Reviewer's report

**Title:** Genetic influences on Attention Deficit Hyperactivity Disorder symptoms from age 2 to 3

**Version:** 1  **Date:** 10 May 2010

**Reviewer:** Dorret I Boomsma

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This is a relatively small twin study (312 same-sex twin pairs) of mixed ethnicity (85% Caucasian), in which detailed information at a relatively young age was collected regarding ADHD symptoms. Genotype information for parents and offspring was obtained for a series of candidate genes.

I have a series of questions regarding diagnosis, genotyping and statistical analysis.

**Introduction:** Please note this reference (which reports on age 3 through 12) is missing from (page 3) of longitudinal studies: Rietveld et al. Heritability of attention problems in children. Longitudinal results from a study of twins age 3 to 12. J Child Psychology Psychiatry, 45, 577-88, 2004

**Diagnosis:** page 4 states that parents were invited, page 5 mentions parent ratings: were the twins rated by a single or by both parents? If not: only by mother or could father or mother complete the instrument? Was the same rater assessing the children at both ages? There is a fair amount of literature on rater bias effects (especially contrast effects for ADHD) that should be discussed with respect to this study.

What is the correlation between the 2 assessment instruments (within time points)? A bivariate genetic analysis should establish if it is justified to sum the two scales, and even then it is probably more powerful to model the association with genotypes within the bivariate model than simply with sum scores. Sum scores have the additional disadvantage that it will be difficult for the field to replicate any findings, as most studies will probably use only of the instruments and not both.

**Genotyping:** 31 polymorphisms (table 1) and 19 left in table 2? 9 SNPs were dropped, or 12? Are all VNTRs analyzed as dichotomous polymorphisms?

**Results and analyses:** Please provide twin correlations separately by sex and test for sex x gene interactions. The presence of additive genetic effects only is unusual for ADHD, which often shows genetic dominance. Please discuss (in view of sample size and statistical power).

**Association analysis:** first establish whether there is population stratification, based on the within-families test and then proceed with total association. As the
sample is of mixed ethnicity, would the authors expect stratification? How were MZ twins treated in the within tests? The df somehow seem to suggest that all data were used in this test, but MZ twins obviously do not provide information in the within family test. How were MZ data treated in the overall test?

Provide information on power to detect association and on power to test for differences in association.

Results & table 3: please note that the df in the table are not the df associated with the test statistic. Based on chi-squared values and p-values in the table, the tests sometimes seem 2 degrees-of-freedom tests and sometimes 1 df tests. As noted above the AW test cannot be based on the same information as the AT test and the treatment of MZ data is unclear.

The multiple testing problem (both markers and phenotypes) should be discussed. What are the p-values after correcting for multiple testing? Instead of eye-ball ing results across ages (associations specific to age 2 or age 3) a formal test should be provided (which is relatively easy if association tests are done within the SEM framework).

**Level of interest:** An article of limited interest