Reviewer's report

Title: PRNP variation in UK sporadic and variant Creutzfeldt Jakob disease highlights genetic risk factors and a novel non-synonymous polymorphism

Version: 1 Date: 18 September 2009

Reviewer: Angelica A Saetta

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This manuscript by Bishop MT et al describes the polymorphisms of PRNP gene in both CJD disease (sporadic and new variant cases) and normal control samples (for UK and Scottish individuals). Important data regarding the presence of genetic variation in large number of vCJD and sCJD versus control cases are presented. However there are some flaws that need to be checked and suggested additions to be made.

Major Complulsory Revisions

1) In general the statistical analysis is not clearly presented. A brief paragraph entitled “Statistical analysis” could be added in the Materials and Methods section describing the tests and software used for the correlations made. An added table showing the results of statistical analysis would be very useful for understanding the comparisons described at the Results section. There is a confusion regarding the results of the statistical correlation. The authors in the conclusion section of the Abstract state that the three common genetic variations, codons 129, 117 and 24bp deletion, were equally frequent in CJD and normal cases. On the other hand at the results section they describe statistically significant differences for codon 129 genotype frequencies for CJD cases versus the controls which are not mentioned at the conclusions. Furthermore, the authors state a correlation made between the control groups or sCJD sequenced group versus a group of total NCJDSU sCJD cases. This later group is not mentioned before so it would be very helpful if the authors could describe the different subgroups used for statistical correlations. Nevertheless the statistically significant correlation found could be discussed and commented upon at the discussion section and underlined at the conclusions.

2) It would be helpful if the Materials and Methods section could be divided into paragraphs entitled “patients, DNA samples, Genotyping DNA extraction, PCR-RFLPs, sequencing, statistical analysis”.

3) It seems like controls were genotyped by restriction enzyme analysis although the method has not been described except for codon 129 genotyping. Could the authors specify enzymes and conditions used? It would be useful if a diagram showing the restriction enzyme cutting sites as well as the lengths of the cleavage products could be added.

4) The authors included a figure only for codon 129 genotyping. It could be nice
to present figures of the relevant results for the other detected polymorphisms (the novel one included).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare no competing interests