Title:	Large scale analyses of single residue mutations on residue interaction networks
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Abstract:	The phenotypic effect of single residue mutation in proteins can vary from no effect to complete loss of function. Such varied effects have intrigued structural biologist and biophysicist, over decades, because it has remained difficult to derive a general guiding structural principle to explain changes in structural properties of proteins due to mutations. Usually, detailed structural effects on mutations are obtained by comparison of experimentally determined tertiary structures of wild-type and mutant proteins. Such previous studies have mostly focused on understanding changes in protein thermodynamic stability, which led to development of modeling or prediction of change in protein stability. Moreover, these have been also employed to understand human diseases as it has been shown that of these are due to mutations involving non-synonymous single-nucleotide polymorphisms (nsSNP). The effect on protein function due to single residue mutation can be attributed to impairment of stability, defective interactions with other biomolecules (ligand/proteins), and residue packing density. Despite many studies on single residue mutant structures, the effect on wild type protein residue interaction network (RIN) due to such mutation, mostly, unexplored. In the present study, we have systematically investigated the effect of mutation by comparing RIN of wild type and mutant proteins. Furthermore, we studied the network perturbation using closeness centrality due to mutation. Through these studies, we have explored whether changes in residue interaction network can explain the functional shift in proteins. The comparison of C-□ residue network of wild-type and mutant multi-domain proteins suggested that global network centrality measures remain mostly unchanged on mutation. However, a small subset of proteins showed a large change in global network parameters that could not be correlated to conformational change due to mutation or belonged to specific functional families. Interestingly, local network features show remarkable changes, which seem to propagate in the protein network in some cases to really large spatial distances. Thus, suggesting allosteric effect of mutation. Importantly, this study can provide insights for rational design of protein with a desired feature.
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