Biochemical and structural studies of the prion protein polymorphism

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A hallmark event in transmissible spongiform encephalopathies is the conversion of the physiological prion protein into the disease-associated isoform. A natural polymorphism at codon 129 of the human prion gene, resulting in either methionine or valine, has profound influence on susceptibility and phenotypic expression of the disease in humans. In this study, we investigated the local propensity of synthetic peptides, corresponding to the region of the polymorphism and containing either methionine or valine, to adopt a ?-sheet-rich structure similar to the pathological protein. Circular dichroism studies showed that the methionine-containing peptide has a greater propensity to adopt a ?-sheet conformation in a variety of experimental conditions. The higher ?-sheet tendency of this peptide was also associated with an increased ability to aggregate into amyloid-like fibrils. These results suggest that methionine at position 129 of the prion protein increases its susceptibility to switch