Reviewer's report

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

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Reviewer: Ridha Joober

Reviewer's report:

In this study, the authors proposed to investigate the additive genetic variance across age using twin data. They studied a composite measure of ADHD from 2 parents rating scales: CBCL hyperactivity scale and the RRHSPC. They found a very stable heritability of approximately 0.78 with rG=0.78 and a modest non-heritable influence with environmental influence of approximately 0.22, which did not correlate from age 2 to age as rE was only 0.23. They tested for a number of candidate genes, replicating some of their previous finding at age 3 (DAT1 and NET1) and found some new association only at three years of age (5-HTT and DRD4)

This is an interesting paper because it brings the issue of developmental changes in the arena of molecular genetics and with it, many new questions to the literature. The main one is that if one year of age makes a difference in terms of molecular associations, this will create major difficulties, as stratification for age will be important, and conversely, researcher will split their samples into age groups which will increase the problem of multiple testing. However, given that this study is prospective, the association with the 5-HTT and DRD4 genes at age 3 and not age 2 is very interesting and worth reporting.

However, after multiple testing adjustments, the results are negative except for one single SNP. Given what we know about genetic association studies in behavioural disorders the study must be interpreted mainly negative and the single negative result should be considered worth reporting.

It is interesting to see that even previous significant association reported by the authors on this same sample disappeared, indicating that the fluctuation in symptoms might be at play more than the developmental changes in genetic and environmental determinants. This shows how fragile are positive results in this field, rather than the importance of phase specific genes. I think that the authors should also provide the correlation between the 2nd and 3rd year evaluation in their outcome variables. If the correlations are loose, this will strengthen the hypothesis that fluctuation in evaluations might explain the pattern of observed results. In fact genes may be involved in developmental trajectories more than in any cross sectional phenotype. It might be worth exploring this idea.

Otherwise the paper is very well written,
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests