Reviewer’s report

Title: No association between polymorphisms in the brain-derived neurotrophic factor gene and age at onset in Huntington disease

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Reviewer: Samir Brahmachari

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General
Polyglutamine repeat in huntingtin (HTT) gene is known to cause Huntington’s Disease (HD), a neurodegenerative disorder characterized by loss of striatal neurons. Most of the variance in the age on onset (AO) of HD can be explained by variation in CAG repeats in HTT. It is however of considerable interest to identify other genetic modifiers of HD phenotype, in order to account for the residual variance in AO. Brain-derived neurotrophic factor (BDNF), a member of nerve growth factor family necessary for survival of striatal neurons, is one of the candidate AO genes because its transcription as well as vesicular transport is regulated by HTT. A valine (val) to methionine (met) substitution in the 5’ pro-region of the BDNF protein is associated with human memory and hippocampal function. Neuronal transfection experiments suggest that val/met polymorphism may affect intracellular trafficking and activity-dependent secretion of BDNF. Interestingly, this polymorphism was found to be associated with AO in a previous study (Alberch et al. Neurology. 2005, 65:964-5). It is in this context that the present manuscript by Mai et al describes an association analysis of BDNF in AO. Mai et al report negative evidence for involvement of BDNF based on genotype/haplotype analysis of five SNPs in and around the gene.

Being a replication study, the presentation of the hypothesis should have highlighted the prior evidence of val/met polymorphism in AO and in possible role in protein’s intracellular trafficking. Instead, it highlights the BDNF’s role in various neurological and psychiatric disorders and describes the prior evidence in passing. In study design, it is not clear why SNPs other than val/met were chosen. The authors may possibly scored them in view of the evidence that HTT regulates BDNF transcription. But then this is not mentioned in clear terms. Also not mentioned is the genomic regions of the SNPs other than val/met. A database search shows that they are from intronic and 5’ upstream region. This should have been spelt out, to support the study design. It is mentioned in the Methods section that all the five markers were tagging SNPs. The next section however points out strong LD between all neighboring markers. This seems contradictory and needs further elaboration. Further, results have not been provided for the various markers and the haplotypes – only val/met box plot shown in Figure 1. I wonder why the spread of age of onset is much higher in Val/Val and Val/Met patients compared to Met/Met individual. Authors should explore this and provide some explanation. It is necessary that the manuscript is revised in view of the above comments. Recently, two papers (Di Maria et al PMID 16905325 and Metzger et al PMID 16847693) have appeared on association BDNF in AO. Both of them provide negative evidence. Mai et al’s manuscript needs to discuss their results in light of these new findings which are corroborative.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)