RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

ADHD in Dutch Adults: Heritability and Linkage Study

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Received 13 September 2010; Accepted 23 December 2010

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental phenotype that persists into adulthood. This study investigated the heritability of inattentive and hyperactive symptoms and of total ADHD symptomatology load (ADHD index) in adults and performed linkage scans for these dimensions. Data on sibling pairs and their family members from the Netherlands Twin Register with genotype and phenotype data for inattention, hyperactivity and ADHD index (~750 sib-pairs) were analyzed. Phenotypes were assessed with the short self-report form of the Conners' Adult ADHD Rating Scales (CAARS). Heritabilities were estimated in SOLAR under polygenic models. Genome-wide linkage scans were performed using variance components (VC) in MERLIN and MINX and model-based linkage analysis was carried out in MENDEL with empirical evaluation of the results via simulations. Heritability estimates for inattention, hyperactivity and ADHD index were 35%, 23%, and 31%, respectively. Chromosomes 18q21.31–18q21.32 (VC LOD = 4.58, $p_{emp} = 0.0026$) and 2p25.1 (LOD = 3.58, $p_{emp} = 0.0372$) provided significant evidence for linkage for inattention and the ADHD index, respectively. The QTL on chromosome 2p25.1 also showed suggestive linkage for hyperactivity. Two additional suggestive QTLs for hyperactivity and the ADHD index shared the same location on chromosome 3p24.3–3p24.1. Finally, a suggestive QTL on 8p23.3–8p23.2 for hyperactivity was also found. Heritability of inattention, hyperactivity and total ADHD symptoms is lower in adults than in children. Chromosomes 18q and 2p are likely to harbor genes that influence several aspects of adult ADHD. © 2011 Wiley-Liss, Inc.

Key words: adult ADHD; inattention; hyperactivity; heritability; genome-wide linkage scan

How to Cite this Article:
Saviouk V, Hottenga J-J, Slagboom EP, Distel MA, de Geus EJC, Willemsen G, Boomsma DI. 2011. ADHD in Dutch Adults: Heritability and Linkage Study.
Am J Med Genet Part B 156:352–362.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a pervasive clinically heterogeneous behavioral disorder composed of inattentive-disorganized and hyperactive symptom dimensions [American Psychiatric Association, 1994]. The DSM-IV-TR defines ADHD by a count of symptoms in two dimensions: attention deficit and hyperactivity/impulsivity [Sonuga-Barke, 2005; Chen et al., 2008; Sonuga-Barke et al., 2008]. Confirmatory factor analysis in adolescents demonstrates that the inattention and hyperactivity/impulsivity factors independently contribute variance to the symptoms. However, there is also a general ADHD factor that accounts for the covariation among all symptoms, which implies that there may be etiological overlap of the two dimensions [Chen et al., 2008; Toplak et al., 2009].

Though initially conceptualized as a pediatric condition that manifests in children before age seven, at least 15% of those affected children still meet the full DSM-IV-TR ADHD criteria by age 25 [Faraone et al., 2006]. This rate of persistence depends on the phenotypic definition used and is reaching 65% if the partial remission criteria are applied [Faraone et al., 2006]. Recent evidence suggests that 2.5–7% of adults may experience ADHD symptomatology that may require clinical attention [Fayyad et al., 2007; Simon et al., 2009; Boomsma et al., 2010]. The Conners' Adult ADHD Rating Scales (CAARS) short form measures symptomatology present in inattentive and hyperactive ADHD subtypes (each scale has 9 items), and, independently, overall

Additional supporting information may be found in the online version of this article.

Grant sponsor: Genetic Assessments of Substance Use; Grant Number: 4R37DA018673-06; Grant sponsor: Centre for Medical Systems Biology-2; Grant Number: NWO/SPI 56-464-14192; Grant sponsor: The European Research Council; Grant Numbers: ERC-230374, NWO 480-04-004.

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Published online 3 February 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.b.31170

symptom load (12 items) [Conners et al., 1999] that corresponds to the mixed form of ADHD. The CAARS is an extensively tested psychometric instrument with demonstrated high internal consistency and robust reliability for all three domains [Conners et al., 1999; Erhardt et al., 1999]. The CAARS measures provide high sensitivity (82%), specificity (87%) and overall correct diagnostic classification (85%) for categorical definition of the disorder [Erhardt et al., 1999].

Twin and adoption studies in children suggest that the inattentive and hyperactive dimensions of ADHD are both highly heritable with genetics accounting for over 70% of the phenotypic variance [Nikolas and Burt, 2010] and with the same genetic factors expressed between ages 3 and 12 years in both males and females [Rietveld et al., 2004]. Adult ADHD, as measured by CAARS ADHD index, is characterized by a lower heritability of around 30% and there is some evidence that the same set of genes may play a role after the age of 12 and across the adult life-span [van den Berg et al., 2006; Boomsma et al., 2010].

Linkage studies of ADHD have primarily been performed in pediatric samples. These studies revealed a significant region on chromosome 16 [Zhou et al., 2008b] and multiple additional suggestive loci, on chromosomes 5p13, 14q12, and 17p11 [Fisher et al., 2002; Arcos-Burgos et al., 2004; Hebebrand et al., 2006; Ogdie et al., 2006; Asherson et al., 2008; Faraone et al., 2008; Lesch et al., 2008; Romanos et al., 2008]. A quantitative phenotypic measure of childhood ADHD provided a QTL on 1p36 with the genome-wide significance level of $P < 0.04$ [Zhou et al., 2008a]. Adult ADHD linkage studies also pointed to chromosome 16q23.1–q24.3 as a disease gene harboring region [Lesch et al., 2008] and suggestive linkage to 7p15.1–q31.33 and 14q11.2–q22.3 was reported in a Dutch extended pedigree [Vegt et al., 2010].

Several candidate gene studies demonstrated an association with ADHD phenotypes. Among them, a function-altering 7-repeat allele of the DRD4 gene (OMIM *126452; 11p15.5) shows one of the most consistent associations with ADHD, especially among Europeans [Li et al., 2006; Banaschewski et al., 2010]. A recent meta-analysis of the candidate genes in ADHD confirmed a moderate, but significant association with DRD4 with a substantial degree of heterogeneity in effect sizes across the analyzed studies [Gizer et al., 2009]. The meta-analysis also reported a significant but moderate association with the dopamine transporter gene (DAT1 [aka SLC6A3] OMIM *126455) on 5p15.3 [Gizer et al., 2009]. Among other significantly associated genes DRD5, 5HTT, HTR1B, and SNAP25 have been reported. Additional candidates demonstrated a marked degree of effect heterogeneity (including DBH, ADRA2A, TPH2, MAOA, and SNAP25) suggesting that their impact may be moderated via gene × environment and gene × gene interactions [Gizer et al., 2009]. The cadherin superfamily member CDH13 (OMIM *601364; 16q24.2–q24.3), a calcium-dependent membrane adhesion glycoprotein that lies within a significantly linked region, is an ADHD candidate gene in both children and adults based on the results of genome-wide association scans [Lesch et al., 2008; Franke et al., 2009; Neale et al., 2010a].

Recently, genome-wide association (GWA) studies emerged in ADHD research. No genome-wide significant results have been obtained yet, possibly reflecting the difficulties associated with GWA, such as the need for very large sample sizes in view of the multiple testing penalty. However, SNPs in CDH13 repeatedly keep appearing among the top findings in GWA studies. GWA studies further suggested genetic heterogeneity of the disorder and the potential importance of the rare variants (MAF < 5%) with large effect size. For a detailed review and meta-analysis of GWA studies on ADHD we refer to recent publications by Franke et al. [2009] and Neale et al. [2010b].

In the present study we used linkage analysis to increase our understanding of the genetic basis of adult ADHD. Inattention, hyperactivity/impulsivity, and total ADHD symptom load (ADHD index) have been assessed in an adult linkage sample of the Netherlands Twin Register (NTR) [Boomsma et al., 2010]. We report the variance components (VC) heritability estimates for inattentive and hyperactive symptom dimensions in these Dutch adults as well as the results of genome-wide VC and parametric linkage scans for both dimensions and the total ADHD symptom load (ADHD index).

MATERIALS AND METHODS

Subjects

The NTR focuses on longitudinal phenotypic and biological data collection in Dutch twins and their family members [Boomsma et al., 2006]. The current study analyses phenotype data from the 7th survey [Distel et al., 2007]. A total of 10,850 surveys was returned with at least one item marked for at least one of the ADHD scales. After quality control, data on inattention were available for 10,088 subjects (3,766 males, average age 44.4 and 6,322 females, average age 41.5 years), of which 9,503 responded to every item on the scale, 528 subjects had a missing answer for a single item, and 57 subjects had two missing items. For hyperactivity, the sample consisted of 10,664 subjects (3,953 males, average age 44.4 and 6,711 females, average age 41.7) of which 9,341 responded to every item, 666 subjects had one missing answer, and 81 subjects had two missing items. For the ADHD index, there were 10,641 subjects (3,940 males, average age 44.3 and 6,701 females, average age 41.7). The slight difference in the number of subjects per scale was due to the different number of missing items per scale. Table I describes the linkage pedigree subsamples used in VC and parametric analysis. A group of 192 unrelated subjects completed the CAARS a second time after 6 months to obtain retest data. Detailed description of the ADHD index sample processing and statistics can be found elsewhere [Boomsma et al., 2010].

The study was approved by the Central Ethics Committee on Research involving human subjects of the VU University Medical Centre, Amsterdam, an Institutional Review Board certified by the US Office of Human Research Protections (IRB number IRB-2991 under Federal-wide Assurance-3703; IRB/institute codes, NTR 03-180).

Measures

The 30-item screening self-report form of the CAARS [Conners et al., 1999] was included into the 7th NTR survey and provided a quantitative assessment of the inattentive symptoms (inattention) using a 9-item subscale, hyperactive-impulsive symptoms (hyperactivity) using a 9-item subscale, and the total ADHD

TABLE I. Description of the NTR Linkage Pedigree Sample Utilized for Variance Components (VC) and Parametric Analyses

Analysis method	Sample descriptive characteristics	Inattention	Hyperactivity	ADHD index
VC	Families[a]	349	375	370
	Subjects[b]	1,695	1,926	1,895
	Founders	709	763	749
	Females	944	1,093	1,075
	Families with phenotyped sib-pairs (SP)[c]			
	Two SP	230	249	247
	Three SP	96	99	96
	Four SP	18	21	21
	Five SP	1	1	1
	Six SP	3	4	4
	Seven SP	1	1	1
	Total SP	702	763	752
	Families with genotyped founders (GF)[d]			
	One GF	72	72	70
	Two GF	146	164	166
	Phenotyped MZ pairs[e]	93	104	101
Parametric	Additional phenotypes for founder subjects (FS)[f]			
	One FS	74	69	70
	Two FS	134	150	150
	Additional families with one phenotyped non-founder and[g]			
	One FS	33	32	32
	Two FS	62	64	61

[a]Total number of families with at least two phenotyped non-founder non-MZ subjects.
[b]Total number of subjects, including those without phenotypes (minimal linkage pedigree contains two founder subjects and two non-MZ sibs).
[c]Number of families with phenotyped sib-pairs. Parental phenotypes are not counted here.
[d]Number of families for which the genetic data was available either for one or two of the founders.
[e]Number of MZ twin pairs with both subjects phenotyped. In regard to any other descriptive characteristics in this table, MZ pairs counted as a single subject.
[f]Additional phenotypic information utilized for parametric linkage analysis in the families described in the VC part of the table. The number of families with one or two phenotyped founder subjects in shown.
[g]Number of families used in the parametric linkage scan in addition to the families described in the VC part of the table. The number of families with one phenotyped non-founder and one or two phenotyped founder subjects is shown.

symptom 12-item subscale, known as ADHD index. There were no overlapping items among the three subscales. The items on the inattention and hyperactivity scales correspond to the symptoms that represent the diagnostic criteria of adult ADHD as outlined in DSM-IV-TR. The ADHD index is a tool for the screening of cumulative ADHD symptoms and is designed to discriminate between adults affected with ADHD and a nonclinical group. Every item was scored on a scale from 1 to 4 and a sum score was obtained for each of the phenotypic subscales. Missing items were handled as per CAARS instructions [Conners et al., 1999] which allows the scoring of scales with up to two missing items. Data for 34 participants were discarded due to monotonous responses on every item for every scale.

Genotyping

Over the last few years several microsatellite genotyping steps were undertaken for the NTR families. Details of these steps are provided elsewhere [Yuan et al., 1997; Heijmans et al., 2004, 2005; Vink et al., 2004; Hottenga et al., 2005, 2007; Posthuma et al., 2006]. These steps resulted in a sample of 711 families with 3,412 non-clone individuals (1,438 founders, 1,870 females) with an average of 4.8 subjects per family, with 99.2% of families comprising two generations and 0.8% comprising three generations. Both founders were genotyped in 282 of these families and another 138 families had one genotyped founder. In addition, there were 290 nuclear families with no genotyped founders, and one extended pedigree with four founders without genotypes.

Genotype quality control was undertaken separately within each batch. The physical position of microsatellites was obtained from the direct query in silico PCR on the March 2006 NCBI36/hg18 build of Human Genome [Kent et al., 2002]. Using the physical position and the Rutgers Map Interpolator that utilizes the second-generation combined linkage-physical maps, the genetic position of each marker was obtained [Matise et al., 2007]. Subsequent genetic data quality control with Merlin software [Abecasis et al., 2002] resulted in removal of additional 245 likely erroneous genotypes due to the excess of spurious double recombinants that were not detected in this sample during the previous linkage genome scans that utilized different sources for the genetic map information. Autosomal genomes had 757 markers spaced at an average of 4.76 cM (range 0.0–20.59 cM), with average heterozygosity of 0.76. A total of 936,680 genotypes was available for the autosomal genome. Since the genotyping was done in various subsamples using partially overlapping marker sets, the genotypes for the individual markers were available from 5.6% to 77% (average 36.26%) of all genotyped subjects within the linkage sample (see Supplemental Materials). We would like to emphasize that

the low genotyping rate for some markers was due to the merge of different subsamples, rather than a genotyping quality issue for any of the markers in the final sample. Considering this discrepancy between the genotype numbers per individual markers, the decision was made to perform the linkage scans in a multipoint fashion. Founders had the genetic data for 446 autosomal microsatellites with available founder genotypes ranging from 14.4% to 50.5% of all founder subjects within the sample. For chromosome X a total of 48,439 genotypes for 41 microsatellite markers was available distributed with an average density of 4.90 cM (range 0.03–15.91 - 91 cM), average heterozygosity of 71.59%. 9.8–50.1% of all founders had the genetic information available for the 26 X-linked markers. Supplementary materials offer the detailed information on autosomal and X-linked microsatellite markers, including their physical and cytological position, Rutgers genetic positions, number of genotyped subjects/founders for each marker, and the heterozygosity information.

Phenotype Descriptives and Heritability Analysis

The descriptive statistics for inattention, hyperactivity, and ADHD index within the NTR linkage sample were assessed with PEDSTATS [Wigginton and Abecasis, 2005]. Six months test–retest correlations were evaluated via two-tailed Pearson correlations in a subset of 192 unrelated individuals. Genetic and phenotypic correlations in linkage pedigrees were assessed using Solar v4.3.1 [Almasy and Blangero, 1998]. Heritability was estimated under a polygenic model with age and sex as covariates in Solar v4.3.1 [Almasy and Blangero, 1998]. The significance level was derived by comparison with a sporadic model. X-linked VC were evaluated using the MINX software [Merlin in X] [Abecasis et al., 2002].

Genome-Wide Linkage Analysis

The genetic maps obtained through the Rutgers University Map Interpolator were adjusted so that the most distal marker on the p-arm of each chromosome started at the genetic position of 0.0 cM. These maps were used for both VC and parametric linkage scans. The allele frequencies were estimated with the MENDEL v.10.0 [Lange et al., 2001] using model 1 of option 6. Both genome scans were performed at 1 cM resolution. Both software packages can handle the presence of monozygotic (MZ) twins in the linkage sample. The VC linkage scan of the autosomal genome was conducted with MERLIN v.1.1.2 [Abecasis et al., 2002] using the multipoint identity-by-descent (IBD) information with age and sex as covariates. The MINX version of MERLIN was used for the VC linkage analysis of chromosome X. For the parametric analysis, we first estimated genotypic model parameters for each phenotype using option 14 of MENDEL [Lange et al., 2001, 2005]. Initial parameter estimations were performed with 20 convergence tests with up to 2000 maximum iterations using model 1. Parametric models assumed the normal distribution and included the estimation of common standard deviations and the disease gene allele frequencies. The grand mean, sex, and age were used as predictors. Further, MENDEL's model 2 of option 14 was used to define the individual genotype penetrance for each phenotyped subject. Parametric linkage analysis was performed with the Location Score option 2 [Lange et al., 2001]. The maximum number of adjusted meioses was set to 20. Each genomic position was analyzed in a 5-point analysis using the phenotype markers and 4 adjacent microsatellite markers. 3,530 autosomal and 196 X-linked genomic positions were evaluated with VC and parametric scans.

Empirical Significance Evaluation

To assess the significance of the autosomal portion of the linkage scan results, we conducted a simulation study. MERLIN [Abecasis et al., 2002] was used to generate 10,000 replicates of full autosomal genome scans under the null hypothesis of no linkage, using *de facto* pedigree structures, phenotypes, allele numbers and frequencies, and recombination fractions for each marker used for our actual scans. For the VC results, each of the replicates was analyzed with MERLIN, under the same conditions using all three phenotypic measures. For the parametric scans, first 2,500 replicates were analyzed in the same manner as the actual data using inattention and ADHD index scales. For hyperactivity, 1,000 first replicates were run through the parametric analysis. The maximum LOD score from each analyzed replicates was recorded for each of the phenotypes and arranged into a table to allow empiric evaluation of the results. The reported 95% confidence intervals for the empirical *P* values are obtained with BINOM [Ott, 1991].

RESULTS

The descriptive statistics and heritability estimates for inattention, hyperactivity and ADHD index in Dutch adults are shown in Table II. The trait distributions were approximating normality with a minor kurtosis and are shown in Figure 1. Genetic and phenotypic correlations between the three phenotypic traits are presented in Table III. The total heritabilities were 35% for inattention, 23% for hyperactivity, and 31% for the ADHD index. For the ADHD index, these results are in agreement with our previous results for the estimation of heritability using structural equation modeling [Boomsma et al., 2010]. The X-linked component of heritability was negligible and was the lowest for the ADHD index (0.0) and the highest for hyperactivity/impulsivity (0.07). The 6 months test–retest correlation assessed on 192 unrelated individuals was significant at the level of $P < 0.001$ and stood at 0.54 for inattention, 0.61 for hyperactivity, and 0.62 for the ADHD index.

For the three phenotypes segregation analysis revealed genotypic models with minimal effects of age and gender on genotypic mean values (Table IV). Table V lists the LOD scores observed at the empirical significance levels of 0.01, 0.05, 0.1, and 0.50 for each phenotype in VC and parametric linkage scans as revealed by simulations. The LOD values corresponding to the empirical levels of 0.50 and 0.05 were used to declare the "suggestive" and "significant" areas of linkage [Lander and Kruglyak, 1995].

For the inattention phenotype, the highest VC LOD of 4.58 ($p_{emp} = 0.0026$, 95%CI 0.0017–0.0038; attributed heritability [AH] 38.16%) was observed between the microsatellite markers D18S858 (18q21.31; 81.99 cM) and D18S64 (18q21.32; 86.52 cM). The local area of the significant linkage ($p_{emp} < 0.05$) extended from the

TABLE II. Descriptive Statistics for the Inattention, Hyperactivity, and ADHD Index Phenotypes for Subjects Within the NTR Linkage Sample

	Phenotype		
Statistics	**Inattention**	**Hyperactivity**	**ADHD index**
Mean	15.18	16.04	19.96
Standard deviation	3.41	3.18	3.93
Skewness	0.79	0.57	0.84
Kurtosis	3.72	3.47	4.18
Minimum	10.0	10.0	13.0
Median	15.0	16.0	19.64
Maximum	30.38	30.0	38.0
Variance	11.63	10.11	15.47
H^2 (SE; *P*)	0.3515 (0.0479; 3.73×10^{-15})	0.2297 (0.0464; 10^{-7})	0.3083 (0.0468; 2.24×10^{-12})
X-Linked component of variance (with residual H^2)	0.04 (0.30)	0.07 (0.12)	0.00 (0.31)

H^2, heritability estimate under polygenic model; SE, standard error; *P*, significance level of heritability estimate.

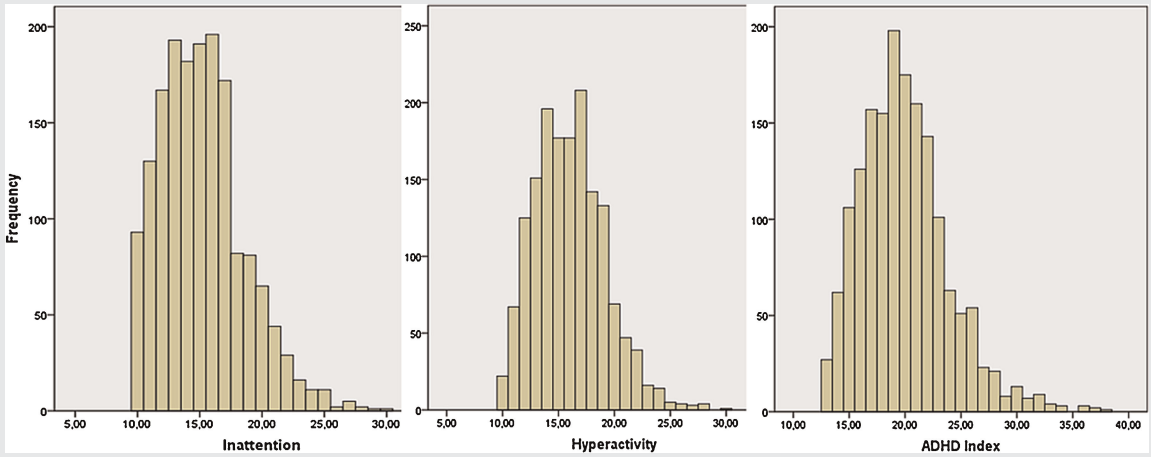

FIG. 1. Inattention, hyperactivity, and ADHD index distribution histograms. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

position of 78–94 cM and of the suggestive linkage ($p_{emp} < 0.5$) from 73 to 106 cM and was surrounded by D18S450 (18q21.1; 72.62 cM) and D18S1161 (18q22.3; 114.23 cM). In the parametric scan, the highest LOD score 3.47 ($p_{emp} = 0.0816$, 95%CI 0.0712–0.0930) was also observed on 18q21.31 at 82 cM between D18S858 and D18S64 with the area of suggestive linkage extending from 81 cM (LOD 3.37, $p_{emp} = 0.0992$, 95%CI 0.0878–0.1116) to 85 cM (LOD 3.16, $p_{emp} = 0.1516$, 95%CI 0.1378–0.1663). No other autosomal genomic area demonstrated significant or suggestive evidence of linkage for inattention.

TABLE III. Genetic and Phenotypic Correlations of the Quantitative Scales

Phenotype	**Inattention**	**Hyperactivity**	**ADHD index**
Inattention	1.0	0.6264	0.8344
Hyperactivity	0.4020	1.0	0.7062
ADHD index	0.6971	0.6170	1.0

Genetic (top right) and phenotypic (bottom left) correlations as estimated by Solar v.4.3.1 using the linkage pedigrees including MZ twins.

The VC scan for the ADHD index QTL did not reveal any suggestive or significant areas of linkage. The maximum VC LOD score was 1.81 ($p_{emp} = 0.6819$, 95%CI 0.6727–0.6910; AH 28.87%) on chromosome 2. However, in the parametric scan, the same area demonstrated a maximum LOD score of 3.58 that reached the empirical significance level of 0.0372 (95%CI 0.0301–0.0454) and fell at 20 cM between D2S2952 (2p25.1; 15.94 cM) and D2S168 (2p25.1; 25.62 cM). The entire region that demonstrated both the significant and the suggestive linkage in that area extended from 16 cM (LOD 2.74, $p_{emp} = 0.1841$, 95%CI 0.1691–0.1998) to 25 cM (LOD 2.30, $p_{emp} = 0.3846$, 95%CI 0.3654–0.4040). The second area

TABLE IV. Mendel Genotypic Models for Parametric Linkage Scan

	Phenotype		
Parameters	**Inattention**	**Hyperactivity**	**ADHD index**
Grand mean	0.394	1.003	0.604
Disease allele frequency[a]	0.32	0.19	0.28
Genotypic means			
1/1	−0.92	−1.14	−0.99
1/2	−0.40	−0.25	−0.43
2/2	1.33	1.39	1.42
Individual offsets			
Age	0.0017	−0.0048	−0.0007
Female	−0.0089	−0.0129	−0.0184
Male	0.0089	0.0129	0.0184
Scale	0.7574	0.8208	0.7648

[a]Disease allele is designated as allele 2.

of interest that demonstrated the evidence of suggestive linkage was observed within 44–49 cM interval on chromosome 3 with the maximum parametric LOD score 2.90 ($p_{emp} = 0.1345$, 95%CI 0.1213–0.1485) at 48 cM and fell between D3S3038 (3p24.3; 41.52 - cM) and D3S1266 (3p24.1; 49.08 cM).

The hyperactivity phenotype did not reveal any areas of significant QTL either in VC or parametric analysis. The maximum VC LOD of 1.64 ($p_{emp} = 0.5876$, 95%CI 0.5779–0.5972; AH 24.04%) was observed over chromosome 4 and did not reach a suggestive level. Twelve autosomal genomic position reached a suggestive level of significance in the parametric scan for hyperactivity QTL and formed three peaks. The maximum parametric LOD of 2.69 ($p_{emp} = 0.2190$, 95%CI 0.1937–0.2459) was observed at 3 cM position on chromosome 8 with the entire suggestive area (2–6 cM) falling between D8S504 (8p23.3; 1.14 cM) and ATT023 (8p23.2; 8.67 cM). The second largest peak of suggestive linkage to hyperactivity of LOD 2.68 ($p_{emp} = 0.2190$, 95%CI 0.1937–0.2459) was observed on chromosome 3p24.3–3p24.1 and fell into the exactly the same area of 44–49 cM where the suggestive signal for the ADHD index was detected in the parametric scan between D3S3038 and D3S1266. A single position 17 on chromosome 2 produced a suggestive parametric LOD of 2.31 ($p_{emp} = 0.4860$, 95%CI 0.4546–0.5175). This signal fell into the same area on 2p25.1 that produced a significant finding between D2S2952 and D2S168 for the ADHD index.

Linkage analysis with the chromosome X markers revealed a maximum VC LOD of 0.01 for hyperactivity (nominal *P*-value reported by MINX = 0.4). Model-based scans also did not reveal any X-linked area of interests with the largest reported parametric LODs of 0.00, 0.49, and −0.84 for inattention, hyperactivity, and the ADHD index, respectively.

Figure 2 demonstrates the results of the autosomal genome linkage scans using the VC (blue) and parametric (red) methods for inattention (A), hyperactivity (B) and ADHD index (C). Figure 3 depicts the linkage results over chromosomes 2 and 18. The detailed results of the genome-wide VC and parametric linkage scans over the autosomal genome together with the corresponding empirical *P* values are provided in the Supplementary Materials.

DISCUSSION

This study in an unselected sample of multiple pedigrees of Dutch ancestry is the first study that performs a heritability assessment and genome-wide linkage scan for quantitatively measured inattention, hyperactivity, and total ADHD symptoms in adults. The CAARS symptom dimensions of inattention (0.54), hyperactivity (0.61) and ADHD index (0.62) were moderately stable over the 6-month period. Adult heritability was 35% for inattention and 23% for hyperactivity. This is substantially lower than the heritabilities (around 70%) reported in younger subjects [Nikolas and Burt, 2010]. ADHD index heritability was in accordance with our previous assessment and stood at 31% [Boomsma et al., 2010].

The reasons for the substantially lower heritability of symptom dimensions in adulthood are not clear. Age × genotype interaction, self-reported nature of the phenotypes, and deficiencies of the

TABLE V. Simulation Study Results: Empirical *P* Values and Corresponding LOD Scores for the VC and Parametric Linkage Analysis

		LOD scores		
Method	**p_{emp}**	**Inattention**	**Hyperactivity**	**ADHD index**
VC	0.50[a]	2.26	1.73	2.05
	0.10	3.17	2.31	2.87
	0.05[b]	3.5	2.52	3.15
	0.01	4.16	2.99	3.79
Parametric	0.50[a]	2.39	2.30	2.12
	0.10	3.36	2.99	3.07
	0.05[b]	3.7	3.26	3.41
	0.01	4.39	3.87	4.15

[a]"Suggestive" LOD score cut-off values.
[b]"Significant" LOD score cut-off values.

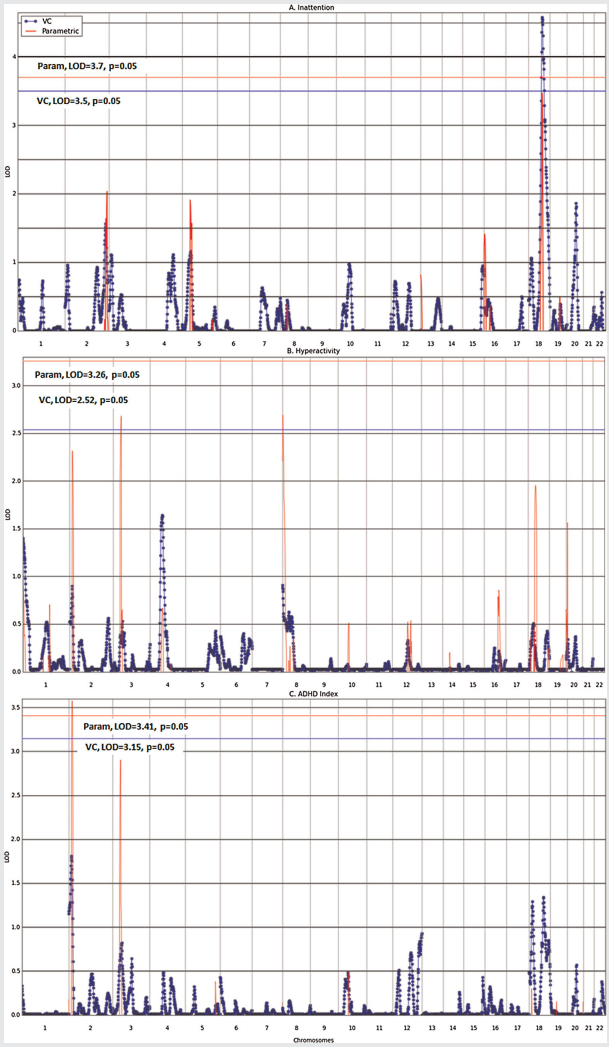

FIG. 2. Autosomal genome linkage results. Results of VC and parametric linkage scan for inattention (A), hyperactivity (B), and ADHD index (C). Horizontal lines define the significance level of 0.05 for each phenotype/method. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

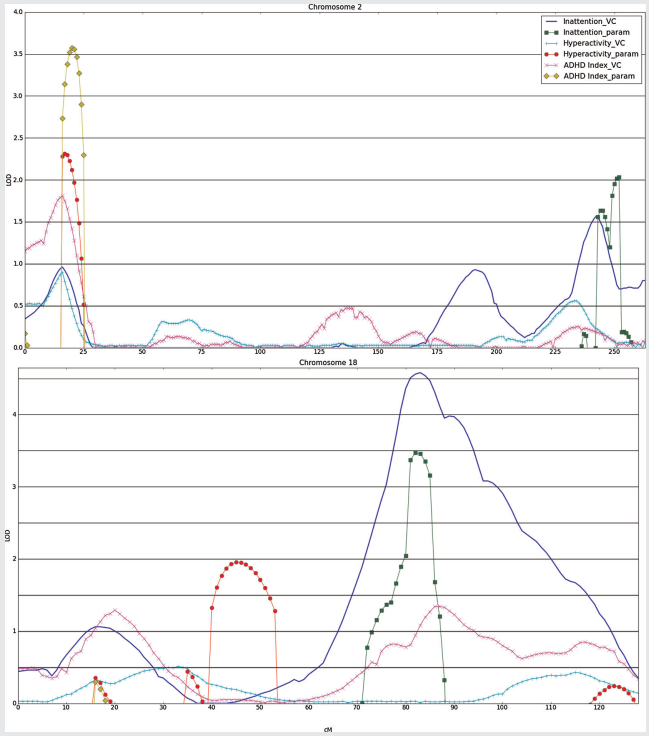

FIG. 3. Linkage results for chromosomes 2 and 18. Results of VC and parametric linkage scans for inattention, hyperactivity, and ADHD index. Negative LOD scores for parametric test are not shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

phenotypic definitions are possible explanations. Future studies on the systematic differences in heritability estimates using quantitative versus qualitative phenotypes may provide also reveal a source of discrepancies. An age-related decline in heritability for the total ADHD symptoms was recently demonstrated using structural equation modeling with ADHD index [Boomsma et al., 2010]. The age at which the heritabilities start to decline was proposed to be somewhere during the adolescence. An increase in unique environmental influences in adults was hypothesized to be one of the factors affecting measures of heritability. These influences may be dependent on genotype × environment interactions. An interaction of maternal smoking or drinking during pregnancy and offspring genotype was shown to be important in ADHD development [Kahn et al., 2003; Brookes et al., 2006; Ficks and Waldman, 2009]. If the effects of such interactions tend to diminish as a child gets older, lower ADHD heritabilities would be expected in adults versus children.

This is the first study to provide statistically significant evidence of adult ADHD QTLs on chromosomes 18q and 2p, using both VC and parametric linkage analysis. We do not provide support for previously reported significant linked or associated genomic areas in children or adults. Currently, the longitudinal genetic architecture of ADHD is under investigation. However, accumulated evidence suggests that while the set of genes that influence the ADHD symptomatology throughout adulthood may remain the same, they may be at least partially different from those influencing the disorder in childhood. In this light, we would like to emphasize that the reviewed evidence of association and linkage presented below comes from studies that focused on childhood ADHD.

Our significant QTL for inattention on chromosome 18q21.1–18q22.3 has previously shown a suggestive linkage in the young genetically isolated population from the Netherlands using the Dutch version of the NIMH Diagnostic Interview Schedule for children that utilizes ADHD DSM-IV diagnostic criteria for the phenotypic definition [Amin et al., 2009]. An intergenic rs2311120 SNP on 18q21.2 was recently reported to be the third most associated SNP after the TDT-bias correction ($P = 1.22E{-}05$) [Neale et al., 2008]. Alongside, other SNPs in the area, including intergenic (rs9973180, rs1454741, rs4891476), as well as two intronic (rs4149601 within NEDD4L, OMIM *606384 and

rs12232751 within CPLX4, OMIM *609586) provided some nominal evidence for an association ($P < 0.001$) with ADHD [Neale et al., 2008]. Interestingly, NEDD4L gene functional SNP rs4149601 was also nominally associated ($P < 0.05$) in an independent International Multi-Center ADHD Genetics (IMAGE) study scan [Lasky-Su et al., 2008]. NEDD4L was previously indicated as a contributor to the human psychiatric and somatic pathologies, such as bipolar disorder, orthostatic hypotension, and essential hypertension [Chen et al., 2001; Dunn et al., 2002]. Another IMAGE study that investigated conduct disorder and ADHD comorbidity demonstrated an association with rs7236632 (18q21.31; $P = 0.63E{-}5$) [Anney et al., 2008]. A candidate gene association approach revealed that an obesity-causing mutation in MC4R (OMIM *155541) that maps to 18q21.32 was associated with ADHD in an extended Palestinian consanguineous family [Agranat-Meged et al., 2008]. Since previous studies have implicated the cadherin superfamily as one of the likeliest candidates for ADHD (CDH13; OMIM *601364) [Zhou et al., 2008b; Franke et al., 2009], other members of the superfamily located under the significant peak on 18q21.1–18q22.3, such as CDH20 (OMIM *605807), CDH19 (OMIM *603016), and CDH7 (OMIM *605806) should be considered as local causative candidates.

Though not significant on the scale of the previously performed positional cloning studies using ADHD phenotypes on a genome-wide scale, chromosomal region 2p25.2–2p25.1 accumulated suggestive evidences of involvement into ADHD etiology and/or pathogenesis. In a sib-pair linkage scan using a high-density SNP set, an intergenic SNP marker, rs1510834, on 2p24.3 demonstrated a LOD of 1.64 [Asherson et al., 2008]. Further, genome-wide association studies demonstrated the nominal association with an intergenic rs2357878 ($P = 0.0008$) SNP marker that maps to 2p25.1 [Neale et al., 2008]. In a family-based association test, rs930421 that is located within MTA3 (OMIM *609050) and downstream of the oxoeicosanoid receptor 1 (OXER 1) on chromosome 2p21 was among the markers that demonstrated an association with the nominal P-value $<10^{-5}$ under a recessive model using the cumulative symptomatology [Lasky-Su et al., 2008]. Phenotypic definitions that comprise the hyperactive-impulsive symptoms revealed an association with rs6719977 (chromosome 2p21) under an additive model [Lasky-Su et al., 2008]. The IMAGE neurophysiologic endophenotype study points to the markers rs1309 (2p25.1; LOD 2.2, nominal $P = 0.0007$) and rs1079417 (2p25.2; LOD 2.02, nominal $P = 0.0011$) as the sources of the largest evidence of linkage for motor timing and digit span (verbal working memory) [Rommelse et al., 2008c]. These phenotypes are proposed to be the heritable traits associated with an increased ADHD risk [Rommelse et al., 2008a,b]. Association with rs2241685 within the myelin transcription factor 1-like gene, MYT1L (OMIM *613084), was among the top 30 single SNPs hits in gene regions in a study that used pooled DNA from the 343 in- and outpatients from Germany [Lesch et al., 2008]. Finally, rs6733379 on 2p22.3 was shown to be nominally associated ($P = 0.43E{-}5$) in a family-based test with the categorically defined conduct problems in subjects with the ADHD under the dominant model of inheritance in European Caucasians [Anney et al., 2008].

We should mention some possible limitations of our study. First, adult ADHD is a relatively new nosological unit that first appeared only in the revised edition of DSM-IV-TR. As such, concerns about validity of current diagnostic criteria have been voiced in the literature [Rosler et al., 2010]. Since the diagnostic scales are based on the current DSM-IV-TR symptom's criteria, our phenotypic definitions might suffer from the same deficiencies as the current diagnostic scheme. Though previous studies supported the idea that adults with ADHD are the best informants of their symptoms and their report has a strong association with the symptoms reported by other informants [Murphy and Schachar, 2000; Kooij et al., 2008], the fact that the self-report ADHD scales were not confirmed by other informants is a second limitation. Third, though the large sample size provided a sufficient power to detect the QTLs at a significant level, the linkage sample was assembled through a series of genotyping batches performed on partially overlapping subsets of subjects. This resulted in areas of decreased information content down to 5.6% of the entire sample of subjects. Though such drops in information result in a loss of power, the use of multipoint IBDs in VC and multipoint (4 microsatellites and a phenotype marker) parametric analysis together with a relatively dense average genetic map (<5 cM) at least partially helped to overcome this problem.

This is currently one of few genetic studies of adult ADHD. As such, the results presented in this manuscript need to be replicated in other samples.

ACKNOWLEDGMENTS

VS was supported by EU Marie Curie Research Training Networks grant (EUTwinsS, PI Dr. Igor Nenadic) and Neuroscience Campus Amsterdam (NCA). MD was supported by Psychometric and Genetic Assessments of Substance Use (4R37DA018673-06). We acknowledge NWO/SPI 56-464-14192, Centre for Medical Systems Biology-2, The European Research Council (ERC-230374) and NWO 480-04-004. We thank Dr. J. Weber (Mammalian Genotyping Service, Marshfield) and Dr. E. Slagboom (Molecular Epidemiology Section, Leiden University Medical Centre, The Netherlands) for microsatellite genotyping. We thank all participants from the Netherlands Twin Register.

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