-old female diagnosed with multifocal vitelliform dystrophy, had 8 variants identified in panel-based filtering, with IMPG1 being the only gene with variants that were inherited in trans (c.563-174T>G, c.2045-7421C>T, c.1291+13335C>T). Functional validation of variants are being conducted.

Conclusions: The findings of the current study support the notion that gene-elusive cases may be partially explained by non-coding variants and highlight the importance of leveraging comprehensive genome analysis for accurate diagnosis. Studies are being conducted to understand the functional impact of these variants and develop therapeutic strategies.