Integration of Protein Stability and Structural Context Scores Improves Bioinformatics Predictions for BRCA1 and TP53 Gene Variants

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Abstract

Introduction: The clinical classification of missense variants and single amino acid deletions is challenging. Bioinformatics tools currently in use by ClinGen Variant Curation Expert Panels do not capture free energy changes in protein stability (ΔΔG), and do not include AlphaMissense, a tool recently developed by Google DeepMind that utilises structural context to predict pathogenicity for all human proteome missense variants. Our study aimed to investigate whether ΔΔG predictions and/or AlphaMissense scores outperform current bioinformatics tools in discriminating pathogenic and benign variants.

Methods: We focussed our analysis on missense variants in BRCA1 and p53, and single amino acid deletions (deletions) in p53, only. ΔΔG values were predicted with FoldX5.0 (missense variants), and AlphaFold2/RosettaRelax protocol (deletions). The performance of ΔΔG, AlphaMissense and two broadly accepted computational tools (BayesDel and Align-GVGD), was evaluated with auROC, Boruta and binary logistic regression. Estimated likelihood ratios towards pathogenicity, using defined reference sets including functional output and clinical classification, were used to define categories that best predict pathogenicity for individual and combined predictors.

Results: In partially-buried/buried residues (Relative solvent accessibility <60%)**,** ΔΔG pathogenicity thresholds (≤1.5/≥2.5kcal/mol) improved currently used prediction approaches for missense variants. AlphaMissense outperformed all individual approaches tested. The best sensitivity and specificity for missense variants was achieved using AlphaMissense combined with ΔΔG. ΔΔG scores ≥ 2.5 kcal/mol in buried residues outperformed currently used prediction approaches for deletions.

Conclusions: Our results indicate that integrating AlphaMissense and ΔΔG improves

computational predictions for BRCA1 and p53 missense variants, and that ΔΔG alone improves prediction for p53 single amino acid deletions.