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:** 28 August 2010

**Reviewer:** Joseph F. Cubells

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Combarros and colleagues present an analysis of SNP genotypes at several candidate genes and risk for Alzheimer disease (AD). They begin with a strong neurobiological hypothesis, namely that modulation of inflammatory processes by norepinephrine (NE) contributes to the disease process in AD. They nicely summarize literature demonstrating that NE neurons in the locus ceruleus degenerate in AD, and evidence from animal model studies implicating NE as a modulator of pathogenic inflammation in the brains of rodents. From this background, they hypothesize that allelic variation at DBH, encoding the NE-synthetic enzyme dopamine β-hydroxylase (DβH), will associate with AD risk, and furthermore that such variation will interact with variation in genes encoding inflammatory cytokines to influence such risk.

They report a modest association between -1021C>T, a SNP that strongly associates with differences in serum DβH activity and is likely to be a functional variant altering transcription of DBH, and risk for AD. Interestingly, that association appeared to be accounted for largely by an association in males 75 or younger. Furthermore, they provide evidence supporting interactions between -1021C>T and a SNP at IL1A.

The manuscript partially replicates prior findings, and as noted is based on a strong theoretical foundation. It is therefore of potential value even given increasing (and well justified) skepticism in the field of complex-trait genetics regarding candidate SNP association studies. However, there are several significant issues that need to be addressed:

**Major compulsory revisions:**

1. Neither the introduction nor discussion address recent data from the laboratory from D.T. O’Connor and colleagues, providing in cella and in vitro evidence supporting the hypothesis that -1021C>T is a functional polymorphism (Chen et al., 2010, J. Hypertension, 28: 76). The findings in that report could alter the potential interpretation of the current results because they imply the possibility that the T allele of the SNP associates with lower serum DβH activity, but higher central DβH activity. It is therefore essential to discuss this paper (as well as additional work by the same group that is in press in J. Hypertension).

2. The authors present only a dominant model, i.e., combining the -1021 TT and CT groups, but do not discuss this or present a rationale for doing so.
3. Given significant differences in allele frequencies at rs1800587 and rs1800795 between subgroups of controls from different regions of Europe, there is a concern that the interactions presented could reflect population substructure instead of biologically based interactions. Addressing population stratification using genomic control or ancestry-informative marker based methods seems warranted in light of this potential problem.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.