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Whole genome sequencing delineates novel non-coding variants and candidate genes in inherited retinal diseases

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Footnotes

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Abstract

Purpose : Whole genome sequencing (WGS) has mainly uncovered deep-intronic splicing variants and structural variants (SVs) in unsolved exome-tested cases with inherited retinal diseases (IRD). The contribution of non-coding variants that regulate gene expression and variants in candidate genes has been generally underinvestigated. Here, we leveraged WGS in a prescreened exome-tested IRD cohort to provide insight into the contribution of non-coding variation and of candidate IRD genes.

Methods : WGS was performed in 82 patients (77 probands) with IRD. Coding and non-coding regions of IRD and candidate genes were analyzed using the in-house Seqplorer tool and Franklin (Genoox). SV analysis was done using ExomeDepth, Manta and Delly. Intronic variants were prioritized using SpliceAI and Alamut Visual. Candidate regulatory variants were assessed *in silico* using multi-omics datasets such as RegRet or *in vitro* reporter assays. Single-cell expression of candidate genes was investigated using retinal single-cell datasets such as the IOB Retina Atlas and Spectacle. Segregation and clinical reassessment were performed when possible.

Results : Novel (likely) pathogenic regulatory variants were found in 4% (3/77), one of which is a promotor variant of *RPGRIP1* c.-152A>C in a coding monoallelic case, predicted to disrupt an OTX2 binding site. Two 5'UTR variants were identified in a monoallelic case (*BBS12* c.-11+3dup) and in a patient with macular disease (*ELOVL4* c.-187T>G) respectively, likely solving the diagnosis in both cases. Coding variants in novel candidate genes represent 6.5% (5/77), such as *ACACB*, encoding a player in lipid metabolism. Variants in genes that were recently implicated in mostly syndromic IRD, such as *ALPK1*, *GRN* and *ITM2B*, facilitated a genotype-driven diagnosis in 9% (7/77). Analysis of non-coding regions in monoallelic cases allowed to pinpoint putative deep-intronic splicing variants in 16% (12/77), illustrated by the first deep-intronic *ALMS1* variant that was shown to lead to pseudo-exon inclusion by minigene assays. Finally, variants in well-established IRD genes were found in 12% (9/77), including 2 SVs (3%, 2/77).

Conclusions : We demonstrate that non-coding regulatory variants and deleterious variants in candidate genes contribute to over 10% of the genetic architecture of our prescreened IRD cohort. Overall, WGS analysis could solve missing heritability in up to 46%.

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