Author's response to reviews

Title: No evidence for association between polymorphisms in GRM3 and schizophrenia.

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Author's response to reviews: see over
The editor
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Dear Sir / Madam

Re: MS 1887460526146881, 'No evidence for association between polymorphisms in GRM3 and schizophrenia.'

Thank you for the opportunity to resubmit this manuscript to BMC Psychiatry. We have addressed all the reviewers comments as described in the accompanying sheet, and now hope the manuscript is suitable for publication.

Yours faithfully

Michael O'Donovan
Professor of Psychiatric Genetics
Reviewer 1.

We note that this reviewer suggests no major revisions. We have undertaken the minor essential revisions suggested, i.e. we provide a schematic showing the position of the SNPs, have made the typological correction in table 1, and provide dbSNP IDs (rs numbers) for consistency for all markers SNPs.

Reviewer 2.

Major compulsory revisions.
1. The reviewer appears to believe our assertion that it is necessary to consider heterogeneity rests upon data from a paper by Chen et al 2005. This is mistaken. Our claim is based upon a synthesis of the findings of Egan and colleagues (2004) and Fujii and colleagues (2003). In these studies, different alleles of the same marker were associated in Japanese and African Americans while Caucasians were not associated with either allele but were with an entirely different marker. If one wishes to interpret these findings as supportive of true association rather than chance, it is necessary to invoke heterogeneity. We have adjusted the text (see page 5 para 3 where we now state ‘What is, however, abundantly clear from two of the studies [6,7] is that it is necessary to invoke genetic heterogeneity ….‘) We hope there is now no further confusion. Given the requirement to postulate heterogeneity, we decided to select the markers based upon findings in samples that are ethnically similar to our own (clearly stated on page 5 para 3) and we agree our findings have no comparison with the study of Chen, but nowhere do we claim they do. We do however discuss that study (page 4, para 2) and see no value in repeating the matter in the discussion.

2. The reviewer states we did not clearly state how we assessed significance. In fact we clearly stated in the methods that haplotype analysis was performed using the program EH plus which is a widely used and widely available program for such analyses. Under this same section, the reviewer says it is ‘too much straightforward to make direct comparison of P values obtained by two different statistical tests’. This is a surprising comment of no apparent relevance. At no point do we make direct comparisons of p values, we would have no idea how to do that. Instead, we discuss at length the complex issues like what constitutes replication while examining the pattern of the data across the relevant studies.

Minor essential revisions.
1. The nomenclature used for the SNPs in all tables and throughout the text has been altered to the dbSNP IDs (rs numbers) for consistency.

2. The typographical error has been corrected.

3. We clearly state that the program EH plus was used for haplotype analysis (page 7 para 1). This widely used program uses the EM algorithm. The reviewer is correct that the total numbers of genotypes for each SNP are slightly different, and this is due to PCR dropout. In table 2 where the authors compare Cardiff haplotypes with those of Egan et al, the number of controls in the analysis ranges from 623 to 693 and the no. of cases ranges from 582 to 652. It would complicate the table to include these numbers as well. However, we have provided the ranges in the legend of table 2 (p19).
4. The Idmax program within the GOLD software package does actually calculate $D'$ and $r^2$ values. We make this clear and have changed the text. The following text has been altered in the methods, page 7, paragraph 1

5. “312” is the correct number of double genotypes which were compared across the seven markers. There were 10 PCR failures from a total of 322 reactions.

6-7. The typographical errors have been corrected.

8. Vertical lines have been removed from tables 1 and 2, and horizontal lines have been added to table 3 for the readers' convenience.

9. All values in tables have been corrected to two decimal places.

10. The frequency of allele 1 of the last SNP in table 1 has been corrected from 0.75 to 0.76.

**Discretionary revisions.**
Changed as suggested