Reviewer's report

Title: Age at onset of Huntington disease is not modulated by variations in the genes coding for TP53 and human caspase activated DNase (hCAD)

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Reviewer: Samir K Brahmachari

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General
In this manuscript the authors' have studied the association of two polymorphisms in two genes namely TP53 as well as human caspase activated DNAse (hCAD) in modifying age of onset in Huntington's disease. Association of these two polymorphisms have been earlier reported in a study in the Indian population. The authors' have carried out this study in a well established cohort of HD patients in which they have carried out similar association studies for different modifiers (J Neurol Neurosurg Psychiatry. 2004 Dec;75(12):1692-6; J Neural Transm Suppl. 2004;(68):105-10; BMC Med Genet. 2004 Mar 24;5(1):7).

Major compulsory revisions

1.. This is just a replication study with absolutely no novelty in the question posed by the author as well as the method followed.. They report negative results and conclude that age at onset of Huntington disease is not modulated by variations in these genes.

2.. If the genes have been earlier shown to be associated through two polymorphisms, it is possible that there could be different sets of polymorphisms within the same genes in the studied population which could also modulate the age of onset. The authors have not excluded this possibility as their study only seeks to validate the earlier polymorphisms. Therefore their conclusions of no involvement of these two genes in modifying age of onset are rather far fetched. It is well documented that similar genes can have different population specific mutations. The authors would have to exhaustively screen for other variations in these genes before they make these conclusions. Not only variation data but also sequence from different genomes are abundantly available. The authors could make use of this information for prioritizing polymorphisms which would enable construction of haplotypes for identification of other mutations which could be modifiers.

3.. Since the authors have earlier tested variations in other genes in the same cohort, they could now look at the effect of all of them in conjunction, which might give a more comprehensive picture.

4.. The data presented in the manuscript is very minimal and more rigorous association studies needs to be carried out before these conclusions can be made. The results and discussion section is very poorly written which is also because, there is hardly any result which has been presented.

5.. The title of the manuscript suggests that many variations would have
been screened before authors would have made these conclusions.
6. The manuscript is not suitable for publication in the current state.
More rigorous study needs to be carried out.

**What next?:** Reject because too small an advance to publish

**Declaration of competing interests:**

'I declare that I have no competing interests' below.