Author's response to reviews

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

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Author's response to reviews: see over
Dear Sir,

Thank you for the reviewer comments. We have revised the manuscript in order to address the concerns of the reviews as follows:

**Review 1:**

1) As suggested, the analysis of the dataset was re-run with the exclusion of the 13% of the sample with IQ’s under 70, and results added to the revised manuscript. This analysis does not alter the conclusions of the study.

2) Many of the previous datasets have included all available ADHD probands. Typically previous positive studies have included a similar proportion of around 1:3 inattentive to combined subtype. There is no evidence from previous papers indicating a specific association with the inattentive sub-type. For example, in the original publication from Swanson and colleagues they used a sample of combined subtype with no significant co-morbidity. We now include a brief discussion of this point.

3) We now report that there were no mendelian errors detected following genotyping and that the sample is in H-W equilibrium. Genotypes were obtained from 87% for the VNTR and 96% for the 120bp repeat markers of the sample and repeated if there was any ambiguity in the genotyping call.

4) We thank the author for this important point. We set out to test whether previously described associations could also be detected in this sample. We now add a comment in the discussion that this analysis does not exclude the possibility of association with other DRD4 markers.

**Review 2:**

1) The reference to the 4-repeat allele rather the 2-repeat allele was an error in the manuscript and we thank the authors for pointing this out. This has been revised.

2) The Leung reference was not available when the manuscript was originally written. We have now added this citation to the manuscript and revised our descriptions of findings from the previous studies in Asian populations.

3) We have repeated the analysis for the IQ>70 group alone (see point 1 above).

4) We agree with the authors that case-control analysis in addition to within family tests of association would be useful. We have addressed the points raised in several ways.
   - Include comparison of allele frequencies in our ADHD probands with published control frequencies for Asian populations.
   - Data is not however from only 45.6% of the probands. TDT and HHRR analysis as implemented in UNPHASED uses allele frequencies to estimate transmission ratios for probands with missing parental genotypes.
   - We included a discussion of the possible selection of less severe or co-morbid cases as described by West et al., 2002).
- We have no evidence for biased genotyping but now include the reference to potential bias effects for negative association with minor alleles (less than 50% minor allele frequency)

5) Haplotypes were determined using HHRR UNPHASED, as was the D’ value.

6) There are several points here:
- We have resolved the issue of low IQ cases (see above).
- We now discuss the possibility that there is heterogeneity between DAT1 and DRD4 with regard to ADHD associations; although there has as yet been no formal test of this in the literature. I would not however agree with the reviewer that genetic heterogeneity is expected if ADHD is the result of multiple genetic and environmental risk factors, since additive/epistatic effects of multiple genes is just as likely.