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A structure-based framework to investigate variant effects in cancer and other diseases

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The growing volume of genomic data has led to a surge in missense variants. However, many of these remain classified as Variants of Uncertain Significance (VUS) or have conflicting annotations, limiting their utility in diagnostics and precision medicine. Predictive tools often lack resolution into how such variants affect protein function at the molecular level. To address this, we present MAVISp (Multi-layered Assessment of VarIants by Structure for proteins), a modular framework that integrates structural modeling, free energy calculations, and interaction analyses to characterize the mechanistic impact of protein-coding variants. Available as a publicly accessible web resource (https://services.healthtech.dtu.dk/services/MAVISp-1.0/), MAVISp includes curated data for over 700 proteins and more than five million variants, with ongoing updates by a team of expert biocurators. We will showcase its utility through selected case studies, illustrating how MAVISp enables the interpretation of structural stability changes, disruption of protein–protein and protein–DNA interactions, and perturbations of post-translational regulation. In particular, we will present examples of applications to proteins involved in DNA repair, DNA damage response, and autophagy, highlighting how structural insights can refine variant prioritization and support functional reclassification. This integrative strategy bridges the gap between sequence-based prediction and protein-level mechanisms, facilitating the interpretation of mutational landscapes in cancer and beyond.

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