Reviewer's report

Title: NQO1 gene rs1800566 variant is not associated with the risk for multiple sclerosis

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Reviewer: Carles Vilarino-Guell

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Agundez et al present the association of one SNP located in NQO1 with MS susceptibility risk, disease course and severity in a Spanish population. This is a rather simple study attempting to replicate some positive association previously described in MS patients from Greece. The study is well design and the conclusions drawn are overall appropriate however the length of the manuscript is excessive for the message it conveys.

Major Compulsory Revisions
None

Minor Essential Revisions

In the abstract background the authors should mention the previously described association for NQO1 in MS, as it is one of the main reasons to do their study.

Some references seem to be missing. Most noticeably:
“A number or reports have suggested a possible role of oxidative stress and lipid peroxidation in the inflammatory processes and in the pathogenesis of MS.”

And
“The enzymatic activity of NQO1 depends fundamentally on a single nucleotide polymorphism (SNP) at the NQO1 locus, rs1800566 (C609T), which produces a proline-to-serine substitution at amino acid 187 (P187S)”

At the end of the introduction the authors claim “In an attempt to identify additional factors involved in MS susceptibility, we genotyped the SNP rs1800566 in the NQO1 gene in Spanish MS patients and healthy subjects” which is inaccurate. The authors are not attempting to identify additional factors but attempting to replicate a previously described association in an independent population.

Comprehensive table legends must be added to define what the data presented is. For example, in table 3 the first genotype count is 178 (61.4, 55.8-67.0), what those three numbers are escapes me. In addition these tables should be simplified to facilitate reading (suggestion: remove gender specific analysis since nothing is significant), and should provide n and % for genotype and alleles. It is also unclear what statistical method was used for each group of analysis.
The authors claim “genotype frequencies were not influenced by gender”, but they actually mean that association between the variant and disease risk was not observed when analyzing gender separately. This should be addressed.

They also failed to identify an association with “each MS phenotype” when they mean disease course. Although they are following the model of Stavropoulou et al, analysis of RR and SP patients separately is not appropriate (although common) as disease duration has an effect on the phenoconversion from RR to SP. We suggest the authors analyze these two groups together and call them RR onset.

In the discussion the authors present the limitations of their study, two of those: small sample size and lower than expected OR are dependent on each other and therefore the same. We suggest the authors combine these two caveats into one. (ie. if the OR was lower than expected our sample size would not be sufficient to …)

Maybe I did not get enough coffee today, but I could not find table e-2.

Although grammatically correct, some language polishing may be required. As example:
“Some experimental data suggests” would be better as “It has been suggested/proposed/…”

“These data suggest that NQO1 rs1800566 polymorphism is not related with the risk for MS” would be better as “Our results indicates that NQO1 rs1800566 does not have an effect on MS disease risk”

In addition, the authors used the word “related” when meaning “associated”, which should also be corrected.

Discretionary Revisions

There are several sections of this manuscript which are not entirely relevant to the study and could be easily removed. Including from “It has been suggested that findings from…” in the first paragraph until the end of the second paragraph. The last three lines of paragraph three as well as Table 1. In addition, the first paragraph of the discussion, which is a repeat of the introduction; and the third paragraph of the discussion are also irrelevant to this study.

Similarly, sentences such as “This enzyme is encoded by the NQO1 gene (chromosome 16q22.1, Gene Identity 1728) (link http://www.ncbi.nlm.nih.gov/gene/1728)” Appear unnecessary and should be excluded.

Or “Genotyping for rs1800566 allelic variant was performed … using TaqMan Assays (C2091255_30, Life Technologies, Alcobendas, Madrid, Spain) designed to detect the SNP rs1800566”; in this sentence “allelic variant” and “designed to detect the SNP rs1800566” is redundant.
Also “Mean age at onset of MS did not differ significantly between patients carrying NQO1 rs1800566 C/C (mean + SD = 32.1 ± 10.2 years), C/T (mean + SD = 33.5 ± 11.6 years) and T/T (mean + SD = 32.4 ± 12.0 years), (p= n.s. for the comparison of carriers vs non-carriers of variant alleles). The last section in brackets is redundant.

The authors should be able to substantially improve this manuscript and make it more concise and easy to read by carefully addressing these little issues, and removing unnecessary paragraphs from the introduction and discussion.

We also suggest the authors do not refer to the study by Stavropoulou et al as “the Greek study”.

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

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

**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