Assessing the Utility of the REVEL Score: A Comprehensive Evaluation Across Diverse Genomic and Clinical Contexts

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Introduction: Interpreting germline variant pathogenicity is challenging, even with increased access to genomic data and in silico prediction tools. The REVEL score, an ensemble method combining 13 prediction tools, has become a key resource for classifying missense variants. This study evaluates REVEL's accuracy using gnomAD data, focusing on three aspects: its agreement with ClinVar classifications, its reliability with variants of moderate-to-high prevalence in gnomAD 4.0 (which are generally benign), and its effectiveness across gene pathogenicity mechanisms, such as gain of function and loss of function. This analysis will determine REVEL's utility in diverse clinical settings. **Methods:** It was optimized data processing by selecting 20 genes from the OMIM-morbid database, representing a variety of disorders and disease mechanisms. To test the accuracy of REVEL, it was selected genes with varying features, focusing on pathogenicity mechanisms (such as gain of function, loss of function, or dominant negative), inheritance patterns (autosomal dominant, autosomal recessive, or X-linked), and disorder frequencies. This approach allowed us to evaluate REVEL's performance across diverse gene characteristics and clinical scenarios.It was mapped each gene's REVEL score to its gnomAD frequency, ClinVar classification, and canonical transcript position, and accuracy was tested using Python and Biopython. **Results/Discussion:** Our preliminary analysis showed that the REVEL score performed well for variants with medium-to-high prevalence in gnomAD. REVEL scores were generally consistent with ClinVar classifications, with high accuracy across most gene type, but some care should be taken upon analysing Clinvar classification, as some may have used REVEL or some of its components during interpretation. The tool was effective regardless of pathogenicity mechanisms, inheritance patterns, or disorder frequencies, suggesting broad utility in genomic analysis.

Keywords: Score REVEL, gnomAD, missense variants, ClinVar classifications

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