Reviewer’s report

Title: Genetic polymorphisms involved in dopaminergic neurotransmission and risk for Parkinson's disease in a Japanese population

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Reviewer: George Mellick

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This manuscript reports on a case-control association study of four isolated single nucleotide polymorphisms (SNPs) from four genes MAOB, COMT, DRD2 and DRD4 involved in dopamine metabolism or transmission in relation to risk for Parkinson's disease (PD) in a relatively small Japanese sample of 238 PD cases and 369 hospital-based controls.

While no significant genotype associations were reported overall, there were modest associations reported for the COMT SNP (rs4680) with a trend to increased risk for PD with increased possession of the alternative A allele (p=0.045), and a trend to reduced risk of PD in individuals possessing the alternative G allele at the MAOB rs1799836 locus, the latter being X-linked and not reaching significance in either males or females when analysed separately. The authors also assessed for gene-environment interactions between these SNPs and cigarette smoking (self-reported as ever or never by the subjects). Finally an analysis of risk associated with the increasing dose of reportedly "at-risk" alleles is performed.

The manuscript is clearly written (although probably a little lengthy given the content) and the data analysis is acceptable given the experimental design. However, there are several important and significant limitations to this study that make it difficult for this reviewer to decide on whether the work is “a sound addition to scientific knowledge” or not. Some of my concerns are explained below

1. A long history of case-control association analyses highlight the likelihood that modest associations, such as the ones revealed here, are merely chance findings. Many reviews could be cited that list the reasons for this. The two SNPs with reported trends to association in this manuscript (rs4680 and rs1799836) have been previously studied in many different populations (including Asian populations) and meta-analyses provide no evidence for association (one can refer to the PDGene website for this information [Lill CM, Roehr JT, McQueen MB, Bagade S, Kavvoura F, Schjeide BMM, Allen NC, Tanzi R, Khoury MJ, Ioannidis JPA, Bertram L. The PDGene Database. Alzheimer Research Forum. Available at: http://www.pdgene.org/]. Of course it is possible that there are reasons why the distribution of the COMT and MAOB alleles are different in this specific case-control sample, but it is probably not specifically related to PD-risk.
2. It is difficult to assess the evidence for gene x environment interactions when the environmental variable is crudely measured (such as an ever/never self report) as it is usually important to probe for dose effects and other evidence against chance findings when trying to interpret the results of such an analysis. In this case it is unclear what to make of a p=0.06 for an interaction between smoking and rs4680 genotype status.

3. There are many different genes involved in dopamine metabolism and transmission and each gene has many commonly-occurring polymorphisms. While it is possible to make valid arguments as to why these specific SNPs could influence risk, it seems scientifically unsatisfying to test these without being comprehensive in the approach. The scientific community has moved away from this approach in recent times. As to whether dysfunction of dopaminergic neurotransmission in the CNS impacts on the risk for PD, I think the jury remains out. Some researchers have their doubts (see J.E.Ahlskog “Beating a dead horse: dopamine and Parkinson disease”. Neurology, 2007, 69(17), pp1701-1711 for a discussion on this topic).

Some more specific question and comments that the authors may wish to consider:

(a) What was the age-at-onset for the PD cases in the study? How many had a family history of PD and did any have PARK2 disease?

(b) Is it possible that the increased smoking exposure reported in the hospital-based controls relates to these individuals having smoking-related illnesses rather than a reduced risk of PD due to smoking (thus the apparent protective effect of smoking in this sample may be inflated).

(c) The presentation of the gene-environment interaction data in Table 3 is rather confusing (particularly regarding the choice of the reference group (which seems to be ever smokers with a different choice of specific genotype for each SNP locus).

(d) The idea to investigate the load of “at-risk” alleles is an interesting one, but I feel that having such a small reference group (with only 2 cases and 6 controls who do not possess any “at-risk” alleles) somewhat invalidates this. Perhaps there would be better ways to examine this data.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

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