Reviewer's report

Title: The dopamine beta-hydroxylase -1021C/T polymorphism is associated with the risk of Alzheimer's disease in the Epistasis Project

Version: 1 Date: 19 August 2010

Reviewer: Rita Guerreiro

Reviewer's report:

Combarros O et al. assessed the role of genetic variability in the Dopamine B-hydroxylase, Interleukin 1A and Interleukin 6 genes in the risk of developing Alzheimer’s disease (AD). For this, the authors studied 1757 AD cases and 6295 controls from the Epistasis Project, which include samples from seven different European centers. Additionally, the authors evaluated the genetic interactions between these genes. This is an interesting study, however some issues need to be clarified:

Major Compulsory Revisions

As the authors acknowledge in the discussion section, larger numbers of samples are needed to replicate the associations and interactions found in this study. With this in mind, the authors could add to their own data genotypes from publicly available databases.

Minor Essential Revisions

Abstract section

1- Conclusion subsection:
   a. “Noradrenaline has an important role in the control of inflammation in the brain”. - It is impossible to reach this conclusion with the data presented in this study. In this way, the authors should start the abstract conclusion with a less speculative statement.

Methods section

2- Study population subsection:
   a. When naming the different research groups involved in the project, the authors should refer that the OPTIMA group is from Oxford.
   b. It would be important to know the age ranges for each group.
   c. Although this information is partially referred in the Combarros O. et al. 2009 manuscript, it would be important to state in the present study if these AD cases are late-onset cases, early onset cases, sporadic or with family history.

3- Genotyping subsection:
   a. It is not clear from the text which SNPs were genotyped and which SNPs were imputed in each dataset (Sanger Institute vs Rotterdam).
b. It should be clearly stated in the text that 8 SNPs were assessed in this study and which are these SNPs. Also, one has to assume that all the eight SNPs were genotyped by the Sanger Institute, two of these using a different technology.

c. Table 1: The information provided for each SNP should be consistent:

It should be clearly stated to which reference sequence the position associated with each SNP refers to (which cDNA, genomic or protein sequence); the minor allele frequency should correspond with the gene allele and not the protein amino acid.

4- Statistical analysis

a. What is the rational to divide the data into North Spain and North Europe? Is there any evidence of population substructure in the data? If so, these results should be presented.

b. It should be clearly stated which centers/data are included in each of the created groups (North Spain and North Europe).

Results section

For brevity and simplicity, Tables 3 and 4 could be joined.

Tables

In all the tables what do the bold fonts refer to?

**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