Reviewer's report

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

Version: 2 Date: 23 July 2009

Reviewer: Carles Vilarnio-Guell

Reviewer's report:

The authors have not addressed but argued most of the points provided in the first review of the manuscript. Therefore the comments from the first review still stand. In addition some of the arguments provided by the authors are flawed and are not appropriately addressing the comments.

Re: Full article vs short report

The authors argue the need for a full article due to:

Novel design – There is nothing novel about a genetic association using candidate genes approach.

Genetic coverage of introns and exons – Tagging SNPs have been used for years, they may have not been used in the field of migraine, but tagging SNPs are certainly not the latest breakthrough in genotyping approaches.

Population with enough power – Nowadays a series of 263 cases and 274 controls for a highly prevalent disease is by no means a large series.

Comprehensiveness of the study

The authors argue inappropriately capturing the genetic information on sample size and budget limitations. If the authors can not perform these scale studies they should limit themselves to a more manageable size study as suggested at the end of the original comments, this is not a good excuse to perform badly design association studies.

In addition, increasing the MAF of the SNPs selected do NOT increase the power to detect significant association unless the association are driven specifically by those SNPs or those in LD with them. Failing to capture genetic information can in no way increase the likelihood of identifying a true association. This is a flawed analysis, what the authors should have analysed is the power to detect positive association with the selected SNPs assuming the presence of all SNPs in the gene, not only those with the convenient MAF. Also if these SNPs are in LD with each other as the authors claim, they would not have an effect in the number of tagging SNPs necessary for a comprehensive analysis, which it is obviously untrue.

The authors accept suboptimal coverage in three out of eleven genes... however
they only have data for nine genes. Of those, one was not genotyped at all, three were tagged using a 0.25 MAF approach, and all together the authors failed to genotype 15 SNPs. Therefore the suboptimal coverage in three genes in clearly an understatement, and even if this study is the most complete analysis as stated by the authors is by no means complete.

**Level of interest:** An article of limited interest

**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