Reviewer's report

Title: Genetic analysis of polymorphisms in the kalirin gene for association with age-at-onset in European Huntington disease patients

Version: 2 Date: 3 April 2012

Reviewer: Ralf Reilmann

Reviewer's report:

The authors investigated a possible association of polymorphisms in the kalirin gene with age-at-onset (AAO) in a European cohort of subjects. Since kalirin is thought to be involved in spine genesis and this was shown to be impaired in HD model, SNPs associated with AAO could be a target for disease modifying therapies. The rational of the study is clear and the question under investigation timely and of interest.

The study is methodologically sound and statistically adequate. The results make a relevant contribution to the field.

Compulsory Revisions/Questions:

1. It seems unusual to use either the motor or cognitive symptoms as AAO for HD. The currently established diagnostic criteria require motor symptoms 99-100% specific for HD to establish the diagnosis of HD, which is equivalent to AAO. Could the authors please clarify what they did – either they used classical AAO, i.e. motor (then omit the reference to cognitive in the methods) or did they indeed use cognitive OR motor? Then I would like to see an analysis for the motor and cognitive domain separately and would advise to avoid using the AAO and rather specify what was done, since AAO may be misleading in this context.

2. It is still unclear to me why the authors chose specifically the SNPs listed. Could there be other SNPs that were not covered in this analysis that still could be relevant? Do the authors plan to follow up on this issue?

3. Why was Isoform-2 of the gene looks at and not other isoforms?

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