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# Genome-Wide Association Scan of Quantitative Traits for Attention Deficit Hyperactivity Disorder Identifies Novel Associations and Confirms Candidate Gene Associations

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**Attention deficit hyperactivity disorder (ADHD) is a complex condition with environmental and genetic etiologies. Up to this point, research has identified genetic associations with candidate genes from known biological pathways. In order to identify novel ADHD susceptibility genes, 600,000 SNPs were genotyped in 958 ADHD proband-parent trios. After applying data cleaning procedures we examined 429,981 autosomal SNPs in 909 family trios. We generated six quantitative phenotypes from 18 ADHD symptoms to be used in genome-wide association analyses. With the PBAT screening algorithm, we identified 2 SNPs, rs6565113 and rs552655 that met the criteria for significance within a specified phenotype. These SNPs are located in intronic regions of genes *CDH13* and GFOD1, respectively. *CDH13* has been implicated previously in substance use disorders. We also evaluated the association of SNPs from a list of 37 ADHD candidate genes that was specified a priori. These findings, along with association *P*-values with a magnitude less than $10^{-5}$, are discussed in this manuscript. Seventeen of these candidate genes had association *P*-values lower then 0.01: SLC6A1, SLC9A9, HES1, ADRB2, HTR1E, DDC, ADRA1A, DBH, DRD2, BDNF, TPH2, HTR2A, SLC6A2, PER1, CHRNA4, SNAP25, and COMT. Among the candidate genes, SLC9A9 had the strongest overall associations with 58 association test *P*-values lower than 0.01 and multiple association *P*-values at a magnitude of $10^{-5}$ in this gene. In sum, these findings identify novel genetic associations at viable ADHD candidate genes and provide confirmatory evidence for associations at previous candidate genes. Replication of these results is necessary in order to confirm the proposed genetic variants for ADHD.** 

**KEY WORDS:** ADHD; genome-wilde association; family-based association; candidate gene; CDH13

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## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a complex disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity that has an onset in childhood. Despite a heritability estimate that averages around 76% [Faraone, 2004; Faraone et al., 2005], identifying genes associated with ADHD has been difficult. Using the suspected pathophysiology of the disease as a starting point, some genetic variants have been implicated through candidate gene studies and subsequent meta-analyses. These include *HTR1B, DRD4, SLC6A3/DAT1, SNAP25, DRD5*, and *DBH* [Brookes et al., 2006]. However, apart from some genetic linkage analyses that have identified a few potential disease susceptibility loci, as of yet no hypothesis-free genetic mapping studies have been performed for ADHD. Recent advances in high throughput genotyping technologies have facilitated the cost-effective genotyping of hundreds of thousands of DNA markers. Consequently, genome-wide association studies (GWAS) have become a reality. GWAS hold huge promise for identifying genetic variants that may not be obvious a priori biological candidates. GWAS have already been successful in identifying variants associated with many complex diseases including obesity, age-related macular degeneration, Type I and Type II diabetes, Crohn's disease, prostate cancer, and celiac disease [Herbert et al., 2006; Rioux et al., 2007; Saxena et al., 2007; Yeager et al., 2007; Zanke et al., 2007; Hunt et al., 2008].

The Genetics Analysis Information Network (GAIN) is a public-private partnership between the NIH and the private sector with the goal of promoting GWAS for various complex diseases (http://www.fnih.org/GAIN2/home_new. shtml). Nine hundred fifty-eight ADHD-parent trios from the International Multicenter ADHD Genetics Project (IMAGE) were genotyped on a 600K SNP GWAS as part of the GAIN initiative. We recently reported the initial findings of the IMAGE GWAS sample using a DSM-IV diagnosis of ADHD combined type in a family based association analysis [Neale et al., 2008a]. These findings showed no genome-wide significant associations but found several promising candidates with $P$-values $<10^{-5}$.

Using DSM-IV ADHD combined type diagnoses, as a primary phenotype is an obvious first choice for association analyses, primarily because it is the most severe and common ADHD subtype and is known to have a relatively high sibling risk ratio of around 5–10 [Chen et al., 2008]. Despite these advantages, there is also value in using quantitative measures of specific aspects of ADHD as the primary phenotypes in GWAS analyses. Although not commonly used, there is compelling evidence that the use of quantitative measurements of ADHD is ideal for genetic association studies of ADHD, as mounting evidence suggests that ADHD is a disorder on the extreme end of a continuum observed in the population. Twin studies have found high heritability estimates for ADHD when a quantitative measurement of ADHD symptoms is used to measure the dimensionality of the disorder [Edelbrock et al., 1986; Biederman et al., 1993; Chen et al., 1994; Boyle et al., 1997; Sherman et al., 1997; Faraone et al., 2005]. Due to their high heritability, the use of such quantitative ratings generated from the number and severity of the 18 ADHD symptoms described in the DSM-IV are good quantitative measures to use in genetic association analyses. Since the presence of these symptoms is necessary to diagnose the disorder they are often recorded in other samples, making replication efforts easy. Using ADHD symptoms also allows for the analysis of inattentive and hyperactive-impulsive components in combined type individuals, separately. In this manuscript we generated three basic quantitative traits and three statistically derived quantitative measures from the ADHD symptoms and then used them as the phenotypes of interest in GWAS analyses. The statistically derived phenotypes use a methodology that Lasky-Su et al. [2007, 2008] implemented previously in the IMAGE sample to identify and replicate an association with *DRD4*.

## METHODS

### Subjects

Families were collected by the International Multicenter ADHD Genetics (IMAGE) project. Families were identified through ADHD probands aged 5–17 attending outpatient clinics at the data collection sites in Europe and Israel. A total of 958 affected proband-parent trios were initially selected for the GWAS scan. Family members were Caucasians of European origin from seven countries around Europe including Belgium, Germany, Ireland, The Netherlands, Spain, Switzerland, and The United Kingdom, as well as Israel. Of these, 936 probands were initially ascertained as having DSM-IV combined type ADHD. Twenty-two probands who did not meet combined subtype ADHD diagnosis were included because they either met the criteria for the inattentive or hyperactive subtypes, or they missed the DSM-IV combined type diagnosis by a single item. Exclusion criteria were autism, epilepsy, IQ $<70$, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD.

### Clinical Measures

Prior to entry into the study, all probands underwent clinical evaluations by a pediatrician or child psychiatrist and both existing and new patients were included in the study. Patients had to meet clinical criteria for ADHD-combined type before being enrolled in the study. Wherever possible, families withdrew stimulant medication for 1 week prior to research assessments to allow for more accurate ascertainment of the current level of ADHD symptoms and behaviors. Alternatively we ensured as far as possible that ratings were based on medication free periods. Probands were excluded from the study if the last medication free period was more than 2 years ago.

***Parental account of childhood symptom (PACS).*** PACS is a semi-structured, standardized, investigator-based interview developed as an instrument to provide an objective measure of child behavior [Taylor et al., 1986a,b]. A trained interviewer administers PACS with parents, who are asked for detailed descriptions of the child's typical behavior in a range of specified situations. Such situations are defined either by external events (e.g., watching television, reading a book or comic, playing alone, playing with friends, going to bed, traveling) or by behaviors shown (e.g., crying, worried talk, tempers, fighting with siblings). Interviewers then make their own ratings on the basis of a formal training and written definitions of the behaviors to be rated, on a 4-point scale of

severity and frequency in the previous week and previous year. Inter-rater reliability is high with product-moment correlations for pairs of interviewers ranging from 0.79 to 0.96. The Hyperactivity subscale is made up of attention span (time spent on a single activity, rated separately for four different kinds of activity), restlessness (moving about during the same activities), fidgetiness (movements of parts of the body during the same activities), and activity level (rated for structured situations such as mealtimes and car journeys), with other subscales covering defiant, emotional and other comorbid disorders including autistic spectrum disorders.

***Rating scales.*** Rating scales used to quantify ADHD symptoms included the Long Version of Conners' Parent Rating Scale (CPRS-R:L), Long Version of Conners' Teacher Rating Scale (CTRS-R:L) [Conners, 1996], parent version of the Strengths and Difficulties Questionnaires (SDQ) and teacher version of SDQ. In order to exclude autism spectrum disorders that might confound the analysis of ADHD, both probands and siblings were screened using the Social Communication Questionnaire in conjunction with the pro-social scale from the SDQ. Individuals falling above these thresholds were further evaluated using the autism spectrum disorder section of the PACS interview.

***DSM-IV diagnoses.*** All raw data was centralized and stored on a secure database at the MRC Social Genetic Developmental Psychiatry research center in London. A standardized algorithm was applied to PACS to derive each of the 18 DSM-IV ADHD items, providing operational definitions for each behavioral symptom. These were combined with items that scored 2 or 3 from the teacher rated Conners' ADHD subscale, to generate the total number of items from the DSM-IV symptom checklist. Situational pervasiveness was defined as some symptoms occurring within two or more different situations from the PACS interview, as well as the presence of one or more symptoms scoring 2 or more from the ADHD subscale of the teacher rated Conners'.

## Quantitative Trait Information Used in the Analyses

Six quantitative traits were generated for use in the association analyses, three from the CPRS-R:L and three from the PACS. Both the CPRS-R:L and the PACS assess the DSM-IV symptoms of ADHD in children and adolescents. The inattentive and hyperactive-impulsive symptoms included are: (1) inability to pay attention to details; (2) difficulty with sustained attention in tasks or play activities; (3) listening problems; (4) difficulty following instructions; (5) problems organizing tasks and activities; (6) avoidance or dislike of tasks that require mental effort; (7) tendency to lose things like toys, notebooks, or homework; (8) distractibility; (9) forgetfulness in daily activities; (10) fidgeting or squirming; (11) difficulty remaining seated; (12) restlessness; (13) difficulty playing quietly; (14) always seeming to be "on the go;" (15) excessive talking; (16) blurting out answers before hearing the full question; (17) difficulty waiting for a turn or in line; (18) problems with interrupting or intruding. Three quantitative measures were generated using both the CPRS-R:L and PACS, resulting in a total of six quantitative measures to be used in GWAS analyses. In the PACS, each symptom is given a value of 0 or 1 to demarcate the absence or presence of the symptom respectively. Three basic measure that were generated using data from the PACS, including a count of (1) the number of exhibited hyperactive-impulsive symptoms; (2) the number of exhibited inattentive symptoms; and (3) the total number of exhibited ADHD symptoms. In all three cases, a binary measure indicating the presence or absence of each symptom was measured and the totals were generated by summing over all symptoms, making the maximum number of symptoms 9, 9, and 18 respectively. In the CPRS-R:L each symptom is given a score ranging between 0 and 3, where 0 indicates that the behavior is not characteristic of the individual and exhibited rarely and 3 indicated that the behavior is very characteristic of the individual and is exhibited very frequently. The three remaining phenotypes were generated using data from the CPRS-R:L with the Family-based association testing-principal components (FBAT–PC) methodology [Lange et al., 2004b]. Because this approach has been presented and implemented elsewhere [Van Steen et al., 2005; Herbert et al., 2006; Lasky-Su et al., 2007, 2008], we do not provide the details here. In summary, FBAT–PC uses a weighted sum of the inputted phenotypes to construct a composite phenotype that is then used in the association analysis. The weights for the composite phenotype are generated to maximize the heritability at each SNP while remaining statistically independent of any subsequent association tests. By maximizing the heritability at each SNP we mean that the genotypic information is maximally correlated with the composite phenotype. Because we are using the between information on an SNP-by-SNP level, the composite generated is different for each SNP/phenotype combination. In this application, we use FBAT–PC with three different sets of inputted variables to generate three separate quantitative traits to be used in the association analyses: ordinal measures of (1) the 9 inattentive symptoms; (2) the 9 hyperactive-impulsive symptoms; and (3) the total number of ADHD symptoms. In total six phenotypes were analyzed using additive, dominant, and recessive models. Considering that there are six phenotypes and three genetic models, 18 GWAS analyses were performed. When presenting the findings, the results only adjust for multiple comparisons for a single GWAS analysis (i.e., we adjust only for the statistical tests within the specified phenotype and genetic model). We do not adjust for the comparisons across all 18 GWAS analyses and acknowledge that by doing this none of these findings achieve genome-wide significance on an experiment-wise level. Therefore, when we claim "significance" we are referring to any statistical test that has a $P$-value less than 0.05 after adjusting for the statistical tests performed for a single GWAS analysis. The Spearman rank correlation between the total symptom count and inattentive and hyperactive-impulsive symptom counts was 0.78 and 0.73, respectively, while the correlation between inattentive and hyperactive-impulsive symptom counts was 0.20. Because the FBAT–PC methodology generates a different weighting scheme for each phenotype/SNP combination, the correlation among the composite phenotypes is more difficult to assess.

## Genotyping

Details of the genotyping and data cleaning process were reported elsewhere [Neale et al., 2008a]. Briefly, genotyping was performed by Perlegen Sciences using the Perlegen platform. The Perlegen Array has 600,000 tagging SNPs designed to be in high linkage disequilibrium with untyped SNPs for the three HapMap populations. Genotype data cleaning and quality control procedures were done by The National Center for Biotechnology Information (NCBI) using the GAIN QA/QC Software Package (version 0.7.4) developed by Gonçalo Abecasis and Shyam Gopalakrishnan at the University of Michigan. A copy of the software is available by e-mailing gopalakr@umich.edu or goncalo@umich.edu. Data were removed on the basis of the following quality control metrics: (1) call rate $<95\%$; (2) gender discrepancy; (3) per-family Mendelian errors $>2$; (4) sample heterozygosity $<32\%$; (5) genotype call quality score cut-off $<10$; (6) a combination of SNP call rate and minor allele frequency (MAF) (a) $0.01 \leq \text{MAF} < 0.05$ and call rate $\geq 99\%$; (b) $0.05 \leq \text{MAF} < 0.10$ and call rate $\geq 97\%$; and (c) $0.10 \geq \text{MAF}$ and call rate $\geq 95\%$); (7)

Hardy–Weinberg equilibrium *P*-value of *P*-value < 0.000001; and 8) duplicate sample discordance. We also examined the QQ plots for all of the phenotype and genetic model combinations to insure that our results did not have more than expected low-*P*-values. The process was also done with ADHD diagnosis in the cleaning of these data.

### Statistical Analyses

FBAT is a generalization of the TDT, which allows valid testing of association with any phenotype, sampling structure, and pattern of missing marker allele information [Horvath et al., 2001, 2004; Lange et al., 2004a]. The PBAT program incorporates the FBAT–PC methodology. We analyzed our data using the FBAT–PC methodology in the context of the PBAT screening algorithm. By using information from families that are not informative for a given SNP (a.k.a. the between information), PBAT selects a set of SNPs with the most power to detect association in a manner that does not bias the statistical test of association in the informative families [Lange et al., 2003a,b]. This reduces the number of independent comparisons by restricting the analysis to an abridged set of SNPs. Simulations show that the PBAT screening procedure has increased power over other multiple testing strategies such as the Bonferroni correction [Van Steen et al., 2005]. One criticism of the screening algorithm is that it uses the between family information which can be affected by extreme population stratification [Ionita-Laza et al., 2007]. We have previously shown that IMAGE participants from Israel and Spain show different genetic profiles than the Northern European participants [Neale et al., 2008b]. Combining all of these individuals together results in a heterogeneous sample and although the FBAT statistic is robust against population stratification, the PBAT screening algorithm has some sensitivity towards it. Therefore we performed a cluster analysis in PLINK [Purcell et al., 2007] through a linkage clustering algorithm that is based on pairwise identity-by-state distance, to identify a predominant homogeneous cluster in our sample. Information from this cluster was used to rank-order the SNPs using the PBAT screening algorithm. It is important to note that the subset of individuals was used in the PBAT screening algorithm only. Because the FBAT statistic is robust to population stratification, the entire sample may validly be used in following statistical tests. Using the PBAT screening algorithm we only formally test the top 10 ranked SNPs, and therefore genome-wide significance can be established using a much more liberal threshold than the $10^{-8}$ that has been suggested for formal testing of all SNPs [Dudbridge and Gusnanto, 2008]. In all analyses, we considered additive, dominant, and recessive genetic models. Depending on the genetic model, up to 35,000 additional SNPs had less than 20 informative families and were therefore not used in the analysis. We also examined the association *P*-values of the SNPs in a set of pre-specified ADHD autosomal candidate genes that was generated by the IMAGE study investigators. These genes are as follows: *ADRA1A, ADRA1B, ADRA2A, ADRA2C, ADRB1, ADRB2, ADRBK1, ADRBK2, ARRB1, ARRB2, BDNF, CHRNA4, COMT, CSNK1E, DBH, DDC, DRD1, DRD2, DRD3, DRD4, FADS1, FADS2, HES1, HTR1B, HTR1E, HTR2A, HTR3B, NFIL3, NR4A2, PER1, PER2, PNMT, SLC18A2, SLC6A1, SLC6A2, SLC6A3 (DAT1), SLC6A4, SLC9A9, SNAP25, STX1A, STY1, TPH1*, and *TPH2*. Unfortunately there were no SNPs genotyped in *DRD5*. Finally, we assessed the overlap between the association findings in this manuscript and the findings in the initial manuscript [Neale et al., 2008a] by looking at the SNPs with *P*-values less than 0.0001 in the initial article and *P*-values less than 0.05 in these analyses.

TABLE I. Descriptive Statistics of the Individuals Used in the GWAS Analyses

| | |
|---|---|
| Number of parents | 1865 |
| Number of children | 938 |
| Number of ADHD diagnosed children | 933 |
| Gender distribution of the offspring | |
| Male (percent) | 816 (86.99) |
| Female (percent) | 122 (13.01) |
| Age among offspring (standard deviation) | 10.88 (2.81) |
| Age at onset (standard deviation) | |
| Inattention | 4.31 (1.96) |
| Hyperactive-impulsive | 2.77 (1.85) |
| Average number of inattentive symptoms | 7.98 (1.37) |
| Average number of hyperactive-impulsive symptoms | 8.11 (1.10) |
| Average total number of symptoms | 16.10 (1.92) |

## RESULTS

After the quality control procedures, 438,784 markers were available for analytic use. The PBAT/FBAT programs are not compatible with sex-linked markers. Consequently, we restricted our statistical analysis to 429,981 autosomal markers. A total of 2,803 individuals, 1,865 founders and 938 non-founders were included after the cleaning process. Of these individuals, 29 offspring did not have clinical data and/or parental genotypes resulting in 909 individuals used in the analysis. A summary of the sample is listed in Table I. An example QQ plot is given in Figure 1 and shows no notable deviation from what would be expected under the null hypothesis. Similar plots were found for all of the analyzed phenotypes.

Using PLINK a homogeneous cluster of 1,409 founders, including 660 families with both parents was identified. This cluster was predominantly, but not exclusively made of Northern Europeans. We used these 660 families in the PBAT screening algorithm from which the *P*-values of the top 10 ranked SNPs for each phenotype and genetic model combination were identified and the FBAT statistic was evaluated in the full sample. Two SNPs achieved significance within the

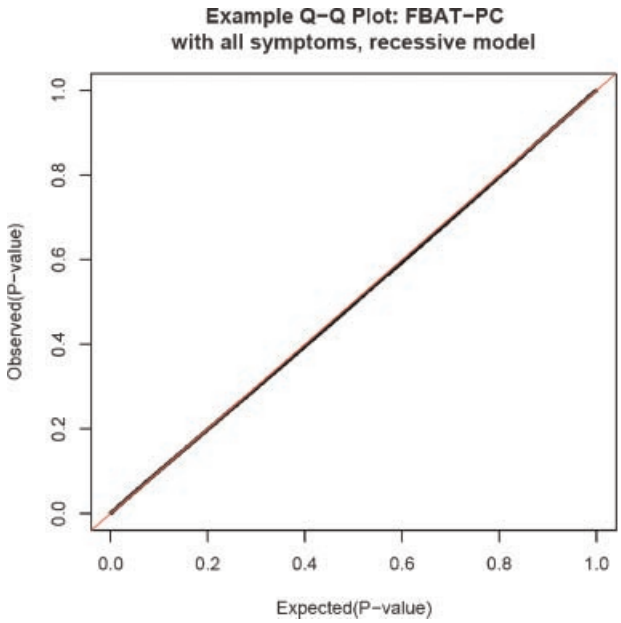


Fig. 1. This is an example QQ plot of the cleaned GWAS data using FBAT-PC with all symptoms using the recessive model. This figure shows that there is no deviation from what would be expected by chance.

TABLE II. A Summary of the SNPs That were Significant Within a Phenotype Using the PBAT Screening Algorithm with Various Quantitative Phenotypes

| SNP | Phenotype | Genetic model | Minor allele frequency | Number of informative families | *P*-value | Power ranking | Gene, location |
|---|---|---|---|---|---|---|---|
| rs6565113 | FBAT–PC with all symptoms | Additive | 0.470 | 656 | 0.005 | 1 | Intron in *CDH13* |
| rs552655 | FBAT–PC with inattentive symptoms | Dominant | 0.468 | 489 | 0.004 | 2 | Intron in *GFOD1* |

specified GWAS analysis. We did not adjust for the tests from all 18 GWAS analyses, but we only adjusted for the SNPs selected from the PBAT screening algorithm for the phenotype and genetic model that was used. If we adjust for selected SNPs from all 18 GWAS analyses, these SNPs do not achieve significance. Rs6565113 was significant for the FBAT–PC phenotype using all symptoms and an additive model while rs552655 was significant with the FBAT–PC using inattentive symptoms and a dominant model. Additional details include the minor allele frequency of the SNP, the number of informative families, the *P*-value, and the power ranking is listed in Table II. Rs6565113 is located in an intronic region of CDH13. Figure 2 illustrates the association *P*-values for all SNPs in CDH13 under the same model and phenotype as the significant effect. Correlations between the FBAT–PC composite phenotype and the 18 individual ADHD symptoms show that rs6565113 is most strongly associated with "excessive talking" and "difficulty with sustaining attention" whereas rs552655 is more strongly associated with "loses things" and "difficulty with sustaining attention."

Among all 18 GWAS analyses, there were 58 association tests with 46 unique SNPs that had a *P*-value $<10^{-5}$. The association analyses identified two SNPs in *IL16*, two SNPs in *LOC390980*, and one SNP in or proximal to each of the following genes: *CLYBL, FHIT, FOXP1, HAS3, LPL, MEIS2, NAPRT1, OXER1, DMTR2, GRIK1, SLCO3A1, ZNF423*, and *ZNF544*. A summary of these findings can be found in Table III, which lists the associated SNP with other relevant information including the genetic model, the number of informative families, the *P*-value, the location, and any flanking genes within 10 kb from the SNP. Flanking genes are provided to consider the potential LD between the SNP and nearby genes.

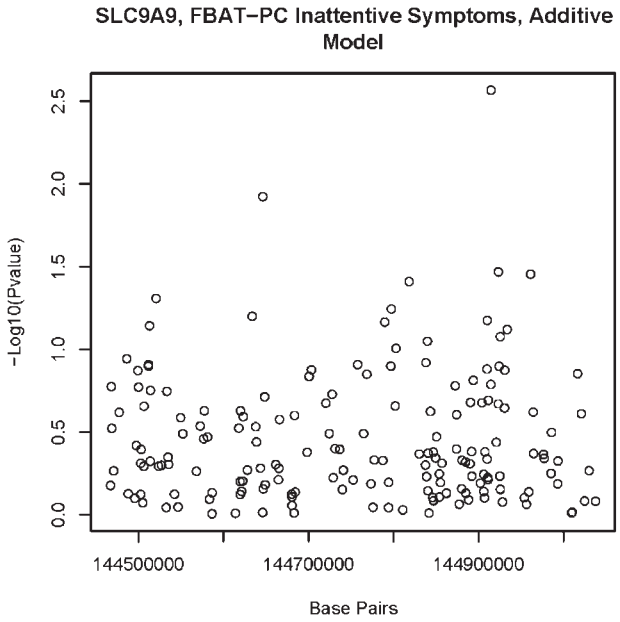


Fig. 2. This figure represents the negative log *P*-values for SNPs in *SLC9A9* using the FBAT-PC methodology with inattentive symptoms using the additive model.

There were numerous associations at the candidate gene SNPs with a *P*-value <0.01. Table IV lists the number of significant SNPs for each candidate genes, the number of different haplotypes these SNPs represent using the criteria by Gabriel et al. [2002], and the lowest association *P*-value at each candidate gene by phenotype. SLC9A9 had 53 nominally significant *P*-values that were less than 0.01 and three association *P*-values with a magnitude of $10^{-5}$ in two distinct regions of the gene. RS1001478 is in an intronic region that had *P*-values of $3.89 \times 10^{-5}$ and $1.85 \times 10^{-5}$ for FBAT–PC with all symptoms and hyperactive-impulsive symptoms respectively while RS1992426 is downstream of SLC9A9 and had a *P*-value of $5.96 \times 10^{-5}$ using FBAT–PC with inattentive symptoms. Furthermore RS1875460, RS9819943, RS10513201, RS1875460, and RS1978913 had association *P*-values with a magnitude of $10^{-3}$ or less. Figure 3 illustrates the association findings in SLC9A9 using FBAT–PC with the hyperactive-impulsive phenotype. Nominally significant SNPs in SLC9A9 were found over a broad portion of the gene, covering seven distinct haplotypic regions. Because the number of SNPs and the linkage disequilibrium patterns vary for each candidate gene, this information must be considered in assessing the overall evidence for association at each candidate gene. Genes SLC9A9, ADRAIA, HTR2A, SNAP25, and SLC6A2 had the largest number of SNPs with 181, 47, 40, 28, and 27 respectively whereas ADRA2A, ADRBK1, ADRBK2, DRD4, HES1, and PNMT only had one SNP each. Given the haplotype block structures for these genes, the nominal findings represent anywhere between 1 and 7 distinct regions.

Table V summarizes the overlap of these findings with the initial manuscript [Neale et al., 2008a] by listing SNPs that had a *P*-value <0.0001 in the initial article and a *P*-value <0.05 in any of the analyses presented here. Annotation data for these 25 SNPs, including chromosomal location, possible functionality, and nearby genes, were found using SCAN (http://genemem.bsd.uchicago.edu/newscan/). In addition, Table V lists the overlap between these results and previous genetic findings for other psychiatric disorders (https://slep.unc.edu/evidence/).

## DISCUSSION

In this analysis we used six quantitative phenotypes, derived from the 18 DSM-IV ADHD symptoms, and three genetic models to perform 18 GWAS analyses with 909 trios (660 trios were used in the screening algorithm, but the full sample was used in the actual analysis). No SNPs achieved genome-wide significance after adjusting for multiple comparisons among all GWAS analyses. By using the PBAT screening algorithm to select the 10 highest-powered SNPs per phenotype/genetic model combination, 2 SNPs did achieve significance within a single GWAS analysis.

TABLE III. A Summary of the Association Findings With *P*-Values Less Than $10^{-5}$ Using the Various Phenotypes

| Phenotype | SNP | Genetic model | Number of informative families | *P*-value | Chr | Base pairs | Flanking gene/function |
|---|---|---|---|---|---|---|---|
| FBAT–PC all symptoms | rs1018040 | Additive | 363 | 4.64E−06 | 1 | 216772437 | |
| | rs1018040 | Dominant | 351 | 2.97E−06 | 1 | 216772437 | |
| | rs930421 | Recessive | 261 | 5.64E−06 | 2 | 42834743 | *OXER1*, downstream |
| | rs7577925 | Dominant | 499 | 2.55E−06 | 2 | 133756989 | *FLJ34870*, intron |
| | rs1350666 | Additive | 571 | 8.30E−06 | 4 | 75443454 | *EREG*, promoter |
| | rs708188 | Recessive | 176 | 7.21E−06 | 12 | 28111983 | |
| | rs522958 | Recessive | 265 | 1.03E−06 | 12 | 28119834 | |
| | rs1514928 | Additive | 261 | 3.05E−06 | 14 | 61748056 | |
| | rs8047014 | Additive | 648 | 3.52E−06 | 16 | 67692550 | *HAS3*, promoter |
| | rs260461 | Dominant | 376 | 8.38E−06 | 19 | 63462695 | *ZNF544*, intron |
| | rs130575 | Additive | 389 | 4.67E−06 | 22 | 33189793 | |
| | rs130575 | Dominant | 376 | 6.20E−06 | 22 | 33189793 | |
| FBAT–PC hyperactive-impulsive symptoms | rs1018040 | Additive | 363 | 8.20E−06 | 1 | 216772437 | |
| | rs6719977 | Additive | 663 | 1.67E−06 | 2 | 42839307 | *OXER1*,downstream |
| | rs6808138 | Additive | 379 | 5.38E−06 | 3 | 162875270 | |
| | rs6808138 | Dominant | 373 | 8.21E−06 | 3 | 162875270 | |
| | rs17641078 | Additive | 322 | 4.73E−06 | 9 | 1046959 | *DMRT2*, coding exon |
| | rs17641078 | Dominant | 315 | 8.44E−06 | 9 | 1046959 | *DMRT2*, coding exon |
| | rs708188 | Recessive | 176 | 2.17E−06 | 12 | 28111983 | |
| | rs522958 | Recessive | 265 | 7.59E−07 | 12 | 28119834 | |
| | rs363512 | Dominant | 209 | 3.89E−06 | 21 | 29972688 | *GRIK1*, intron |
| | rs41441749 | Dominant | 470 | 1.49E−06 | 6 | 18899702 | |
| FBAT–PC inattentive symptoms | rs4147141 | Additive | 383 | 7.90E−06 | 1 | 69351840 | |
| | rs4650135 | Additive | 595 | 5.45E−06 | 1 | 69457585 | |
| | rs4650135 | Dominant | 254 | 6.07E−06 | 1 | 69457585 | |
| | rs11786458 | Additive | 272 | 8.76E−06 | 8 | 40371858 | |
| | rs12679254 | Recessive | 327 | 2.08E−06 | 8 | 74436745 | |
| | rs11790994 | Additive | 233 | 2.47E−07 | 9 | 97469087 | |
| | rs10895959 | Recessive | 232 | 3.00E−06 | 11 | 105835372 | |
| | rs17079773 | Additive | 361 | 4.71E−06 | 13 | 23496384 | |
| | rs17079773 | Dominant | 263 | 6.60E−06 | 13 | 23496384 | |
| | rs7495052 | Recessive | 327 | 2.83E−06 | 15 | 90353033 | *SLCO3A1*, intron |
| | rs17281813 | Recessive | 672 | 3.46E−06 | 16 | 48308291 | *ZNF423*, intron |
| | rs13330107 | Recessive | 327 | 8.50E−06 | 16 | 75436363 | |
| | rs478597 | Additive | 502 | 8.08E−06 | 12 | 116235808 | |
| Total ADHD symptom count | rs272000 | Recessive | 311 | 9.10E−06 | 2 | 116372265 | |
| | rs17367118 | Additive | 269 | 8.69E−06 | 2 | 123358081 | |
| | rs1918172 | Additive | 36 | 5.18E−06 | 2 | 156596746 | |
| | rs11719664 | Additive | 183 | 2.48E−06 | 3 | 21930202 | |
| | rs6791644 | Recessive | 254 | 8.32E−06 | 3 | 60746148 | *FHIT*, intron |
| | rs17651978 | Recessive | 449 | 6.05E−06 | 3 | 71103180 | *FOXP1*, intron |
| | rs2290416 | Additive | 549 | 8.51E−06 | 8 | 144728743 | *NAPRT1*, coding exon |
| | rs10767942 | Dominant | 383 | 7.90E−06 | 11 | 32478583 | |
| | rs7992643 | Dominant | 595 | 5.45E−06 | 13 | 99353039 | *CLYBL*, intron |
| | rs4147141 | Additive | 254 | 6.07E−06 | 1 | 69351840 | |
| Hyperactive-impulsive symptom count | rs11590090 | Recessive | 208 | 2.51E−06 | 1 | 113115086 | |
| | rs1202199 | Dominant | 291 | 8.52E−06 | 6 | 20264153 | |
| | rs7816032 | Recessive | 139 | 2.25E−06 | 8 | 19831171 | *LPL*, promoter |
| | rs8041675 | Additive | 695 | 3.98E−06 | 15 | 35129894 | *MEIS2*, intron |
| | rs13353224 | Additive | 222 | 8.54E−06 | 16 | 63551405 | |
| | rs2014572 | Additive | 676 | 7.32E−06 | 19 | 62451830 | *LOC390980*, promoter |
| | rs10421632 | Additive | 694 | 9.68E−06 | 19 | 62456582 | *LOC390980*, promoter |
| Inattentive symptom count | rs10227331 | Recessive | 415 | 3.79E−06 | 7 | 156987699 | |
| | rs2769967 | Recessive | 404 | 3.63E−06 | 9 | 81079178 | |
| | rs1471225 | Additive | 669 | 8.09E−06 | 15 | 27675688 | |
| | rs7172689 | Additive | 512 | 3.86E−06 | 15 | 79320750 | *IL16*, intron |
| | rs7172689 | Dominant | 478 | 1.50E−06 | 15 | 79320750 | *IL16*, intron |
| | rs4128767 | Dominant | 545 | 1.28E−06 | 15 | 79330462 | *IL16*, intron |

Using the PBAT screening algorithm, we found two SNPs that were significant within the GWAS analysis for the specified phenotype and genetic model. Rs6565113, an intronic SNP in Cadherin 13 (CDH13), achieved significance within the FBAT–PC phenotype including all ADHD symptoms. CDH13 acts as a negative regulator of neural cell growth [Takeuchi et al., 2000] and is expressed in brain regions that structural imaging has also shown to have volumetric reductions in ADHD-diagnosed individuals [Takeuchi et al., 2000; Valera et al., 2007]. The SNP is located in the region where a linkage peak was identified with the IMAGE data using an affection status phenotype [Asherson et al., 2008]. In addition, a recent

TABLE IV. The Lowest Association *P*-Value for each Phenotype Identified From the SNPs Within Each ADHD Candidate Gene

| | | | *P*-value of most strongly associated SNP for each candidate gene* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | FBAT–PC | | | Symptom count | | |
| Candidate gene | SNPs | Number of haplotype blocks | All | H-I | I | All | H-I | I |
| *SLC6A1* | 4 | 2 | 0.0013 | 0.0041 | | | | |
| *SLC9A9* | 32 | 7 | $3.89 \times 10^{-5}$ | $1.85 \times 10^{-5}$ | $5.96 \times 10^{-5}$ | 0.0013 | $2.38 \times 10^{-4}$ | 0.0078 |
| *ADRB2* | 1 | 1 | | | | | | 0.0051 |
| *HTR1E* | 1 | 1 | | | | 0.0053 | | |
| *DDC* | 4 | 1 | | | 0.0055 | | | $5.3 \times 10^{-4}$ |
| *ADRA1A* | 6 | 3 | 0.0023 | 0.0016 | | | 0.0092 | 0.0050 |
| *DBH* | 5 | 1 | 0.0089 | | 0.0017 | 0.0059 | 0.0054 | 0.0057 |
| *BDNF* | 2 | 2 | 0.0051 | 0.0004 | | | | |
| *DRD2* | 1 | 1 | | | | 0.0051 | 0.0013 | |
| *TPH2* | 4 | 1 | | 0.0084 | | 0.0051 | | 0.0023 |
| *HTR2A* | 3 | 3 | | 0.0046 | | 0.0088 | | 0.0046 |
| *SLC6A2* | 1 | 1 | | | | | | 0.0009 |
| *PER1* | 1 | 1 | 0.0055 | | | | | |
| *CHRNA4* | 1 | 1 | | | 0.0019 | | | |
| *SNAP25* | 6 | 2 | | | 0.0036 | $4.84 \times 10^{-4}$ | 0.0012 | 0.0045 |
| *COMT* | 1 | 1 | | 0.0044 | | | | |
| *SYT1* | 1 | 1 | 0.0026 | | | | | |

All, all ADHD symptoms; HI, hyperactive-impulsive symptoms; I, inattentive symptoms.
*$P$-values are only presented for a gene is the at least one SNP in the gene had a $P$-value $<0.01$.

GWAS analysis found and replicated the association of several SNPs in CDH13 (OMIM = 601364) with methamphetamine dependence [Uhl et al., 2008]. A common comorbidity of ADHD is substance abuse/dependence, which makes this gene a viable candidate for ADHD as well. Clearly, future replication efforts are required to either verify or refute this gene as a genetic variant for ADHD. Rs552655 achieved significance with the FBAT–PC phenotype for inattentive symptoms. Although this is not an obvious biologic candidate, rs552655 is located in GFOD1 (UGID:699845), encoding glucose-fructose oxidoreductase domain containing 1, a protein predicted to be involved in electron transport and metabolic processes (e.g., Entrez Gene, URL: http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch= 54438&ordinalpos=3&itool=EntrezSystem2.PEntrez.Gene.Gene_ResultsPanel.Gene_RVDocSum'). Although there is no overlap between this finding and previous ADHD studies, a meta-analysis of genome-wide linkage studies found two markers near GFOD1 that were associated with schizophrenia (D6s274–D6S1586 with a $P$-value of 0.033 and 6PTER–D6S274 with a $P$-value of 0.016) [Lerer et al., 2003].

We identified 58 statistical tests with 46 unique SNPs that had uncorrected association signals at $P$-values $<10^{-5}$. Although none of the genes in Table III have been identified as good candidate genes for ADHD, GRIK1, and SLCO3A1 have been implicated as potential candidates for other psychiatric disorders. Genes involved in glutamatergic transmission, including GRIK1 (a.k.a. GluR5 kainate receptor gene), have been suggested as candidate genes for schizophrenia and mood disorders [Shibata et al., 2001]. Decreased expression of GRIK1 was detected in the perirhinal cortex for major depressive disorder, bipolar disorder, and schizophrenia, suggesting that this may be an important factor in the etiology of these psychiatric disorders [Beneyto et al., 2007]. Additional evidence suggests that SLCO3A1 may be associated with schizophrenia. A whole genome scan was performed using a measure of QT prolongation that was drug induced in schizophrenic patients. This study identified DNA polymorphisms in SLCo3A1 associated with QT prolongation in schizophrenic patients [Volpi et al., 2008]. Another study found nominal significance with SLCO3A1 in early-onset major depressive disorder [Verma et al., 2008]. There is some overlap between these GWAS findings and previous ADHD linkage results. The association finding in the promoter region of EREG, rs1350666, is proximal to the linkage region identified by Arcos-Burgos et al. [2004]. rs7992643, a SNP in an intronic region of CLYBL is also proximal to a peak LOD score identified in another ADHD linkage study [Bakker et al., 2003]. This finding also had overlap with linkage peaks for schizophrenia [Blouin et al., 1998] and bipolar disorder [Detera-Wadleigh et al., 1999]. rs8041675 is in an intronic region of MEIS2 and is proximal to an ADHD linkage finding at D15S194 [Bakker et al., 2003]. There was also overlap between the 18 GWAS analyses and linkage results from other psychiatric disorders. rs7577925 was found to be proximal to

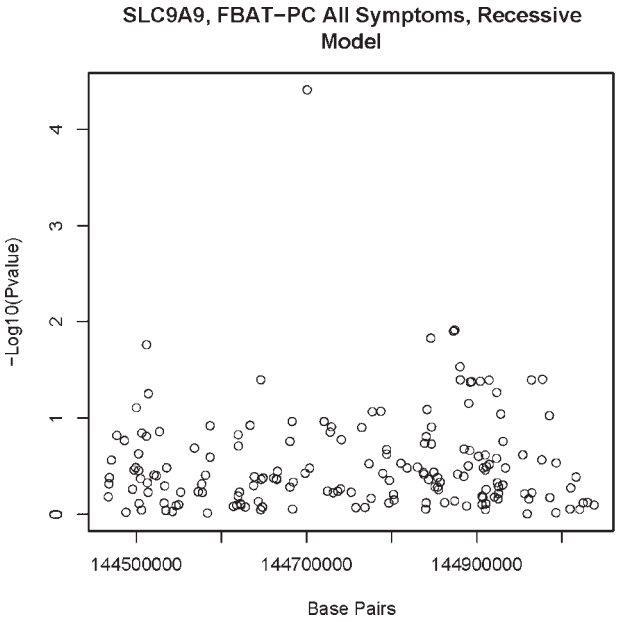


Fig. 3. This figure represents the negative log $P$-values for SNPs in *SLC9A9* using the FBAT-PC methodology with all ADHD symptoms using the recessive model.

TABLE V. The SNPs That Have a *P*-value <0.0001 in the Neale et al. [2008a] Article and a *P*-Value <0.05 in any of the GWAS Analyses Presented in this Article

| Rs number | Chr | Position | Alleles | Gene | Function | Gene to the left | Gene to the right | Previous findings with other psychiatric disorders |
|---|---|---|---|---|---|---|---|---|
| rs4241112 | 2 | 122378682 | CT | | | *TSN* | *AX747402* | |
| rs349158 | 3 | 62054285 | CT | *PTPRG* | intron | *FHIT* | *AK094634* | BP [2007] |
| rs17689952 | 4 | 167158604 | AG | *TLL1* | intron | *CPE* | *SPOCK3* | |
| rs12505502 | 4 | 91787046 | GT | *MGC48628* | intron | *MMRN1* | *TMSL3* | BP [2007] |
| rs13120644 | 4 | 56293259 | CG | | | *NMU* | *EXOC1* | |
| rs876477 | 4 | 20766026 | CT | *KCNIP4* | intron | *C4orf28* | *BC014938* | ND [Li et al., 2008] |
| rs1541665 | 5 | 170075495 | CT | *KCNIP1* | intron | *KCNMB1* | *GABRP* | SCZ [Lewis et al., 2003] |
| rs17673653 | 5 | 170099172 | AT | | | *KCNIP1* | *GABRP* | |
| rs1062793 | 6 | 80468115 | AG | *SH3BGRL2* | mrna-utr | *BX648161* | *ELOVL4* | ADHD [Ogdie et al., 2003] |
| rs13215768 | 6 | 4618712 | AG | | | *KU-MEL-3* | *CDYL* | |
| rs3734552 | 6 | 137154326 | AG | *MAP3K5* | intron | *MAP7* | *PEX7* | SCZ [Lerer et al., 2003] |
| rs6570426 | 6 | 141239039 | AT | | | *BC038188* | *AK097143* | |
| rs6919857 | 6 | 137182147 | CT | | | *MAP3K5* | *PEX7* | |
| rs9389835 | 6 | 141312353 | CT | | | *BC038188* | *AK097143* | |
| rs964647 | 6 | 88993111 | AT | | | *CNR1* | *RNGTT* | |
| rs703965 | 10 | 80625073 | CT | *ZMIZ1* | intron | *AK098249* | *PPIF* | SCZ [Fallin et al., 2003; Faraone et al., 2006] |
| rs11221064 | 11 | 127192523 | CG | | | *BC030092* | *ETS1* | |
| rs17754282 | 11 | 87622650 | GT | | | *RAB38* | *CTSC* | |
| rs3782309 | 12 | 26750663 | GT | *ITPR2* | intron | *SSPN* | *C12orf11* | |
| rs17722514 | 13 | 89511946 | CT | | | *SLITRK5* | *BC038529* | |
| rs922781 | 15 | 58857636 | CG | *RORA* | intron | *BC035094* | *BC033962* | |
| rs4149601 | 18 | 53967789 | AG | *NEDD4L* | intron | *AK056031* | *CR596491* | SCZ/BP [Maziade et al., 2005] |
| rs9676447 | 19 | 54116059 | CT | *NUCB1* | intron | *TULP2* | *DHDH* | |
| rs957794 | 21 | 45583194 | CG | | | *AK056166* | *COL18A1* | |
| rs957795 | 21 | 45583147 | AG | | | *AK056166* | *COL18A1* | |

BP, Bipolar Disorder; SCZ, Schizophrenia; ND, Nicotine Dependence.

a schizophrenia linkage peak [Moises et al., 1995] and rs363512 is in the same region as rs2154490, which was nominally associated with bipolar disorder in a recent GWAS analysis (Anon., 2007). Although many of these associations are with other psychiatric disorders, the comorbidity among these conditions suggests that these genes may be more promising to follow-up in replication.

There were many positive associations with specified ADHD candidate genes. Among the candidate genes, the strongest evidence for association was for SLC9A9, which codes for a sodium/hydrogen exchanger that is expressed in the brain. Nominally significant SNPs in SLC9A9 were found over a broad portion of the gene, covering seven distinct haplotypic regions. This suggests that there may be more than one genetic signal in this gene, however replication of the findings is necessary before anything can be concluded. SLC9A9, which is located on chromosome 3q24, has been suggested as a strong candidate for ADHD because it is located at a translocation breakpoint in a family having multiple cases of ADHD [de Silva et al., 2003].

The overlap between the findings in this article and the initial association analysis with these data provide a list of SNPs that are consistently nominally significant among at least two ADHD phenotypes. This robustness suggests that these SNPs are good candidate to take forward to replication. In addition, a large portion of these SNPs are located in regions where there have been previous reports for significant findings of various psychiatric diseases including ADHD, schizophrenia,

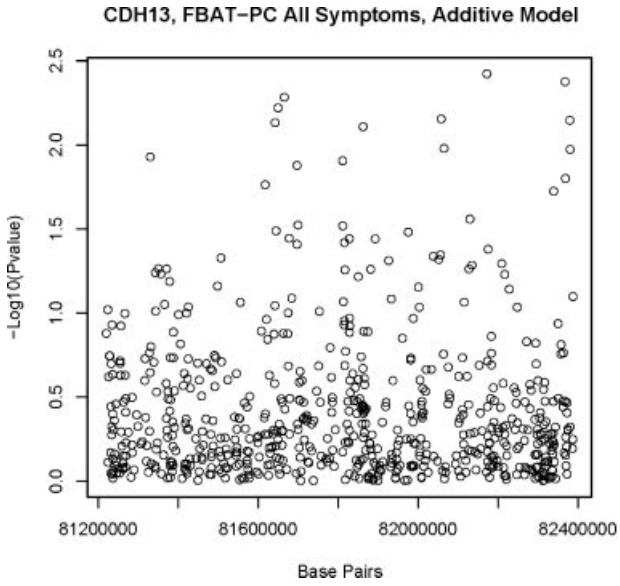


Fig. 4. This figure represents the negative log *P*-values for SNPs in *CDH13* using the FBAT-PC methodology with all ADHD symptoms using the additive model.

nicotine dependence, and bipolar disorder. rs1062793 is actually in a region that was previously reported to have some level of association with ADHD itself [Ogdie et al., 2003].

Despite not finding genome-wide significant associations of SNPs with the quantitative ADHD phenotypes after adjusting for all 18 GWAS analyses, the results presented in this article should be considered a valuable dataset for replication in independent populations. Using ADHD symptoms, as the quantitative trait should greatly facilitate replication efforts compared to other quantitative traits, as these measures are commonly used and likely to be included in other datasets.

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