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Protein dynamics elucidates the phenotypic effects of nsSNVs coupled to functionally critical residues BRANDON BUTLER, AVISHEK KUMAR, Arizona State University, SUDHIR KUMAR, Temple University, BANU OZKAN, Arizona State University — Biological processes are facilitated largely by protein-protein interactions. Thus, non-synonymous single nucleotide variants (nsSNVs) on interface sites can impair protein function. We investigated the conformational dynamics of interface sites on 333 complexes using a site-specific structural dynamic flexibility metric (DFI). We found interfaces have lower DFI as compared to non-interfaces. Moreover, interface sites with damaging nsSNVs were found to have significantly lower DFI than those with benign nsSNVs, which relates structural dynamics to functional significance. In a new analysis, we considered a small fraction of interface residues known as "hotspots", which account for a large portion of the total binding free energy. Hotspots are critical for function, but, importantly, residues that are dynamically coupled to them are also critical. Using a new dynamic measure, functional-DFI (fDFI), on the same set of complexes we considered hotspots as input for f-DFI and estimated their impact on other residues harboring nsSNVs. Based on the f-DFI results, dynamics-based metrics can be useful in assessing phenotypes of residues that are not obvious as critical for function but can be damaging since they are coupled to functionally critical residues.

Brandon Butler
Arizona State Univ

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