Genome-wide linkage and association study of ADHD in adults

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Participants

Linkage: 752 adult sib-pairs from 463 pedigrees registered with the Netherlands Twin Register; mean age 44 years.
GWA: Unrelated Caucasian adults from the Netherlands Twin Register (NTR) and Netherlands Study of Anxiety and Depression (NESDA). 3032 subjects (1090 M) , mean age 47 years.

Phenotypes

ADHD was assessed by the Conners Adult ADHD Rating Scales (CAARS; Conners CK, Erhardt D & Sparrow E (1999)). The ADHD index was used for analysis.

Genotyping, Quality Control and Imputation

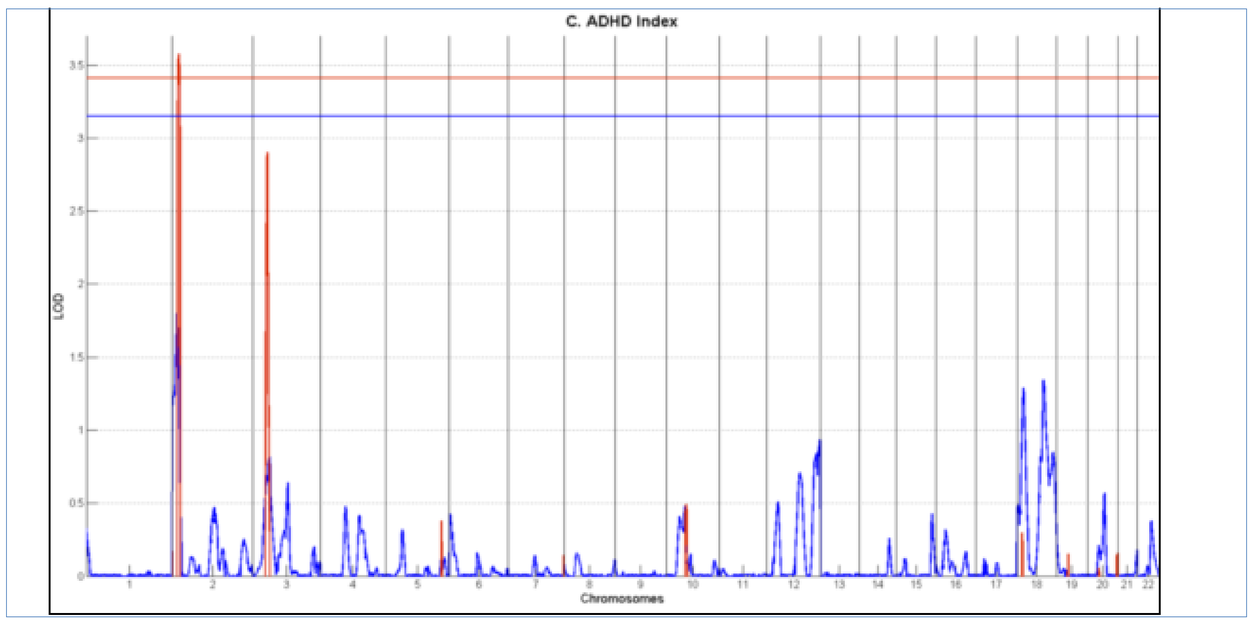
Microsatellite data: Autosomes had 757 markers spaced at an average of 4.76 cM and average heterozygosity of 0.76.
Genotyping was done in various subsamples using partially overlapping marker sets.
SNP data: Perlegen 600k SNP / Illumina Human660W-Quad.
Imputation with IMPUTE to ~2.5 million SNPs [Hapmap build 36].
Quality control of genotype data and imputation was conducted on the full set of all genotyped individuals.

Linkage and Genome-wide association tests

Linkage: multipoint variance components Merlin v.1.1.2 ; parametric linkage using Mendel with age and sex as covariates.
GWA: 2,489,077 SNPs were analyzed with MAF of at least 0.005. Additive model with ADHD index residuals upon regression over sex, age, and MDD status with mach2qtl. From the resulting p-values the genomic inflation factor λ was calculated (1.03).

Linkage

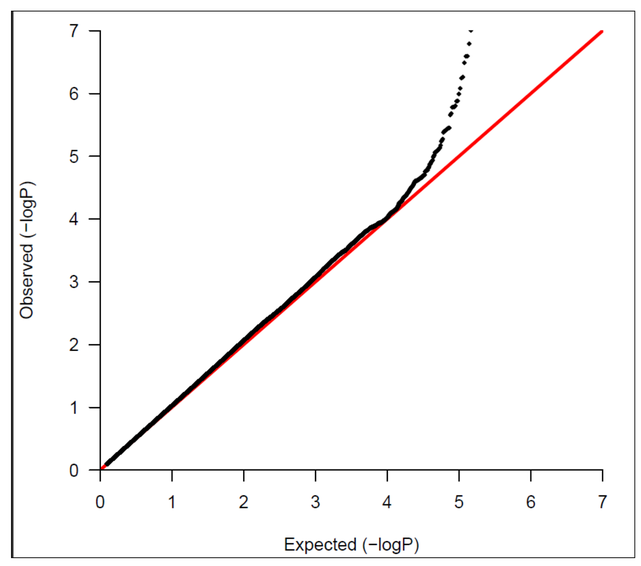
VC (blue) and parametric (red) linkage scan for ADHD index. Same color horizontal lines define the significance level of 0.05 for each method.

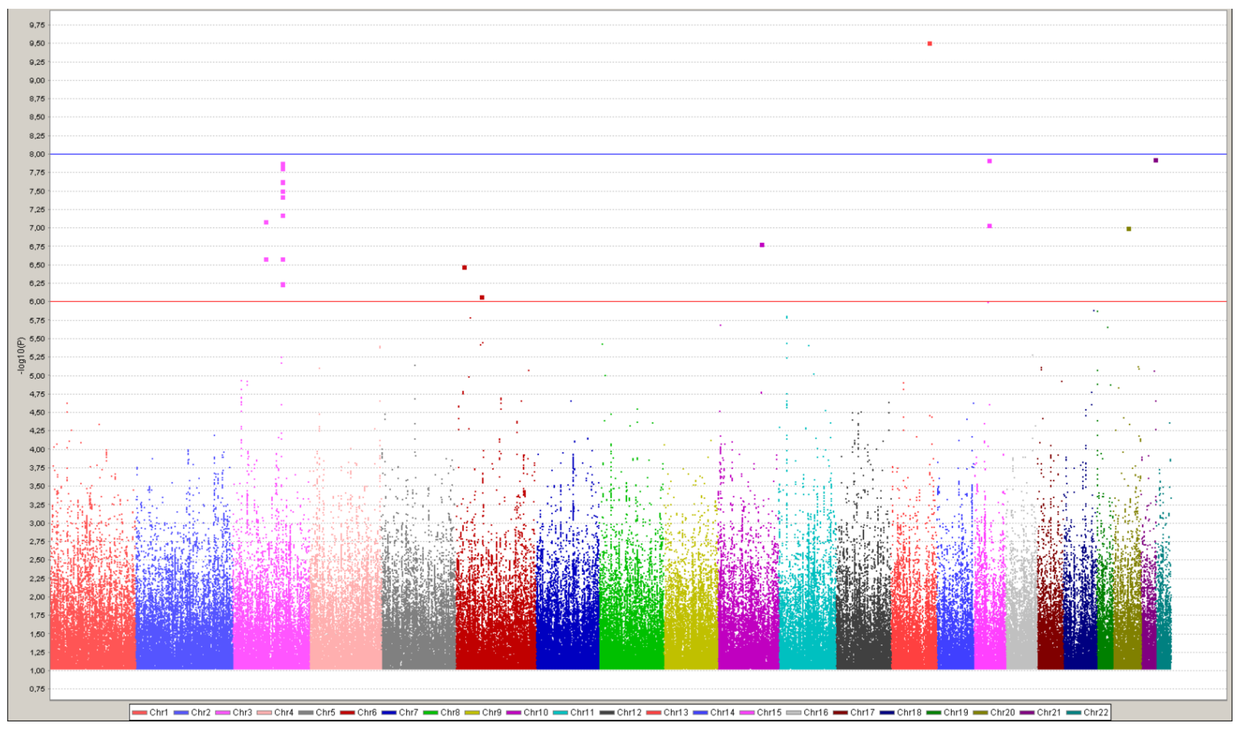


VC did not show significant linkage [max LOD 1.81] on chromosome 2. In the parametric scan, the same area had a LOD score of 3.58 with empirical significance level 0.0372 (95% CI 0.0301-0.0454) and fell between D2S2952 and D2S168 (2p25.1). The second area of interest was on chromosome 3 with max parametric LOD score 2.90 (p_{emp} = 0.1345, 95% CI 0.1213-0.1485) between D3S3038 and D3S1266.

Saviouk , et al. ADHD in Dutch Adults: Heritability and Linkage Study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, under revision

GWA ADHD index: Q-Q plot and Manhattan plot





Results

ADHD is a heritable trait in adults (Boomsma et al. Genetic epidemiology of Attention Deficit Hyperactivity Disorder (ADHD Index) in Adults, *PLoS One.* 12;5(5):e10621, 2010). h^2 = ~30%

Linkage areas on chromosomes 2p25.1 and 3p24.

GWA: top three p-values for SNPs in:

- SLC15A1 (13q32.3;p=3.03x10^{-10})
- CRYAA (21q22.3;p=1.14x10^{-08})
- ALDH1A2 (5q21.3;p=1.18x x10^{-08})

A series of SNPs with low p-values was found on 3q21.1, in the 3'UTR of MYLK (Myosin Light Chain kinase) gene.

Other top hits: CYP2A6 (p=2.2x10^{-6}), PHACTR1 (p=3.25x10^{-7}); CD2AP (p=8.28x10^{-7}); USH1C (p=1.57x10^{-6}); TSHZ1 (p=1.32x10^{-6}); PIAS4 (p=1.33x10^{-6})

Overrepresented pathway : apoptosis (CD2AF, PIAS4, GSTA2, ALDH1A, PLCG2, MYLK)

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