Author's response to reviews

Title: No evidence for association between tau gene haplotypic variants and susceptibility to Creutzfeldt-Jakob disease

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Dear Prof. Morgenstern,

Thank you very much for your interest in our manuscript. We have prepared a revised version following the suggestions made by the Referees. Their points have been handled as follows:

Referee 1: Yong-Sun Kim
1. "Gene maps of the MAPT showing six polymorphisms had better be added in Fig. 1."

Figure 1, as requested by Referee 1, has been included.

2. "In table 3 & 4, the genotype frequency of six polymorphisms should be added."
3. "Table 3 & 4 and table 5 & 6 had better be combined."

We have modified and rearranged table 3, 4, 5 and 6.

4. "The degree of linkage disequilibrium between six MAPT polymorphisms, including PRNP codon 129 should be indicated in new table."

Figure 2 showing a LD plot between the six MAPT SNPs plus PRNP codon 129 has been included.
5. In table 1, the MM frequency of PRNP codon 129 in UK sCJD population (46%) was very similar with control population (45%). But, in previous studies (Palmer MS et al. Nature 1991, 352:340-342; Windl O et al. Hum Genet 1996, 98: 259-264), the MM frequencies of this polymorphism in UK sCJD were very high as 95.5% and 83%. This point should be comment in discussion.

As suggested by Referee 1, we have included a comment in the discussion addressing his point on codon 129 distribution in UK sCJD (page 7, line 6).

Referee 2: Sabina Capellari
1. I understand that the lack of differences between groups justify the pooling of the data but since the gold standard of genetic association studies requires ethnically matched controls it appears appropriate to include a comment about this aspect in the discussion. Indeed, the role of ethnicity on the association of MAPT H1 haplotypes and disease has been also recently pointed out (Winkler et al, Eur J Hum Genet 2007).

We have added a comment in the discussion recognizing this limitation of our study (page 8, line 2).

2. Controls and vCJD groups are not age-matched. Furthermore, the disease groups comprise a high proportion of probable CJD cases. Also these limitations of the study should be mentioned in the discussion.

Comments on those points have been included in the discussion (page 7, third paragraph) (page 8, line 4).

3. A part of the discussion is just a repetition of the result section and should be reduced (while the remaining part should be expanded as stated above).

We have rearranged and reduced the discussion, trying to avoid redundant parts and including new comments addressing the points raised by the Referees.

4. Table 2 is mentioned before table 1. pag 15 sequences is misspelled. Consistency in the indication of frequencies must be checked in Table 5 and 6. The titles of tables 4 and 6 do not read well.

We have made all these changes suggested by Referee 2.

5. It could be interesting for the reader to also have the data showing the MAPT haplotype association with sCJD considered as individual groups (as in Table 3
Our tables are bigger and more complex in this revised version, as a result of merging them and including genotype information. Therefore, we have chosen not to follow the discretionary revision for the sake of simplicity.

Hoping this will meet your approval,

Yours sincerely,

Pascual Sánchez-Juan

Santander, October 31st, 2007