Reviewer's report

Title: No Evidence for the Association of DRD4 with ADHD in a Taiwanese Population Within-Family Study

Version: 1 Date: 13 April 2005

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General

The MS "No evidence for the association of DRD4 with ADHD in a Taiwanese population within-family study" by Brookes et al. describes a study using two DRD4 VNTR polymorphisms on subjects recruited in Taipei. The reason for this study is to test the association of these polymorphisms with ADHD, documented in a number of prior studies, mostly in Caucasian ADHD probands. The 7-repeat DRD4 allele associated with ADHD is at low frequency in Asian populations, and hence an analysis of Taiwanese ADHD subjects is an important addition to the literature. The current Taipei ADHD population had previously been shown by this group to be associated with a VNTR polymorphism in the dopamine transporter gene.

While the authors finding of no association with DRD4 using a within-family approach appears sound, there are a number of corrections/additions that would enhance the value of this publication, and lead to better support for this conclusion. Specifically:

Introduction

1) The introductory statement that "Their data suggests that in Asian populations the 4-repeat allele is a derivative of the Caucasian 7-repeat allele (referring to Ref. 19)" is incorrect. This Ref. (and prior work, i.e., Ding et al., PNAS 99: 309-414, 2002) proposed that the 2-repeat allele, common in Asian populations, is a 7-repeat derivative. Further data describing this derivation is presented in Ref. 35.

2) While the authors discuss Ref. 17,18 to cite prior work on DRD4 in Asian ADHD populations, another recent reference was not cited (Leung et al., Amer J Med Genet. 133B:54-56. 2005). Given that the authors results differ from these prior publications, a better (and accurate) description seems warranted.

Method

3) A discussion of the low average IQ scores in this sample appears warranted, either here or in the Discussion. Low IQ ADHD probands are usually excluded from genetic studies, since non-genetic effects (such as minimal brain damage) can lead to a diagnosis of ADHD. Including low IQ probands will likely decrease the power to find genetic effects.

Results

4) While Table 1 is useful, this is data from only 45.6% of the 216 ADHD probands (i.e., the ones in which both parents are available). While tests such as the HHRR and TDT can be useful in protecting against unseen admixture, they suffer from other errors. For example, even small genotyping errors, known to be a problem at this locus, can introduce positive (and negative) results (see Mitchell et al., Am J Hum Genet 72:598-610, 2003). Additionally, in light of published bias in
selecting only trios for genetic analysis in behavioral disorders like ADHD (see West et al., Mol Psychiatry 7:962-966, 2002) it would be useful to have the genotype of all ADHD probands. With less than half the families analyzed, it is unclear if this is a random sample. The complete ADHD genotypes/allele frequencies could then be compared to published Asian genotype frequencies (above), and to the "selected" subset in Table 1. It is perhaps time to do both population and family-based analysis in the same sample before any conclusions can be drawn.

5) In Table 2, how were the DRD4 haplotypes determined? While the two VNTRs used are in strong LD in Caucasian 7-repeat populations, they are not in strong LD in Asian 2-repeat populations (Ding et al., above; Ref. 35). Was phase inferred? Please clarify.

Discussion

6) The authors list a number of possible explanations for their results, all of which are valid. Two more should likely be added. First, it is unclear if comparable ADHD samples are being investigated, since all prior work utilized individuals with higher average IQ scores than presented in this study (as noted above). This should be resolved or discussed. Second, since an association with DAT has already been observed with this sample, it is possible that there is reciprocity in ascertainment (i.e., positive DRD4 results have negative DAT results and vice versa), as reported in some prior studies. Such results might be expected if ADHD is the result of multiple genes/environmental interactions.

In conclusion, while this is a worthwhile concise study, a) additional genotyping/allele frequency data (as discussed above) needs to be presented, b) a number of errors corrected and c) more extensive discussion of relevant literature included. With this additional DRD4 data on all samples, the relevance of the study would be enhanced greatly, and allow better interpretation of the results in the context of prior work.
Declaration of competing interests:

I am currently applying for patents relating to the DRD4 gene. They should not effect my unbiased review of this MS.