Reviewer's report

Title: Two-stage case-control association study of dopamine-related genes and migraine

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Reviewer: Carles Vilarnio-Guell

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Major Compulsory Revisions

The manuscript of Corominas et al. report an association study for eight genes involved in the dopamine system in a migraine sample series from Spain. Their first cohort indicated a possible significant association; however replication in an independent cohort was not supportive of these findings. The SNPs associated in the first cohort were not significantly associated in a German study indicating a likely false positive nature for the association. Therefore this is in essence a negative association study, and as such over 3,500 words to describe the study are excessive. The authors should consider rewriting the study as a short report. Just to highlight this excess, the statistical descriptions are an overkill, power analysis in the methods are unnecessary, and the equipment used to extract and measure the concentration of their DNA is irrelevant. Also the long and convoluted description of positive findings in the results and discussion is inappropriate since the association is not replicated in the second cohort.

In addition, we feel that the study is not comprehensive. The authors have attempted to cover a wide range of dopamine genes but have traded in genetic coverage for this increased number of genes. The authors have used a minor allele frequency of either 0.15 or 0.25; far over the standard 0.05 used in most studies. On top of these decreased capture of genetic information they have not attempted to re-genotyped or identify alternative SNPs for any of those that failed genotyping. In the extreme case, they did not even have a single tagging SNP in DRD4 while still presenting data on the tables and mentioning it in the text. Others like SLC6A3 had 5 tagging SNPs ungenotyped out of the 9 SNPs originally selected; this reduced the gene coverage to 0.45 according to the authors’ standards, but will be much reduced assuming a MAF of 0.05 rather than the 0.25 selected for this gene.

Discretionary Revisions

We suggest to the authors to reconsider this study, maybe it would be more appropriate to take the focus of out the high number or genes and analyze one or two genes comprehensively.

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