Reviewer's report

Title: Association analysis of a highly polymorphic CAG Repeat in the human potassium channel gene KCNN3 and migraine susceptibility

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Reviewer: George Kirov

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General
The authors have examined the distribution of alleles of a highly polymorphic CAG repeat in migraine sufferers and controls. This polymorphism has been examined in a number of studies in several disorders, but it does appear to be a good candidate for migraine. I was asked to comment specifically on the sample size. I regard this as a decent sample size which should not constitute a problem for publication. Very similar samples sizes were used in some recent papers on this condition, e.g. the Moessner et al 2005 paper that I discuss in more detail below.
I was also asked to provide a general review of the paper. There are a number of problems and overall it appears that this paper was not written well and some of the more up-to-date references are not mentioned. However all this can be easily amended by the authors. Here are some specific remarks.
1. The authors should describe both CAG repeats in the gene in slightly more detail (the other repeat is much less polymorphic)
2. The authors should cite more studies that have examined ion channels in migraine, or perhaps just provide a reference to a review of such studies. Most such studies have been negative. This will provide a better context for their own work.
3. On p4, second paragraph: this is highly confusing. The authors have tried to cram too much information into a single sentence. They should provide more information on the CACNA1A gene in familial migraine.
4. The authors have not mentioned that FHM2 is now known to be caused by mutations in the ATP1A2 gene (although the reference is in their reference list, ref 11). This is important for two reasons: It shows that two familial forms of migraine have now been shown to be caused by mutations in ion channels. Secondly, their argument that the KCNN3 gene is close to the locus for FHM2 becomes invalid, as the gene for this condition is identified.
5. The prevalence of migraine is given as 33% in women and 13.3% in men on page 3, but as 12% on page 12. These are two different studies, which not surprisingly, found different prevalence rates. They can be cited together, or the authors could choose one of them, but the way they are cited can confuse the reader.
6. On page 12 the authors state that other studies have shown that the long CAG repeats are more common in patients with schizophrenia and bipolar disorder. They cite two of the early studies. There have been numerous studies since then and overall the conclusion is that this repeat is not involved in the pathogenesis of either of these psychiatric disorders. The authors could instead cite a meta-analysis (Glatt et al, 2003) that draws that conclusion.
7. The authors probably submitted their paper before they became aware of the work by Moessner et al, (Headache, Feb 2005, 45:132-136). These authors examined this repeat in a similar number of migraine patients and controls from Germany. Obviously this work needs to be cited and discussed in the revised manuscript.
8. It appears to me that the p-values in Table 1 (and text) are not correct. I estimate that when the number of alleles longer or shorter than 19 repeats in patients and controls are compared, the p-value is 0.15, and when migraine patients with and without aura are compared, it is 0.4. Although these are not significant either, they differ from what the authors have stated.
Despite the many points I raise above, I actually think that this paper should be published (after extensive revision). The reason is because the Moessner et al 2005 paper performed a very similar work but concluded that the repeat is involved because the 15 CAG allele was extremely rare in controls and about 1.6% in patients. To me this looked like a false-positive result and the present paper confirms this, by showing a similar frequency of this allele in their patients and controls. This will be useful for other teams planning to replicate the results. I think that negative association papers should be published, as otherwise we will see publication bias.

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

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

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests