

Preferred Left-Handed Conformation of Glycyls at Pathogenic Sites

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Abstract : The role of glycyl residues in the protein structure has lingered within the research community for the last several decades. Glycyl residue is the only amino acid that is achiral due to the lack of a side chain and can, therefore, exhibit Ramachandran conformations that are disallowed for L-amino acids. The structural and functional significance of glycyl residues with L-disallowed conformation, however, remains obscure. Through statistical analysis of various datasets, we found that the glycyls with L-disallowed conformations are over-represented at disease-associated sites and tend to be evolutionarily conserved. The mutations of L-disallowed glycyls tend to destabilize the native conformation, reduce protein solubility, and promote inter-molecular aggregations. We uncovered a structural motif referred to as “ β -crescent” formed around the L-disallowed glycyl, which prevents β -sheet aggregation by disrupting the alternating pattern of β -pleats. The L-disallowed conformation of glycyls also holds predictive power to infer the pathogenic missense variants. Altogether, our observations highlight that the L-disallowed conformation of glycyls is selected to facilitate native folding and prevent inter-molecular aggregations. The findings may also have implications for designing more stable proteins and prioritizing the genetic lesions implicated in diseases.

Keywords : Ramachandran plot, β -sheet, protein stability, protein aggregation

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