Reviewer's report

Title: Case-control and family-based association studies of candidate genes in autistic disorder and its endophenotypes: TPH2 and GLO1

Version: 1  Date: 4 December 2006

Reviewer: Maricela Alarcon

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MS #: 248980651137726

Title: "Case-control and family-based association studies of candidate genes in autistic disorder and its endophenotypes: TPH2 and GLO1"

Date: December 4, 2006

The manuscript entitled, 'Case-control and family-based association studies of candidate genes in autistic disorder and its endophenotypes: TPH2 and GLO1', tests the association of two candidate genes with the qualitative diagnosis of autism and a few biological autism-related traits. The genes involved in the etiology of complex disorders, such as autism, are largely unknown, so this report is of special interest to those of us in this field. No major changes are necessary, but I have a few comments that may help the presentation of the results or expand the Introduction.

Compulsory revisions:

Regarding the presentation of results –

Table 2 shows the TDT results for single and haplotype tests for SNPs at TPH2 and the FBAT results for the autistic patients.

Table 4 shows the case-control results as a function of country-of-origin, TDT results for affected and unaffected siblings and FBAT tests for autistic patients and unaffected siblings.

If the same sample is used throughout the study, why is the presentation of the results not consistent? Were different tests performed on the 3 SNPs? The only difference between the gene results should be the haplotype tests and the endophenotypes tests for TPH2. Please clarify.

Minor essential revisions:

It is not necessary to include ‘n.s.’ adjacent to the reported p values

In the Introduction, the authors provide a brief definition of ‘endophenotype’ (“clinical, biochemical or morphological characteristics especially frequent among affected individuals”, pg 4). Please expand the definition to include the additional criteria that must be met before a trait can be considered an endophenotype. For example, the trait should be more frequent in unaffected relatives of affecteds versus the general population, the trait must be heritable, etc.

Are there any linkage studies that support the involvement of regions 12q21.1 and 6p21.3-q21.2 in autism etiology?

Please provide a reference for the statement, “… perform quantitative-trait analyses employing the best-characterized endophenotypes in autism research, namely cranial circumference, 5-HT blood levels and urinary peptide excretion rates” (pg 5). Also, please describe how these traits are characteristic of affected individuals versus the general population and provide support suggesting that they will be adequate for genetic analysis (e.g., heritabilities).

Lastly, a minor point, in Table 1, the authors show there are 60 individuals with autism, 14 simplex families, and 23 multiplex families from the AGRE sample. If there are 15 simplex families and at least 46 affecteds in the multiplex families (i.e., two per family), there would be a total of 61 individuals with autism. The table states there are 60. Perhaps there is a typo.

Discretionary revisions:
The authors had access to an Italian affected sample as well as a Caucasian-American sample. Although large samples are necessary for statistical tests, the pooling of samples of distinct ancestry may increase heterogeneity and thereby decrease the chance of finding a real association. Was any attempt made to test for heterogeneity between the Italian and Caucasian-American samples since the data were pooled for the TPH2 analysis?

The gold-standard instrument in autism research is the ADIR. Unfortunately, the Italian version of this questionnaire was not available for the corresponding sample. Thus, the association analysis of TPH2 with the binary motor/verbal stereotypies (as surrogates for repetitive/stereotypic behaviors) may not have been adequate. Could the authors focus on the Caucasian-American sample and test for quantitative association of this trait using items from the ADIR? Even if the sample is small, it may be possible to see a trend for association and determine whether it would be worthwhile to obtain additional families from AGRE for an expanded analysis.

What next?: Accept after discretionary revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.