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CTpredX: Enhancing Missense Variant Pathogenicity Prediction in Childhood Cancer Predisposition Genes

Effective clinical genome interpretation relies on accurately distinguishing between benign and pathogenic rare variants. Current genome-wide trained variant prioritization tools often lack precision and may overlook key parameters defining gene-disease relationships. We hypothesized that developing predictors based on curated, disease-specific gene sets could significantly enhance the performance of these tools.

We developed CTpredX, a machine learning-based predictor specifically tailored for a curated set of childhood cancer predisposition genes (CCPGs). CTpredX was trained through an Extreme Gradient Boosting algorithm using ClinVar annotations as a ground truth, integrating multiple variant annotations, constraint scores, and existing pathogenicity predictors.

CTpredX outperformed existing genome-wide tools in distinguishing pathogenic from benign variants within CCPGs, achieving an AUC-ROC=0.98 in the testing dataset. Benchmarking against established prediction tools also demonstrated superior performance in terms of accuracy in distinguishing pathogenic from benign variants at high confidence levels. Additionally, CTpredX re-classified 56% of ClinVar's variants of uncertain significance (VUS), with 37.8% of them re-classified as benign and 18.3% as pathogenic.

CTpredX provides a robust tool for pathogenicity prediction of missense variants in childhood cancer, supporting the feasibility of disease-specific variant classifiers. A user-friendly R-shiny interface facilitates broader use in clinical and research settings.

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