Author's response to reviews

Title: FOXP2 gene and language impairment in schizophrenia: association and epigenetic studies

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Author's response to reviews: see over
Major changes from the previously submitted paper are indicated in the comments below. Since the main text was revised thoroughly, minor changes are not highlighted in the main text of the paper.

Referee 1:

The paper is generally well written. The methods appear straightforward. There are a few issues which require clarification: 1-Describe the biological significance of rs2253478 SNP and its association with the item Poverty of speech, 2-The authors should further explain their recommendation about a more exploration of language variables in schizophrenia, 3-The authors should provide any other published reports on FoxP2 protein levels in schizophrenic samples.

As required by referee 1, potential biological significance of rs2253478 has been clarified in the Discussion section (page 11). Briefly, the functionality of this polymorphism has not been addressed. It is not located in the promoter region, and there is no information of a role as enhancer of splicing. It could be in linkage disequilibrium with another polymorphism being the causative factor. Regarding our recommendation about a more exploration of language variables in schizophrenia, after our results we consider it would be very important to perform a rigorously study of language variables in schizophrenia and polymorphisms of FOXP2. As far as we know, we don’t know about any report of FOXP2 protein levels in schizophrenic patients.

Referee 2:

Major Compulsory Revisions:

1. The authors treat an essentially disappointing SNP-haplotype association study on equal footing with interesting investigations of FOXP2 methylation and expression in the human brain. I would propose that the authors significantly shorten the association study part of their results section and place Table 1, which is a comprehensive listing of essentially non-significant data, in the supplement. In this way, this data will still be available, without distracting the reader from the core message of the manuscript.
The authors agree that the table may be distracting the reader from the main idea, so it was conveniently moved to the Additional file 4.

2. The background section seems to direct the reader towards a study of Darwinian selection, while the data relate to an entirely different subject. The authors should re-write this section to point the readers to the pertinent literature relating FOXP2 gene function to neurodevelopmental disorders involving, among other features, impaired language development. A recent review by D.F. Newbury and co-workers (Genome Med. (2010) 2, 6), in particular the papers mentioned in their Table 1, may help to define the scope of this manuscript. The latter may also include Autism Spectrum Disorder and Gilles de la Tourette Syndrome as manifestations of perturbed language development in humans. As a consequence the list of references should be drastically reduced.

The authors decided to start the background section with some evolutionary explanations of the origins of schizophrenia and the way FOXP2 gene has evolved since the separation of the human and chimpanzee lineages, to emphasize why FOXP2 was selected for an association study involving this illness. The relationship between the gene and developmental disorders has been widely accepted as well as the object of many revisions, including the one of Newbury et al. That is why we focused our background in the evolutionary-aspects of schizophrenia, a uniquely human illness, and FOXP2 gene, which is related to one specific human trait. It is clear for us that FOXP2 is not exclusively a “language gene”, but certainly it must play a role in this trait, as all the research literature points to. Newbury citation had not been previously-introduced, because by the time the first draft of our paper was finished, it had not been published.

3. Likewise the abstract is not intelligible and does not really summarize the findings reported. Therefore the abstract needs to be re-written entirely.

According to our explanation of the point number 2, we have slightly modified the abstract to clarify the ideas.

Minor essential revisions:
1. Figures 2 and 3 seem to be switched (relative to the text of the results section and the Legends).

This was properly changed.

2. On page 11, line 9 from bottom, the authors indicate that the have tested “structural variations of the FOXP2 gene ...”. From what follows I guess they mean gene mutations (repeat expansion) or SNP haplotypes. The authors should clarify this and enter the appropriate description.

Since this part was confusing, the text was properly changed in order to be clearer.

3. At multiple instances the language of this manuscript differs from common English usage. Improvements are clearly in need.

The main text was thoroughly revised.

Referee 3:

Major Compulsory Revisions

1) The number of the cases is too low in methylation and expression studies (experiments in figures 3 and 4). Without increasing the number of the cases, appropriate statistical analyses cannot be done.

The authors were aware of the low number of cases in the methylation study. That is why no statistical analyses were performed in these experiments and why we recommend in the last paragraph of the discussion (page 13) that further studies with a larger sample should be done in order to confirm our results.

2) The degree of methylation seems too variable among the cases (both in controls and patients). There is no information available regarding autopsied cases (for example, drug therapy age and sex etc.) Such information is important because many drugs used for Schizophrenia have some effect on methylation of genes.
The comment is certain. Unfortunately, exact information concerning therapy of the cases was not available for the authors.

Minor Essential Revisions

1) *Figures 2 and 3 should be correctly numbered.*

This was properly changed.