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Substitutions at residue 211 in the prion protein drive a switch between CJD and GSS syndrome, a new mechanism governing inherited neurodegenerative disorders

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Abstract

Human prion diseases are a heterogeneous group of fatal neurodegenerative disorders, characterized by the deposition of the partially protease-resistant prion protein (Pr^{Pres}), astrocytosis, neuronal loss and spongiform change in the brain. Among inherited forms that represent 15% of patients, different phenotypes have been described depending on the variations detected at different positions within the prion protein gene. Here, we report a new mechanism governing the phenotypic variability of inherited prion diseases. First, we observed that the substitution at residue 211 with either Gln or Asp leads to distinct disorders at the clinical, neuropathological and biochemical levels (Creutzfeldt-Jakob disease or Gerstmann-Sträussler-Scheinker syndrome with abundant amyloid plaques and tau neurofibrillar pathology). Then, using molecular dynamics simulations and biophysical characterization of mutant proteins and an *in vitro* model of PrP conversion, we found evidence that each substitution impacts differently the stability of PrP and its propensity to produce different protease resistant fragments that may contribute to the phenotypical switch. Thus, subtle differences in the PrP primary structure and stability are sufficient to control amyloid plaques formation and tau abnormal phosphorylation and fibrillation. This mechanism is unique among neurodegenerative disorders and is consistent with the prion hypothesis that proposes a conformational change as the key pathological event in prion disorders.

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