



**Profile of the vCJD epidemic:**

- **Cover paper- J. W. Ironside (February 2005) Human Prion Diseases**
- **Parchi *et al.* (1999) Classification of sporadic Creutzfeld-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Ann. Neurol.***
- **Clarke & Ghani (2005) Projections of future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility *R. J. Soc. Interface.***
- **Lasmezas *et al.* (2005) Risk of oral infection with bovine spongiform encephalopathy agent in primates. *Lancet.***

## **Human Prion Diseases**

JW Ironside, February 2005

An ever- widening spectrum of human prion diseases has been reported since Creutzfeldt-Jakob disease (CJD) was initially described in the 1920s (Table 1). This includes sporadic, familial and acquired diseases, the commonest of which is sporadic CJD (1,2). The naturally occurring polymorphism at codon 129 of the prion protein gene (PRNP) influences susceptibility to sporadic CJD (Table 2). In comparison with normal population there is an excess of homozygotes at codon 129 in the PRNP in sporadic CJD (particularly methionine homozygotes), with a reduction in the percentage of heterozygotes (2).

The clinical and neuropathological features of sporadic CJD are both variable; this variability is substantially influenced by the PRNP codon 129 genotype and the isotype of PrP<sup>Sc</sup> in the brain as determined by Western blotting studies (1,3). PrP<sup>Sc</sup> occurs in 2 major biochemical isoforms in sporadic CJD (type 1 and type 2), so there are at least 6 different possible combinations of PrP<sup>Sc</sup> isotype and PRNP codon 129 genotype: MM1, MM2, MV1, MV2 VV1 and VV2, each of which appears to be associated with distinctive clinical and pathological features in sporadic CJD (1). Whether these different isoforms represent different strains of the transmissible agent in sporadic CJD remains to be established; the agent strain in variant CJD is similar to bovine spongiform encephalopathy (BSE), but different from sporadic CJD (4).

To date, all patients with variant CJD who have been tested genetically are methionine homozygotes at codon 129 in the PRNP, and variant CJD exhibits a striking uniformity of clinical, pathological and biochemical features in contrast to sporadic CJD (2,3). It remains to be seen whether BSE infection will manifest as a clinical disease in individuals with a MV or VV codon 129 PRNP genotype, and if so, whether these cases will have similar or different clinical and pathological features to variant CJD. Subclinical infection with vCJD by blood transfusion has been reported in an individual who was MV at

codon 129 in the PRNP, but showed no neurological disease or brain pathology at the time of death (5).

The PRNP codon 129 polymorphism also appears to influence disease incubation period in other acquired forms of human prion diseases, including kuru (6) and the cases of iatrogenic CJD following growth hormone therapy in France (7). In both diseases, individual who are heterozygous (MV) at codon 129 in the PRNP had a longer disease incubation period (which in kuru may be over 40 years) than MM or VV homozygotes. If this is also the case for BSE infection in humans, we might expect to see other codon 129 genotypes affected over an unknown timescale in the future. The results of the retrospective tonsil and appendix study has suggested that more cases of BSE infection may have occurred in the UK than the numbers of clinical cases of variant CJD would so far indicate (8). This study raises the possibility that some BSE infections may have occurred in individuals with VV or MV codon 129 PRNP genotype who have not yet (or perhaps may never) manifest a clinical disease. Continuing surveillance for all forms of CJD is required in the UK to address this possibility.

Members are invited to note particularly references 1 and 2 below: (Parchi *et al* 1999, which is provided to members) and the NCJDSU Annual Report "Creutzfeldt-Jakob disease surveillance in the UK". [www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk)

References:

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**Table 1. Classification of human prion diseases**

Idiopathic:	Sporadic Creutzfeldt-Jakob disease
	Sporadic fatal insomnia
Inherited:	Familial Creutzfeldt-Jakob disease
	Gerstmann-Sträussler-Scheinker syndrome
	Fatal familial insomnia
Acquired:	Human source: Iatrogenic Creutzfeldt-Jakob disease
	Kuru
	Bovine source: Variant Creutzfeldt-Jakob disease

**Table 2. Codon 129 *PRNP* polymorphisms in CJD and normal population in UK**

Codon 129 polymorphism	methionine/methionine	methionine/valine	valine/valine
Normal	39%	50%	11%
Sporadic CJD	66%	17%	17%
Variant CJD	100%	-	-