The Road to Atomistic Pathology

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Variant classification of missense alterations remains a significant challenge. The predictive capacities of methods that focus on the sequence (e.g. in-silico predictors) are limited and are typically combined with additional lines of evidence (e.g. population frequency, family studies, and functional studies) to obtain robust classification. However the utilization of alternative evidence categories is limited by availability and cost. Biophysical principles provide a promising complementary source for additional lines of evidence, because protein structures provide a rich set of features that elucidate protein function and dysfunction. We present the analysis of a series of missense variants using biophysical methods, such as model building (Kim, Chivian, & Baker, 2004), and stability calculations (Schymkowitz et al., 2005), combined with structural-biological insight. This integrated biophysical approach offers additional predictive power as well as mechanistic insight into the mode of disruption. We find that analyzing variants in the context of the protein structure yields an atomistic view that explains why variants at similar locations in the sequence have different clinical outcomes. We have successfully applied this approach in the past to explain challenging variants in a variety of genes (Martin et al., 2017; Peng et al., 2018; Powis et al., 2018). We illustrate for several cases how active sites can be affected while leaving stability unchanged and how variants can have significant impacts on protein folding and stability.

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