A112 · From Surface to Core: Mechanistic Interpretation of Rare Disease VUSes through Structure-based Analysis

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Rare disease sequencing studies increasingly identify large numbers of variants of uncertain significance (VUS), many of which remain unresolved because of limited understanding of the underlying mechanism. Advances in structural bioinformatics, protein interaction modeling, and variant effect prediction have improved the evaluation of candidate disease-associated variants, but existing approaches typically address isolated components of interpretation and rarely integrate structure, interaction, stability, and disease-relevant evidence within a unified analytical framework. Here, we present an automated, end-to-end workflow for the systematic identification and mechanistic prioritization of missense variants through two complementary mechanisms: disruption of protein–protein interactions (PPI) and destabilization of protein folding through substitution of buried core residues. This framework integrates disease-relevance annotation, variant-to-structure mapping, interactome prioritization, PPI interface characterization, ΔΔG-based stability analysis, and conformational dynamics assessment, within an end-to-end workflow. Application of the workflow to rare disease VUS data from the Myopathy and Muscular Dystrophy cohort at Children's Rare Disease Collaborative at Boston Children's Hospital demonstrates its ability to systematically prioritize candidate disruptive variants while maintaining scalability and mechanistic interpretability. Collectively, this work establishes a generalizable framework for structure-based analysis of rare disease VUSes.

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