A case report of Frontotemporal Dementia syndrome associated with recently discovered N-terminal domain mutation in prion protein gene

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BACKGROUND: Pathogenic mutations in the prion protein gene (PRNP) are the cause of familial human prion diseases (inherited prion diseases, IPD) such as familial Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. IPD are associated with point mutations or insertion/deletion mutations of octapeptide repeats. The prion protein conformation contains an unstructured N-terminal region and a structured C-terminal region (fig. 1). More than 30 point mutation linked to IPD have been found in the open reading frame of PRNP, situated in the C-terminal domain. Moreover, single nucleotide polymorphisms (SNP) in the ORF (particularly, SNP at codon 129) are considered to be susceptibility factors for IPD (1). The N-terminal domain did not seem to be involved in prion replication.
Additionally, recent studies found an association between PRNP gene mutations and other neurodegenerative clinical pictures: among these, 3 point mutations associated with FTD clinical features have all been reported in the C-terminal domain of the protein. Until recently, pathogenic point mutations in the N-terminal domain were unknown (2).

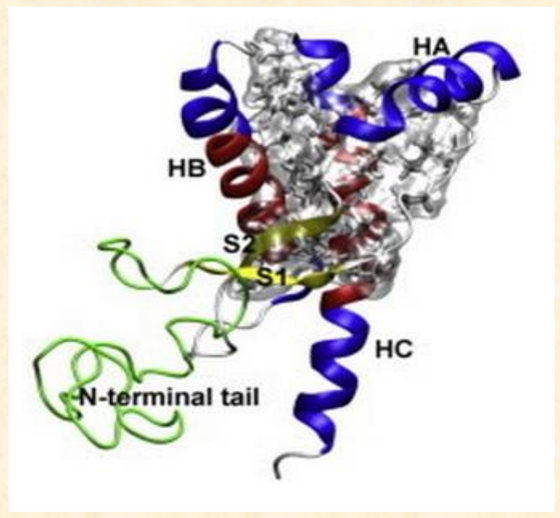

Fig. 1 (Mead S et al, 2006)

AIMS: We report on a case of Frontotemporal Dementia (FTD) syndrome associated with a recently discovered genetic variant in the N-terminal domain of prion protein gene (*PRNP*).

MATERIALS AND METHODS: A 67-year-old man was referred for cognitive impairment, behavioural symptoms, postural instability and abnormal gait, rapidly progressive over 1 month.
Past medical history: diabetes, chronic bronchitis, arterial hypertension, alchool abuse. Family history: his mother developed a cognitive impairment in later life.
The differential diagnosis of his symptoms included a frontotemporal dementia (suggestive features: cognitive impairment, behavioural symptoms, family history), a secondary dementia on a metabolic base (hyperglicemia/alcohol related dementia), a vascular dementia (risk factor: arterial hypertension), a subacute encephalitis (paraneoplastic or infective) and a Creutzfeldt-Jakob disease (because of the rapid course of the disease and the postural instability).
He underwent clinical and neuropsychological assessment, brain MRI, EEG, lumbar puncture, dosage of paraneoplastic antibodies and genetic screening of PRNP.

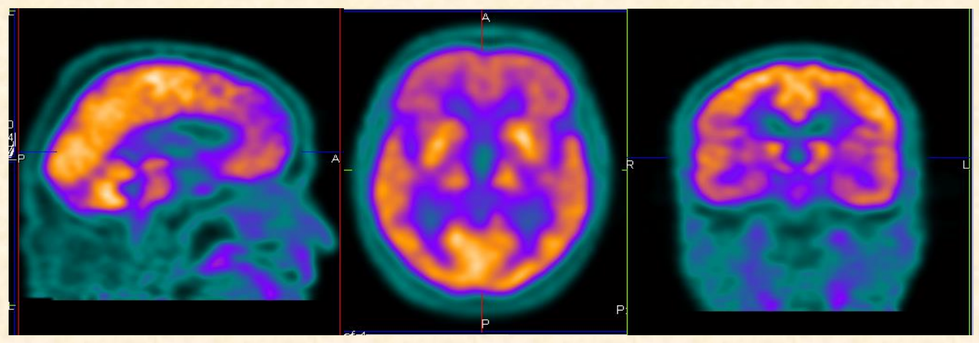

Fig. 2

RESULTS: Clinical and neuropsychological tests were suggestive of a behavioural variant of FTD (MMSE: 17/30; frontal lobe syndrome: apathy, loss of empathy, mutism, perseveration). A PET scan showed bilateral hypometabolism in the prefrontal area and in the insular lobe (fig. 2). An MRI scan revealed atrophy in the same areas (fig. 3)., together with signs of cerebral vascular disease. This findings, taken together, satisfy the criteria for the diagnosis of probable bvFTD (according to Rascovsky et al, 2011). Cerebrospinal Fluid (CSF) analysis showed slightly positive 14.3.3 protein and normal levels of tau protein. A subsequent genetic analysis revealed a novel variant in PRNP, leading to an aminoacidic substitution (P39L) in the N-terminal domain of the protein (fig. 4).

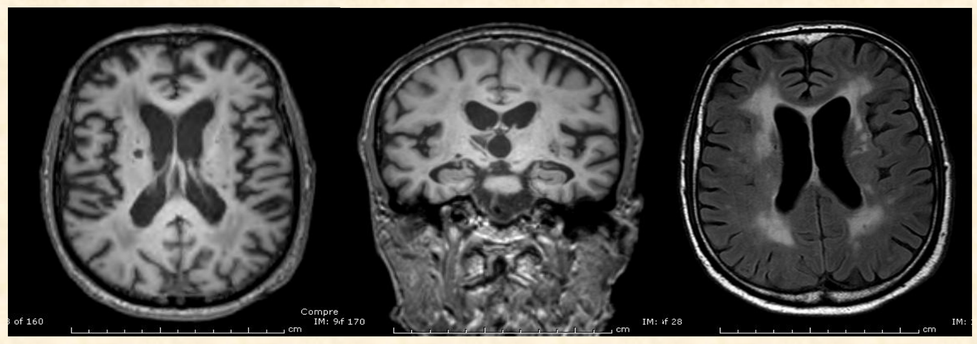

Fig. 3

DISCUSSION AND CONCLUSION: So far, point mutations associated with Creutzfeldt-Jacob Disease and 3 point mutations associated with FTD clinical features have all been reported in the C-terminal domain of the protein (2). To date, P39L is the only potentially pathogenic point mutation in the N-terminal domain of PrP described; this mutation has recently been found in association with FTD syndrome in two patients from Southern Italy (2). Conclusions: further studies are required to clarify the pathogenic role of the mutation, particularly its segregation with the disease and its absence in non-affected people.

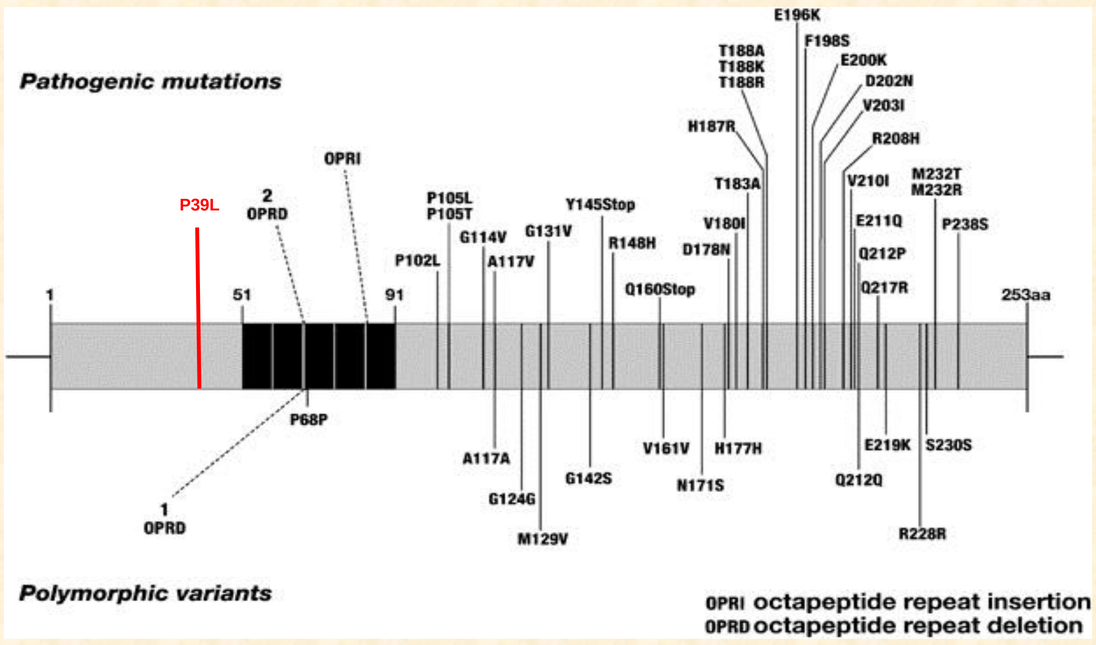

Fig 4 (Chen W et al, 2014)

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(2) Bernardi L, et "Novel N-terminal domain mutation in prion protein detected in 2 patients diagnosed with frontotemporal lobar degeneration syndrome". Neurobiology of Aging 2014; 35: 2657.e7-2657.e11