Prion protein gene M232R variation is probably an uncommon polymorphism rather than a pathogenic mutation

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Sir, Nozaki et al. (2010) present a 10-year surveillance study in Japan with important implications for inherited prion disease diagnosis and counselling of families. The most frequent mutations reported were V180I and M232R, however, we are concerned about the conclusion that M232R is pathogenic. It is important to correctly understand the pathogenicity of variants to inform counselling of those at risk in families and to take precautionary public health measures to prevent transmission of iatrogenic prion disease from gene carriers. Additionally, the pathogenicity of M232R would be surprising from the perspective of the pathobiology of prion disease because this amino acid is cleaved from the mature cell surface prion protein in the C-terminal signal peptide when a glycolipid anchor is attached (Stahl et al., 1987). To date, all definite inherited prion disease mutations alter the amino acid sequence of the mature protein (Collinge, 2001).

Nozaki et al. (2010) described 216 patients with inherited prion disease. Of these, 33 cases had the missense variant M232R [1.8% allele frequency (95% CI 0.013–0.026) in 881 cases with PRNP sequenced] with a clinical phenotype very similar to sporadic Creutzfeldt–Jakob disease including the absence of family history. Screening of 466 general Japanese population controls did not reveal the M232R allele (95% CI 0–0.008). Several other reports of M232R exist in the literature in association with disease, predominantly from eastern Asia (Kitamoto et al., 1993; Koide et al., 2002; Zheng et al., 2008; Choi et al., 2009) although a single case has been reported in Germany (Windl et al., 1999), and all cases so far have sporadic Creutzfeldt–Jakob disease-like aetiology.

Without segregation analysis, the possibility remains of in-accurately labelling a variant as pathogenic because of the chance occurrence of a rare benign polymorphism in sporadic Creutzfeldt–Jakob disease. We recently reported approximately two decades of screening PRNP in neurological cases with suspected prion disease (Beck et al., 2010). In an attempt to clarify the global extent of rare probably benign alleles, we went on to sequence PRNP in the Centre d’Etude du Polymorphisme Humain human diversity panel (Cann et al., 2002). In this screen we found two individuals with M232R heterozygosity in the Japanese healthy control population, suggesting an allele frequency of >3% in this population (95% CI 0.019–0.213). M232R has also been reported in three non-Creutzfeldt–Jakob disease cases [3% allele frequency 95% (CI 0.010–0.085) from a screen of 50 cases] providing additional evidence supporting the non-causative nature of this low-frequency allele (Shiga et al. 2007). The absence of M232R in 466 Japanese control individuals described by Nozaki et al. (2010) might be explained by chance, or alternatively, the presence of population substructure in Japan (Yoshida and Kubo, 2008). Pathogenicity and modification of phenotype are not mutually exclusive attributes of genetic variation and it remains possible that M232R modifies the phenotype of sporadic Creutzfeldt–Jakob disease similar to the effect of PRNP codon 129. We also note a similar absence of family history in the large series of V180I patients.
In summary, we highlight the presence of M232R in healthy or non-Creutzfeldt–Jakob disease individuals at a frequency incompatible with a causal role in prion disease.

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**References**


