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Structural Insights into Inherited Human Prion Diseases: An Experimental and Computational Approach

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Abstract

Prion diseases are a group of invariably fatal disorders characterized by a spongiform neurodegeneration of the brain caused by prions. According to the protein-only hypothesis, during prion diseases the cellular prion protein (PrP), PrP^{C}, is converted into an abnormal form, denominated PrP^{Sc}, by a not well-elucidated process of conversion of the α-helix motives into β-sheet secondary structures. One of the strongest arguments supporting the protein only hypothesis is the link between prion diseases and inherited human mutations in the *PRNP* gene. Several point mutations leading to familial Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker (GSS) disease and fatal familial insomnia have been identified in the *PRNP* gene. The current understanding of the mechanisms by which these mutations cause disease remains limited. Mutations may increase the likelihood of misfolding by thermodynamic destabilization of PrP^{C}. Mutants of PrP may escape quality control cellular pathway and accumulate inside the cell. In addition, mutations may change surface properties promoting an abnormal interaction between PrP and other not yet identified interactors. High-resolution 3D structure of mutated PrP, may help decipher the structural requirements making these molecules more susceptible for spontaneous conversion into the infectious form, and may help understand the molecular mechanism at early stages of the disease. In this study, the high-resolution 3D structure of the truncated recombinant human PrP (residue from 90 to 231) containing the GSS-related Q212P mutation is described. The substitution of a glutamine by a proline at the position 212 reveals novel structural differences in comparison to the known PrP structures. The most remarkable differences involve the C-terminal end of the protein and the β_2–α_2 loop region. This new structural layout might provide further insights into the early events playing along with the conformational transition of PrP^{C} into PrP^{Sc}. The spontaneous formation of prions in familial cases may indeed be due to the disruptions of the hydrophobic core formed by the β_2–α_2 loop and the α_3 helix.