Reviewer's report

Title: Genomic NGFB variation and chronification in multiple sclerosis: case control study and expression analyses

Version: 2 Date: 11 September 2008

Reviewer: Antonio Alcina

Reviewer's report:

The authors have studied the association of 10 SNPs from the NGFB gene with MS. Two of the SNPs genotyped in 1120 unrelated MS patients and 869 controls resulted in a positive association, the rest typed in 263 rr patients and 259 controls were negative. They also measure the expression of NGFB from PBMC in 23 males and 10 females patients.

1.- The data are interesting for the two SNPs found positively associated, mainly for the rs6330 considering the acceptable size of the cohort. The rs*30 was not associated in the whole MS cohort, though after stratification in sex and MS course it appeared associated with males and rr males. In this last case the sample size decreases so much that the power may be low and I would not draw the conclusions stated in the abstract and discussion. Similarly, I think you do not have enough power to conclude that the other 8 SNPs found negatively associated are really not associated because of the small sample size. So as a suggestion I would simplified the presentation of results mainly removing stratifications in Table 2 (and perhaps in table 1) and removing "expression analysis" from the title.

2.- Though is valuable the effort in doing the expression analysis using PBMC from a few ms patients, taking account the many factors affecting the expression of NGFB (sex, menstruation, perhaps treatment, tissue and others), I don’t think the sample numbers is enough large to get true significant results. So the conclusion stated in the Abstract and Discussion is in my opinion over interpreted, and should be modified.

In relation with the rs*30, in the promoter region of NGFB, something specific to do to clarify its effect in the expression level of the gene would be to set up a in vitro-reporter assay. On the rs 6330, if it affects the binding to its receptor, this has to be shown. In absence of this data, the functional relevance of these two SNPs in the expression level of the gene and the functional activity of the product is quite speculative. In my opinion, the relationship between these two SNP and their affects in the gene is not supported by the data presented in this paper and therefore most of the conclusions are over interpreted.

In summary, these are interesting and valuable data deserving publication but the results are presented with to much stratification and speculative conclusion.
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 that I have no competing interests