A GWA Meta-Analysis of Continuous Measures of ADHD Symptoms in Nine Population-Based Pediatric Cohorts

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Background

Common SNPs explain a substantial part of the liability to ADHD. Recently we also found that polygenic scores based on a meta-analysis of ADHD clinical diagnosis predict continuous measures of ADHD symptoms in the general population. Next, we performed a genome-wide association (GWA) meta-analysis in population-based cohorts of ADHD symptoms.

Subjects & Methods

Nine population-based cohorts including 17,560 children with genome-wide genotype data had maternal or teacher rated ADHD symptom data at preschool and school age. Each cohort performed a linear regression of the symptom score on genotype dosages (imputed against the 1000 Genomes reference panel), sex, age and principal components. A p-value based meta-analysis was performed as well as gene-based tests and pathways analyses. In addition, two cohorts assessed SNP-based heritability (total n=2,000). GCTA was ran in two cohorts (NTR and GenR) to estimate SNP-based heritability.

Results

SNP-based heritability was 34% ($p < .05$) for teacher and 9% (non-significant) for maternal ratings of Attention Problems. In the GWA meta-analysis, no SNPs reached genome-wide significance, and no genes or pathways were associated with ADHD symptoms at a false-discovery rate of 5%. In both the individual variant and gene-based association tests the top results included the genes PBX4 and WASL. As both genes are expressed in the brain, these seem promising results. A previous study that analyzed all published GWA studies on ADHD found enrichment of genes involved in directed neurite outgrowth; this finding seems to overlap with our result for WASL.

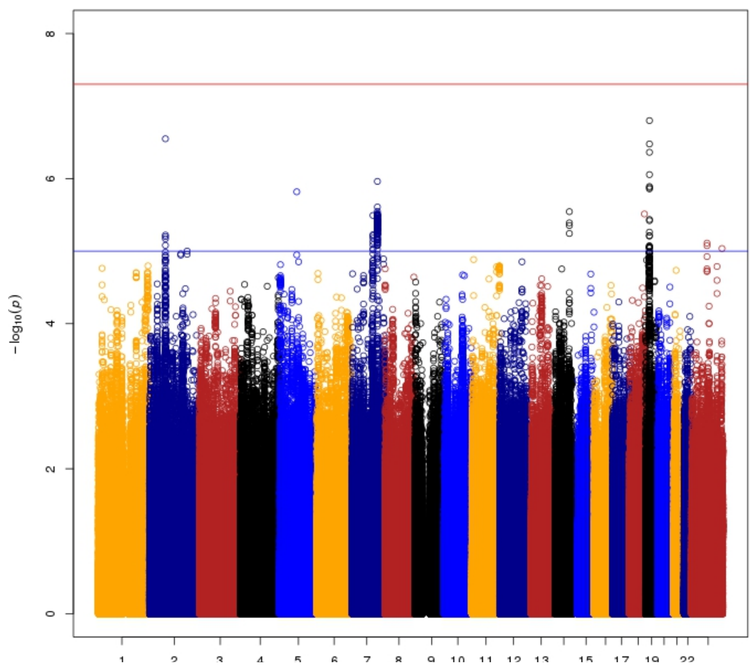

Figure 1. Manhattan plot of the meta-analysis results based on at least 10,000 individuals.

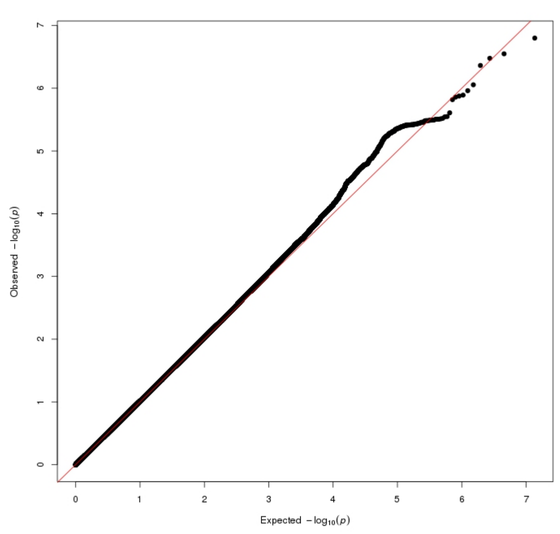

Figure 2. QQ-plot of all meta-analysis results based on at least 10,000 individuals.

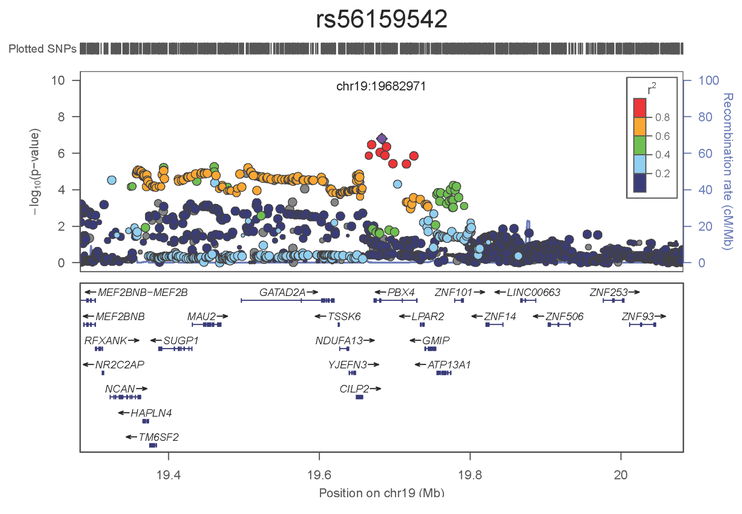

Figure 3. Association plot zoomed in on the region surrounding rs56159542 in PBX4

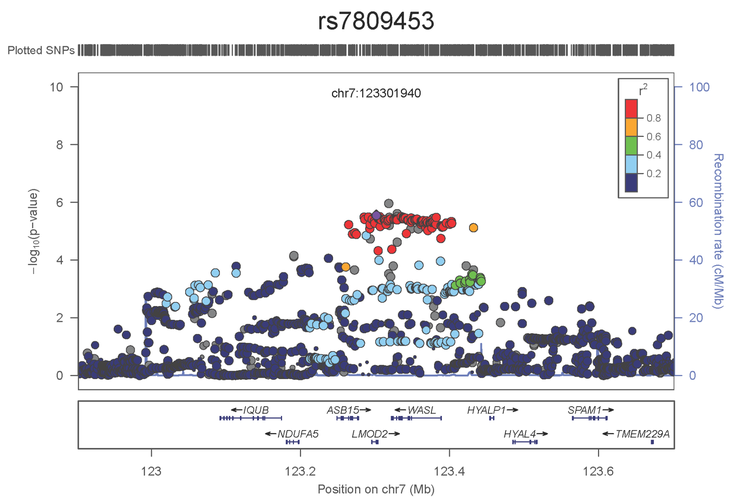

Figure 4. Association plot zoomed in on the region surrounding rs144768233, downstream of WASL.

Conclusion

Our results overlap with previous studies that suggest that genes involved in neurite outgrowth play a role in ADHD etiology. GWA studies of larger samples are needed to detect genetic variants for ADHD; the inclusion of population-based cohorts in GWA studies of ADHD can help to increase sample size and hence improve statistical power for gene finding.

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