

Genome-wide association studies in ADHD

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Abstract Attention-deficit/hyperactivity disorder, ADHD, is a common and highly heritable neuropsychiatric disorder that is seen in children and adults. Although heritability is estimated at around 76%, it has been hard to find genes underlying the disorder. ADHD is a multifactorial disorder, in which many genes, all with a small effect, are thought to cause the disorder in the presence of unfavorable environmental conditions. Whole genome linkage analyses

have not yet lead to the identification of genes for ADHD, and results of candidate gene-based association studies have been able to explain only a tiny part of the genetic contribution to disease, either. A novel way of performing hypothesis-free analysis of the genome suitable for the identification of disease risk genes of considerably smaller effect is the genome-wide association study (GWAS). So far, five GWAS have been performed on the diagnosis of ADHD and related phenotypes. Four of these are based on a sample set of 958 parent–child trio’s collected as part of the International Multicentre ADHD Genetics (IMAGE) study and genotyped with funds from the Genetic Association Information Network (GAIN). The other is a pooled GWAS including adult patients with ADHD and controls. None of the papers reports any associations that are formally genome-wide significant after correction for multiple testing. There is also very limited overlap between studies, apart from an association with *CDH13*, which is reported in three of the studies. Little evidence supports an important role for the ‘classic’ ADHD genes, with possible exceptions for *SLC9A9*, *NOS1* and *CNR1*. There is extensive overlap with findings from other psychiatric disorders. Though not genome-wide significant, findings from the individual studies converge to paint an interesting picture: whereas little evidence—as yet—points to a direct involvement of neurotransmitters (at least the classic dopaminergic, noradrenergic and serotonergic pathways) or regulators of neurotransmission, some suggestions are found for involvement of ‘new’ neurotransmission and cell–cell communication systems. A potential involvement of potassium channel subunits and regulators warrants further investigation. More basic processes also seem involved in ADHD, like cell division, adhesion (especially via cadherin and integrin systems), neuronal migration, and neuronal plasticity, as well as related transcription, cell

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polarity and extracellular matrix regulation, and cytoskeletal remodeling processes. In conclusion, the GWAS performed so far in ADHD, though far from conclusive, provide a first glimpse at genes for the disorder. Many more (much larger studies) will be needed. For this, collaboration between researchers as well as standardized protocols for phenotyping and DNA-collection will become increasingly important.

Review

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder. The prevalence of the disorder in children is estimated at 5.3%, estimates for adults vary from 1 to 4% (Faraone et al. 2000b; Kessler et al. 2006; Kooij et al. 2005; Polanczyk and Rohde 2007). A large number of studies, including family, adoption and twin studies suggest that ADHD is among the most heritable of neuropsychiatric disorders: ADHD was found to segregate in families with different studies finding risk increases of two to eightfold for parents and siblings of affected children (reviewed by Faraone and Doyle 2001). Adoption studies showed that the biological parents of hyperactive children carry a higher risk for ADHD compared to adoptive parents (Cantwell 1975; Morrison and Stewart 1973), and that first-degree adoptive relatives of probands with ADHD have a lower disease risk than the first-degree biological relatives of non-adopted ADHD probands (Sprich et al. 2000). More than 20 twin studies have been published in the last 32 years, most reporting estimates of heritability for ADHD between 60 and nearly 100%, with a mean of 76% (Faraone et al. 2005; Haberstick et al. 2008; Heiser et al. 2006; McLoughlin et al. 2007; Schultz et al. 2006).

The genetic architecture of ADHD is not currently clear. A polygenic transmission model seems likely (Faraone and Doyle 2001; Morrison and Stewart 1974), although some authors have suggested more dominant gene effects (Acosta et al. 2004; Deutsch et al. 1990; Maher et al. 1999; Morrison and Stewart 1974). Since it is also known that environmental factors play a role in ADHD etiology (for review see Banerjee et al. 2007), the disorder seems best described as being of multifactorial origin.

Identifying the individual genes contributing to the genetic variance of ADHD has proven difficult. Two approaches have been available for this type of research until recently: hypothesis-driven candidate gene association studies and hypothesis-free genome-wide linkage analysis. Although hundreds of candidate gene studies have been reported (see for example Bobb et al. 2005; Khan and Faraone 2006), only a handful of associations have been

replicated across studies, although none of these achieved genome-wide significance (e.g. Faraone et al. 2005; Li et al. 2006). These studies have mainly concentrated on genes involved in neurotransmission, particularly in the catecholaminergic systems involved in the response to ADHD medications. Clearly, the hypothesis-driven approach has been limited by our restricted knowledge regarding mechanisms involved in ADHD pathogenesis. Genome-wide, hypothesis-free linkage analysis has been performed in ADHD using qualitative and quantitative definitions of the disease phenotype (Arcos-Burgos et al. 2004; Asherson et al. 2008; Bakker et al. 2003; Hebebrand et al. 2006; Ogdie et al. 2003; Ogdie et al. 2004; Ogdie et al. 2006; Romanos et al. 2008; Zhou et al. 2008a), and recently also using ADHD endophenotypes at the level of neuropsychological functioning (Doyle et al. 2008; Rommelse et al. 2008c). Although linkage designs have been highly successful in the identification of genes for monogenic diseases, this has not been the case for polygenic or multifactorial disorders. The linkage studies in ADHD have identified a number of genetic loci (potentially) harboring genes for ADHD, but very little overlap was observed between studies, so far. A recent meta-analysis of ADHD linkage studies only confirmed one locus, on chromosome 16 (Zhou et al. 2008c).

Generally, the results of both candidate gene-based association studies and genome-wide linkage studies have not identified major genes for ADHD. In candidate gene studies, individual gene variants have only shown small effects, rarely reaching an odds ratio of 1.3 (e.g. Faraone et al. 2005). This strongly limits the power of genetic linkage designs in ADHD research, as these designs are suited for the identification of individual genetic variants that explain at least 10% of the genetic variance of a trait or disease (Risch and Merikangas 1996). A situation like this calls for a new analytic approach, one which combines the power to detect genetic variants of small effect size, like the association studies, with the possibility to perform hypothesis-free analyses of the entire genome. This has recently become feasible using the genome-wide association study (GWAS) methodology. In GWAS, 100,000 to more than 1,000,000 genetic variants (in this case single nucleotide polymorphisms, SNPs), distributed across the entire genome are genotyped using a microarray platform and (individually) tested for association with a trait or disorder. The selection of SNPs is mostly based on the distribution of linkage disequilibrium (LD) across the genome, as identified by the HapMap project (Frazer et al. 2007; The International HapMap Consortium 2005). This selection is sufficient to obtain information about most of the frequent genetic variation in the genome (Manolio et al. 2008; Pearson and Manolio 2008), especially for the newer platforms, which include around 1,000,000 or more SNPs.

In the short time of their existence, GWAS have already led to the identification of more than 100 genetic variants significantly associated with about 40 different traits and diseases, including a number of psychiatric ones (e.g. Ferreira et al. 2008; O'Donovan et al. 2008; O'Donovan et al. 2009; Sklar et al. 2008). Although highly successful, design-wise (for an overview of GWAS approaches see Neale and Purcell 2008), the GWAS method has not been exploited to the fullest, given its high financial costs (sample sizes of several thousands to ten-thousands may be needed, see for a recent discussion of this matter Burton et al. 2008). Major progress in the field came through a number of GWAS initiatives funded by government and industry, like the Wellcome Trust Case Control Consortium (WTCCC; 2007) and the Genetic Association Information Network (GAIN; Manolio et al. 2007). Among the 13 diseases that were analyzed in the first rounds of these two initiatives, the WTCCC included 1 and GAIN included 4 psychiatric disorders.

GAIN has also been the setting for the first GWAS in ADHD, which was carried out in 958 Caucasian case–parent-trios collected as part of the International Multi-centre ADHD Genetics (IMAGE) study in children (Brookes et al. 2006; Kuntsi et al. 2006). Using the genotyping data from this study, Neale et al. (2008a) reported a classic transmission disequilibrium analysis (TDT) of a categorically defined ADHD phenotype. In addition, Lasky-Su et al. (2008b) performed an analysis using quantitative measures of ADHD symptoms. In the meantime, a second set of genome-wide data has been reported by Lesch and coworkers. These researchers used pools of DNA from 343 ADHD-affected adults and 304 controls for their genome-wide association analysis of a categorical ADHD phenotype (Lesch et al. 2008). Following the first analyses, the GAIN/IMAGE ADHD dataset has since been used for a number of exploratory studies using additional phenotypes and designs, like the age of onset of ADHD symptoms (Lasky-Su et al. 2008a), conduct problems (Anney et al. 2008b), and even a genome-wide gene–environment interaction ($G \times E$) study evaluating genetic variants moderating the effects of maternal expressed emotion on ADHD symptoms (and conduct problems; Sonuga-Barke et al. 2008). In the following paragraphs, we will discuss most of these studies and their most important findings. The two studies exploring conduct problems in the GAIN/IMAGE dataset (Anney et al. 2008b; Sonuga-Barke et al. 2008) are beyond the scope of this review.

As mentioned above, most of the GWAS data so far are derived from one sample of child–parent triads collected as part of the IMAGE study. IMAGE is a consortium of researchers from seven European countries and Israel. IMAGE has ascertained more than 1,400 families through a (preferentially combined subtype) ADHD-affected proband

(Brookes et al. 2006; Kuntsi et al. 2006). The probands were required to be in the age range from 5 to 17 years. All families were of European Caucasian descent. In all families, both parents and at least one sibling, the latter not selected for phenotype, were required to take part in the study. IMAGE participants were extensively phenotyped for ADHD and comorbid disorders, using the Parental Account of Childhood Symptoms (PACS) (Taylor et al. 1986), administered by centrally trained investigators. In addition, rating scale measures were used, including the Long Version of Conners' Parent and Teacher Rating Scales, as well as the parent and teacher version of the Strength and Difficulties Questionnaires (SDQ) (Conners 2003). A standardized algorithm was applied to PACS to derive each of the 18 DSM-IV ADHD items, and, taking into account a number of Conners items, a clinical diagnosis was made. Exclusion criteria included a low IQ (<70), autism, epilepsy, and brain or genetic disorders known to mimic ADHD symptoms. In GAIN, 958 family triads from IMAGE, including the proband and his/her parents were analyzed (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000016.v1.p1). DNA was isolated from blood by Rutgers Cell and DNA Repository (<http://www.rucdr.org/>). The samples were analyzed by Perlegen Sciences on a microarray specially designed for GAIN. The array investigates approximately 600,000 SNPs able to capture information of close to 100% of the common genetic variation in Caucasians (Neale et al. 2008a). Data cleaning of the genotyping results was performed through the National Centre for Biotechnology Information (NCBI), leaving 438,784 SNPs for analysis.

The first paper on the GAIN/IMAGE ADHD genome-wide dataset was based on the 909 complete family triads, for which full genotyping information was available (Neale et al. 2008a). Of these families, 790 contained male probands, 119 female probands. A total of 845 probands had a combined subtype ADHD diagnosis, the average number of symptoms was 16.1. The TDT design was chosen for this study which contained families recruited from all over Europe and from Israel, based on its robustness against population stratification. Earlier research by Neale et al. (2008b) had shown that differences indeed existed between the different genetic backgrounds of the IMAGE participants, especially with the Israeli families of European Caucasian descent. In addition, the family controlled design showed more stability in the presence of non-random genotyping error in GAIN (Anney et al. 2008a). No genome-wide significant results were observed (with the highest P values at $7.45E-06$), although a power analysis presented in the paper suggests that the size of the dataset would have been sufficient to detect at least one genome-wide significant (P value $5.0E-08$) finding for a genetic variant with a minor allele frequency (MAF) of 0.2 causing

an odds ratio of 1.3. A table in the Neale et al. paper presents the highest-ranking 25 SNPs (based on P value) (see also Table 1 in this review).

In a TDT design, the number of observed transmissions of a given allele of a SNP is compared to the expected frequency under the assumption of no association (Spielman and Ewens 1996). Performing the TDT, the authors noted a highly significant imbalance in the number of major and minor allele over-transmissions. Given the large numbers of SNPs analyzed, these numbers would have been expected to be similar. Removing additional SNPs that had failed quality control in one of the other two GWAS based on the Perlegen microarray improved this imbalance partly, suggesting that genotyping error or missingness is (at least partly) responsible for this effect. Therefore, the authors repeated their analysis including a correction factor. Comparison of the presented tables listing the top-25 SNPs before and after correction shows that this resulted in the loss of half of the listed SNPs and a general downward correction of P values. Although, as the authors state, it might be (too) early to explore the biological relevance of the strongest observed associations, it is a fact that the list contains a number of very interesting candidate genes for ADHD (Table 1), most notably those genes that also show association in the GWAS of quantitative ADHD-related phenotypes (Lasky-Su et al. 2008b), as indicated in Table 1. Among these is a SNP close to *CNR1*, which encodes the cannabinoid receptor 1, a gene that falls into a linkage region for ADHD from a primary analysis (Ogdie et al. 2004) and shows suggestive linkage in meta-analysis (Zhou et al. 2008c). *CNR1* was also found associated with the disorder in candidate gene-based association studies (Lu et al. 2008; Ponce et al. 2003). Furthermore, association of *CNR1* with alcohol and drug abuse and dependence has been observed (Zuo et al. 2007). Also of interest are the findings for the especially brain-expressed cytoskeleton-organizer *DCLK1* and the extracellular matrix component *SPOCK3*, as well as the two potassium-channel regulators *KCNIP1* and *KCNIP4* (Table 1).

In an attempt to maximize the power of the GAIN/IMAGE family-based GWAS, Lasky-Su et al. (2008b) published a study focusing on quantitative ADHD phenotypes using the Family-based Association Test (FBAT) suite of programs. Based on the 18 DSM-IV symptoms of ADHD the authors constructed 3 quantitative phenotypes using (1) the number of hyperactive–impulsive symptoms, (2) the number of inattentive symptoms, and (3) the total number of symptoms. These phenotypes were each tested under three different genetic models (additive, dominant, recessive). Furthermore, three additional quantitative traits were constructed based on the Conners ADHD Rating Scales and the PACS using FBAT-PC methodology (Lange

et al. 2004c). This approach constructs a slightly different phenotype for every SNP in order to maximize the heritability at this SNP. Association testing was subsequently limited to the set of ten SNPs per genotype with the highest power to detect association derived from a screening algorithm in the program PBAT (Lange et al. 2004b; van Steen and Lange 2005). In total, this study performed 18 GWAS, increasing the multiple testing burden; correction for multiple testing was limited to the single GWAS.

In addition to increasing power, using symptoms or rating scales as a basis for phenotype selection had the advantage that hyperactive–impulsive and inattentive symptoms could be assessed independently in the combined subtype ADHD of the GAIN/IMAGE participants. However, a prerequisite for this quantitative approach to be valid is that ADHD is a disorder at the extreme of a continuum observed in the population. Evidence suggesting that this is indeed true comes from twin studies showing strong heritability of quantitative measures of ADHD (Lasky-Su et al. 2008b, and references herein) as well as from a proband–sibling comparison in IMAGE (Chen et al. 2008; Thapar et al. 2006). Starting from the cleaned GAIN dataset, Lasky-Su restricted the analysis to 429,784 autosomal SNPs (as FBAT cannot handle X-linked markers) and 909 complete families. 87% of the probands were male, and the mean age of probands was 10.88 years. The average total number of symptoms was 16.11, the number of hyperactive–impulsive symptoms was 8.11 and the number of inattentive ones was 7.98.

Two genome-wide significant findings (corrected for single analysis) emerged from the formal tests, one for rs6565113 in an intron of *CDH13* associated under an additive genetic model with the FBAT-PC-based phenotype derived from all ADHD symptoms, one for rs552655 in an intron of *GFOD1* associated with the FBAT-PC phenotype for inattentive symptoms (dominant model). The *CDH13* finding is especially interesting, since a SNP near this gene also is part of the top-25 in the GWAS by Neale et al. (2008a, b), though the two studies are not entirely independent, of course, and the gene is also found among the top-findings from the ADHD GWAS by Lesch et al. (2008, see below) and falls into the only significant ADHD linkage region identified in the recent meta-analysis (Zhou et al. 2008c). Furthermore, association with SNPs in *CDH13* is one of the most consistent findings in genome-wide studies on a wide variety of phenotypes related to drug abuse and dependence (Uhl et al. 2008a, b), although there is no clear indication, which region of the gene is most important. Possibly, different regions or risk factors might cause different phenotypes. *CDH13* codes for cadherin 13 (or T-cadherin), a member of a family of cell–cell adhesion proteins (Patel et al. 2003), in addition to being a regulator of neural cell growth. *CDH13* shows a brain

Table 1 Findings from TDT-based GWAS by Neale et al. (2008a), including genes in or near which the association finding is present as well information regarding the role of the gene and its possible involvement in psychiatric disorders

SNP	OR	P value	Chr	Position (bp)	Position	Gene function ^a	Additional remarks
rs2295426	0.7103	1.00E-05	14	58446208	Intergenic	Nucleobindin 1, function unknown, expression in multiple organs, including brain, family member	Site is known for CNVs
rs9676447	2.078	1.01E-05	19	54116059	Intron of NUCB1	NUCB2 encodes a satiety molecule that is associated with melanocortin signaling in the hypothalamus (Oh et al. 2006)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs2311120	0.6795	1.22E-05	18	50628121	Approximately 20 kb upstream of RAB27B	Rabs are prenylated, membrane-bound proteins involved in vesicular fusion and trafficking. RAB27B is primarily expressed in testis, but also found in brain. SNP is present in schizophrenia linkage region (Maziade et al. 2005)	
rs964647	1.717	1.34E-05	6	88993111	Approximately 80 kb downstream of CNR1	Encodes Cannabinoid receptor 1, highly expressed in brain and earlier found associated with alcohol and drug abuse and dependence (Zuo et al. 2007) and ADHD CNR1 has earlier been shown associated with ADHD (Lu et al. 2008; Ponce et al. 2003), present in region showing suggestive linkage to ADHD in meta-analysis (Zhou et al. 2008c) and a primary linkage analysis in ADHD (Ogdie et al. 2004)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs9389835	0.7307	1.58E-05	6	141312353	Intergenic		Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs876477	1.903	2.69E-05	4	20766026	Intron of KCNIP4	Encodes Kv channel interacting protein 4 isoform 3, a member of the family of voltage-gated potassium (Kv) channel-interacting proteins (KCNIPs), and may regulate A-type currents, and hence neuronal excitability, in response to changes in intracellular calcium. The KCNIP4 protein also interacts with presenilin. Gene is also found among top-findings from GWAS in schizophrenia (Sullivan et al. 2008) and shows P values at 10^{-5} in GWAS in bipolar disorder (Sklar et al. 2008)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs6570426	0.735	2.74E-05	6	141239039	Intergenic	Lies close to Schizophrenia linkage region (Lerer et al. 2003), with some evidence for nearby linkage region from a primary study in adult ADHD (Romanos et al. 2008) and the ADHD linkage meta-analysis (Zhou et al. 2008c)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs1539549	0.7305	2.88E-05	13	35349881	Intron of DCLK1 = DCAMKLI1	Encodes doublecortin and CaM kinase-like 1, a microtubule-associated protein with microtubule polymerizing activity. Predominantly expressed in fetal and adult brain	

Table 1 continued

SNP	OR	P value	Chr	Position (bp)	Position	Gene function ^a	Additional remarks
rs9484448	0.7385	2.94E-05	6	141260753	Intergenic	Lies close to schizophrenia linkage region (Lerer et al. 2003), with some evidence for nearby linkage region from a primary study in adult ADHD (Romanos et al. 2008) and the ADHD linkage meta-analysis (Zhou et al. 2008c)	
rs7657608	1.356	2.96E-05	4	168390756	Intron of SPOCK3	Encodes a member of a novel Ca(2+)-binding proteoglycan family, a component of the extracellular matrix, high expression in brain, especially the caudate nucleus	
rs9608617	1.376	2.96E-05	22	26236244	Intergenic	Lies within schizophrenia linkage region reported in meta-analysis (Lewis et al. 2003)	
rs6657749	0.6643	2.99E-05	1	212643136	Intron of PTPN14	Encodes a brain-expressed member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. Gene shows P values at 10^{-4} in GWAS in bipolar disorder (Sklar et al. 2008)	Site is known for CNVs. Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs17722514	1.648	3.14E-05	13	89511946	Intergenic		
rs1427324	0.7236	3.50E-05	14	58434446	Intergenic		
rs11221064	1.439	3.89E-05	11	127192523	Intergenic	Close to schizophrenia linkage region reported in meta-analysis (Lewis et al. 2003)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs6919857	0.749	4.79E-05	6	137182147	Within 5 kb upstream of PEX7 and 27 kb downstream of MAP3K5	PEX7 encodes peroxisomal biogenesis factor 7, the cytosolic receptor for a set of peroxisomal matrix enzymes. MAP3K5 encodes a member of the MAPK pathway, that might be involved in apoptotic regulation in the brain	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs12772737	0.7246	4.96E-05	10	116731491	Within 6 kb downstream of TRUB1	Encodes TruB pseudouridine (psi) synthase homolog 1, expressed in many tissues, including brain, which may be responsible for synthesis of pseudouridine from uracil in tRNAs	
rs17754282	1.441	4.97E-05	11	87622650	Intergenic		Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)

Table 1 continued

SNP	OR	P value	Chr	Position (bp)	Position	Gene function ^a	Additional remarks
rs7187223	0.4458	5.21E-05	16	81015234	Intergenic, within 203 kb upstream from CDH13	Encodes cadherin 13, a member of the cadherin superfamily. The encoded protein is a calcium-dependent cell–cell adhesion glycoprotein. This particular cadherin is a putative mediator of cell–cell interaction in the heart and may act as a negative regulator of neural cell growth. Lies within the only significant linkage region for ADHD as determined in meta-analysis (Zhou et al. 2008c). Has earlier shown association with metamphetamine dependence in GWAS (Uhl et al. 2008a). Gene is also found in GWAS in schizophrenia with P values at 10^{-4} (Sullivan et al. 2008) and shows CNVs potentially related to autism (Christian et al. 2008)	Most significant finding in quantitative GWAS by Lasky-Su et al. (2008b). Also shows association with adult ADHD in the GWAS by Lesch et al. (2008)
rs3782309	1.527	5.53E-05	12	26750663	Intron of ITPR2	Encodes a receptor for inositol 1,4,5-trisphosphate, a second messenger that mediates the release of intracellular calcium. Expression in many tissues, including brain. ITPR2 is involved in glutamate-mediated neurotransmission, is one of the main regulators of intracellular calcium concentrations, and has an important role in apoptosis. Shows association with amyotrophic lateral sclerosis (ALS) in GWAS (van Es et al. 2007)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs1541665	0.6338	5.60E-05	5	170075495	Intron of KCNIP1	Encodes Kv channel interacting protein 1 isoform 2, a member of the family of voltage-gated potassium (Kv) channel-interacting proteins (KCNIPs), and may regulate A-type currents, and hence neuronal excitability, in response to changes in intracellular calcium. Lies close to linkage region observed in several primary studies as well as a meta-analysis (Lewis et al. 2003). Gene is also found in GWAS in schizophrenia with p -values at 10^{-4} (Sullivan et al. 2008)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs12505502	1.303	5.62E-05	4	91787046	Intron of MGC48628	Hypothetical gene/protein. Highly expressed in cerebellum, expression also in other parts of the brain and tissues. Gene is also found in GWAS in bipolar disorder with P values at 10^{-5} (Wellcome Trust Case Control Consortium 2007)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)

Table 1 continued

SNP	OR	P value	Chr	Position (bp)	Position	Gene function ^a	Additional remarks
rs922781	1.315	5.62E-05	15	58857636	Intron of RORA	Encodes a member of the NR1 subfamily of nuclear hormone receptors. It can bind either as a monomer or as a homodimer to hormone-response elements upstream of several genes to enhance the expression of those genes. The specific functions of this protein are not known, but it has been shown to interact with NM23-2, a nucleoside diphosphate kinase involved in organogenesis and differentiation, as well as with NM23-1, the product of a tumor metastasis suppressor candidate gene. Close to suggestive linkage region for ADHD (Faraone et al. 2008). Gene is also found in GWAS in schizophrenia with p-values at 10^{-4} (Sullivan et al. 2008)	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs4241112	0.7214	6.06E-05	2	122378682	Intergenic	Within and close to schizophrenia linkage regions (Lewis et al. 2003).	Also shows nominal association ($P < 0.05$) in quantitative GWAS by Lasky-Su et al. (2008b)
rs2678787	0.7228	6.36E-05	18	26436326	Intergenic		Site is known for CNVs

^a Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ± 5 Mb for genome-wide linkage scans, ± 5 kb for GWAS, microarray and CNV studies, and ± 50 kb for signposts)

expression profile consistent with a role in ADHD, being expressed in regions showing volumetric reductions in patients with this disorder (Takeuchi et al. 2000; Takeuchi and Ohtsuki 2001; Valera et al. 2007). Very little is known about the second associated gene, *GFOD1* and its product, glucose-fructose oxidoreductase-domain containing 1, except that it is expressed in brain and possibly plays a role in electron transport (Lasky-Su et al. 2008b).

In addition to the formal testing of ten SNPs for each phenotype Lasky-Su and coworkers also report a more exploratory analysis of all SNPs in the dataset. There were 58 association findings with P values smaller than 10^{-5} , of which 46 SNPs were unique. Some SNPs showed association under more than one genetic model and/or across phenotypes. Although none of the SNPs listed here are genome-wide significantly associated with ADHD, a high percentage of the SNPs is present in brain-expressed genes and/or in linkage regions for ADHD and other psychiatric disorders (see Table 2). A particularly interesting finding from this set includes the SNP in *NOS1*, encoding the neuronal form of nitric oxide synthase. NO acts as the second messenger of the *N*-methyl-D-aspartate receptor and interacts with both the dopaminergic as well as the serotonergic system in the human brain. *NOS1* has been associated with impulsive and aggressive behavior and ADHD (Reif et al. 2009). Association has also been noted with Alzheimer's disease (Galimberti et al. 2008) and schizophrenia, as well as with related neuropsychological performance (Reif et al. 2006).

Lasky-Su and colleagues also reported P values for a selection of predefined (classic) ADHD candidate genes (Brookes et al. 2006). Most significant findings with P values in the range of 10^{-5} were observed for *SLC9A9*. This gene (which was with a total of 181 SNPs the largest gene analyzed) also contained the largest number of associations in terms of SNPs and phenotypes. Other findings at P values of 10^{-4} were for *DDC* and *SNAP25*. The *SLC6A1*, *ADRB2*, *HTR1E*, *ADRA1A*, *DBH*, *BDNF*, *DRD2*, *TPH2*, *HTR2A*, *SLC6A2*, *PER1*, *CHRNA4*, *COMT* and *SYT1* genes showed association at 10^{-3} . *SLC9A9* encodes a sodium/hydrogen exchanger and may be a particularly viable candidate gene for ADHD. It was originally reported disrupted in a patient with ADHD (de Silva et al. 2003) and also shows mutations in patients with autism (Morrow et al. 2008) as well as having been found in multiple GWAS for addiction-related disorders (Uhl et al. 2008a, b).

A GWAS not based on the GAIN/IMAGE sample was published by Lesch et al. (2008). In their study they analyzed 343 German patients with persistent ADHD (mean age 32.9 years with a range from 18 to 65, 54.5% male, 61.5% combined subtype, 31.2% inattentive subtype, 7.3% hyperactive-impulsive subtype) and 304 controls (mean age 32.7, 51.3% male). Patients were diagnosed using the

Table 2 Association findings from quantitative GWAS by Lasky-Su et al. (2008b) with P values $<10^{-5}$, including genes in or near which the association finding is present as well information regarding the role of the gene and its possible involvement in psychiatric disorders

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks	
FBAT-PC all symptoms	rs6565113	Additive	NA [#]	16	81665146	Intron of CDH13	Encodes cadherin 13, a member of the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein. This particular cadherin is a putative mediator of cell-cell interaction in the heart and may act as a negative regulator of neural cell growth. Lies within the only significant linkage region for ADHD as determined in met-analysis (Zhou et al. 2008c). Has earlier shown association with metamphetamine dependence in GWAS (Uhl et al. 2008a). Gene is also found in GWAS in schizophrenia with P values of 10^{-4} (Sullivan et al. 2008) and shows CNVs potentially related to autism (Christian et al. 2008)	Gene also shows association with adult ADHD in the GWAS by Neale et al. (2008a) and Lesch et al. (2008)	
	rs1018040	Additive	4.64E-06	1	216772437	Intergenic	Region lies close to linkage interval for anorexia nervosa (Devlin et al. 2002)		
	rs1018040	Dominant	2.97E-06	1	216772437				
	rs930421	Recessive	5.64E-06	2	42834743	Exon of MTA3	Encodes metastasis associated 1 family, member 3, a component of the nucleosome-remodeling and histone- deacetylase multiprotein complex (NuRD). MTA3 plays a role in maintenance of the normal epithelial architecture through the repression of SNAIL transcription in a histone deacetylase-dependent manner, and the regulation of E-cadherin levels. Expressed in multiple tissues, including brain, especially cerebellum	Close to rs6719977 associated with FBAT-PC hyperactive-impulsive symptoms and rs10865184 showing association with ADHD symptom count in interaction with maternal criticism	
	rs7577925	Dominant	2.55E-06	2	133756989	Intron of NAP5 (FLJ34870)	Encodes Nck-associated protein 5, a peripheral clock protein 2. Expressed in brain (especially cerebellum) and other tissues. Function unknown. Within schizophrenia linkage region observed in meta-analysis (Lewis et al. 2003)		
	rs1350666	Additive	8.30E-06	4	75443454	Within 15 kb upstream of EREG	Encodes epi-regulin, a member of the epidermal growth factor family, which can bind to the EGF receptor and may be a mediator of localized cell proliferation. As a mitogen it may stimulate cell proliferation and/or angiogenesis		
	rs708188	Recessive	7.21E-06	12	28111983	Intergenic	Within 5 kb of genome-wide significant association for type 2 diabetes (Zeggini et al. 2007)		
	rs522958	Recessive	1.03E-06	12	28119834	Intergenic			

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
	rs1514928	Additive	3.05E-06	14	61748056	Within 110 kb downstream of SYT16	Encodes synaptotagmin XVI, which may be involved in the trafficking and exocytosis of secretory vesicles in non-neuronal tissues. Is Ca(2+)-independent and expressed in brain	Site known for CNVs
	rs8047014	Additive	3.52E-06	16	67692550	Within 5 kb upstream of HAS3, within 20 kb downstream of TMCO7	HAS3 encodes hyaluronan synthase 3 isoform a, a protein involved in the synthesis of the unbranched glycosaminoglycan hyaluronan, or hyaluronic acid, which is a major constituent of the extracellular matrix. Expressed in brain and other tissues TMCO7 encodes transmembrane and coiled-coil domains 7, a protein of unknown function. Expressed in brain and other tissues	
	rs260461	Dominant	8.38E-06	19	63462695	Within intron or 3'UTR of ZNF544	Within linkage region for ADHD as identified in meta-analysis (Zhou et al. 2008c)	
	rs130575	Additive	4.67E-06	22	33189793	Intergenic	Encodes zinc finger protein 544, a zinc-regulated transcription factor expressed in brain and many other tissues	
	rs130575	Dominant	6.20E-06	22	33189793		Present in or near (suggestive) linkage regions for schizophrenia reported in meta-analysis (Lewis et al. 2003), for nicotine dependence (Saccone et al. 2007; Kelsoe et al. 2001)	
FBAT-PC hyperactive-impulsive symptoms	rs1018040	Additive	8.20E-06	1	216772437	See above	Encodes metastasis associated 1 family, member 3, a component of the nucleosome-remodeling and histone-deacetylase multiprotein complex (NuRD). MTA3 plays a role in maintenance of the normal epithelial architecture through the repression of SNAIL1 transcription in a histone deacetylase-dependent manner, and the regulation of E-cadherin levels. Expressed in multiple tissues, including brain, especially cerebellum	Close to rs930421 associated with FBAT-PC all symptoms and rs10865184 showing association with ADHD symptom count in interaction with maternal criticism
	rs6719977	Additive	1.67E-06	2	42839307	Within 2 kb downstream of MTA3		
	rs6808138	Additive	5.38E-06	3	162875270	Intergenic		Site known for CNVs
	rs6808138	Dominant	8.21E-06	3	162875270			
	rs41441749	Dominant	1.49E-06	6	18899702	Intergenic		

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
	rs17641078	Additive	4.73E-06	9	1046959	In coding exon of DMRT2	Encodes doublesex and mab-3 related transcription factor 2, a potential regulator of sex differentiation. Expressed in multiple tissues, including brain. Falls into/close to suggestive linkage regions for autism (Allen-Brady et al. 2008; Szatmari et al. 2007b) and close to suggestive linkage region for nicotine dependence (Li et al. 2008)	Site known for CNVs
	rs17641078	Dominant	8.44E-06	9	1046959			
	rs708188	Recessive	2.17E-06	12	28111983	See above		
	rs522958	Recessive	7.59E-07	12	28119834	See above		
	rs363512	Dominant	3.89E-06	21	29972688	In intron of GRIK1	Encodes glutamate receptor, ionotropic, kainate 1. Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes. This gene product belongs to the kainate family of glutamate receptors, which are composed of four subunits and function as ligand-activated ion channels. Earlier association studies suggest involvement of the gene in epilepsy en Parkinson's disease (Lasky-Su et al. 2008b). Gene is also found in GWAS in bipolar disorder with <i>P</i> values at 10^{-4} (Wellcome Trust Case Control Consortium 2007)	
FBAT-PC inattentive symptoms	rs552655	Dominant	n.a.#	6	13478466	Intron of GFOD1	Encodes glucose-fructose oxidoreductase domain containing 1 a gene expressed in brain and other tissues. The protein is predicted to be involved in electron transport and metabolic processes. Finding lies within linkage region for schizophrenia from meta-analysis (Lewis et al. 2003)	
	rs4147141	Additive	7.90E-06	1	69351840	Intergenic		
	rs4650135	Additive	5.45E-06	1	69457585	Intergenic		
	rs4650135	Dominant	6.07E-06	1	69457585			
	rs11786458	Additive	8.76E-06	8	40371858	Intergenic		Close to linkage region for schizophrenia (Stefansson et al. 2002)
	rs12679254	Recessive	2.08E-06	8	74436745	Within 10 kb of AK128216	Gene of unknown function	
	rs11790994	Additive	2.47E-07	9	97469087	Intergenic	Within suggestive linkage region for ADHD in meta-analysis (Zhou et al. 2008c)	

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
	rs10895959	Recessive	3.00E-06	11	105835372	Intergenic	Within suggestive linkage region for schizophrenia in meta-analysis (Lewis et al. 2003)	
	rs478597	Additive	8.08E-06	12	116235808	Intron of NOS1	Encodes (neuronal) nitric oxide synthase 1. In the brain and peripheral nervous system, NO displays many properties of a neurotransmitter; it is implicated in neurotoxicity associated with stroke and neurodegenerative diseases and neural regulation of smooth muscle. NOS1 has recently shown association with traits related to impulsivity, including hyperactive and aggressive behaviors in adult ADHD, cluster B personality disorder, and autoaggressive and heteroaggressive behavior (Reif et al. 2009). Earlier, this gene was shown associated with Alzheimer's disease and schizophrenia (Galimberti et al. 2008; Reif et al. 2006)	
	rs17079773	Additive	4.71E-06	13	23496384	In intron of SPATA13	Encodes spermatogenesis associated 13, potentially involved in cell migration	Site known for CNVs
	rs17079773	Dominant	6.60E-06	13	23496384		Expressed in brain	
	rs7495052	Recessive	2.83E-06	15	90353033	In intron of SLCO3A1	Encodes solute carrier organic anion transporter family, member 3A1, which might be involved in the regulation of extracellular vasopressin concentration in human brain and thus might influence the neuromodulation of neurotransmission by cerebral neuropeptides such as vasopressin. In/near suggestive linkage regions for autism (Szatmari et al. 2007b) and major depression (Holmans et al. 2004). Gene was associated with nicotine dependence at P values of 10^{-3} in locus-wide association study (Berrettini et al. 2008)	
	rs17281813	Recessive	3.46E-06	16	48308291	In intron of ZNF423	Encodes zinc finger protein 423, expressed in multiple tissues including fetal brain and specifically in the substantia nigra, medulla, amygdala, thalamus, and cerebellum. Animal studies show that ZNF423 is required for patterning the development of neuronal and glial precursors in the developing brain, particularly in midline structures (Alcaraz et al. 2006). Close to suggestive linkage region for ADHD in meta-analysis (Zhou et al. 2008c)	Site known for CNVs
	rs13330107	Recessive	8.50E-06	16	75436363	Intergenic	Within suggestive linkage region for ADHD in meta-analysis (Zhou et al. 2008c)	Site known for CNVs

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
Total ADHD symptom count	rs4147141	Additive	6.07E-06	1	69351840	See above	Encodes dipeptyl peptidase 10, which does not possess dipeptidyl peptidase activity but binds to specific voltage-gated potassium channels and alters their expression and biophysical properties. The expression of the gene is highest in brain. The finding lies within a linkage region for schizophrenia observed in meta-analysis and several primary studies (Lewis et al. 2003). In addition, the gene showed association in GWAS of schizophrenia (Sullivan et al. 2008) and bipolar disorder (Wellcome Trust Case Control Consortium 2007) at $P = 10^{-5}$, and contains CNVs potentially linked to autism (Marshall et al. 2008)	Site known for CNVs
	rs272000	Recessive	9.10E-06	2	116372265	Within 50 kb downstream of DPP10		
	rs17367118	Additive	8.69E-06	2	123358081	Intergenic	The finding lies within a linkage region for schizophrenia observed in meta-analysis (Lewis et al. 2003)	
	rs1918172	Additive	5.18E-06	2	156596746	In intron of BC032407	Gene of unknown function	
	rs11719664	Additive	2.48E-06	3	21930202	In intron of ZNF385D	Expression in many tissues including brain. The finding lies within a linkage region for schizophrenia observed in meta-analysis (Lewis et al. 2003) and a recent primary study (Irmansyah et al. 2008). The gene showed association in GWAS of bipolar disorder (Wellcome Trust Case Control Consortium 2007) at P values of 10^{-5}	Site known for CNVs
	rs6791644	Recessive	8.32E-06	3	60746148	In intron of FHH1	Encodes a diadenosine 5',5''-P1,P3-triphosphate hydrolase involved in purine metabolism. FHH1 has a major role in regulating beta-catenin-mediated gene transcription. Expression in many tissues including brain. Gene is also found among top-findings from GWAS in schizophrenia (Sullivan et al. 2008) and is affected by CNVs in autism (Marshall et al. 2008; Sebat et al. 2007)	

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
	rs17651978	Recessive	6.05E-06	3	71103180	In intron or 5' UTR of FOXP1	Encodes Forkhead box protein P1, which belongs to subfamily P of the forkhead box (FOX) transcription factor family. Forkhead box transcription factors play important roles in the regulation of tissue- and cell type-specific gene transcription during both development and adulthood. The gene shows universal expression. FOXP2, another family member is involved in developmental speech and language disorders and directly regulates targets related to neural development and synaptic plasticity and developmental disorders like autism and schizophrenia (Vermees et al. 2007, 2008). In addition, the gene showed association in GWAS of schizophrenia (Sullivan et al. 2008) at $P = 10^{-5}$ and of bipolar disorder (Sklar et al. 2008) at $P = 10^{-4}$	
	rs2290416	Additive	8.51E-06	8	144728743	In coding exon of NAPRT1	Encodes nicotinate phosphoribosyltransferase domain containing 1, which is part of an enzymatic pathway that leads to production of nicotinamide adenine dinucleotide (NAD) from niacin (nicotinic acid), which serves as a coenzyme in cellular redox reactions and is an essential component of a variety of processes in cellular metabolism including response to stress. Expression in many tissues including brain	Site known for CNVs
	rs10767942	Dominant	7.90E-06	11	32478583	Intergenic	The finding lies within/near linkage regions for autism (Duvall et al. 2007; Szatmari et al. 2007b; Trikalinos et al. 2006)	
	rs7992643	Dominant	5.45E-06	13	99353039	Within 15 kb downstream of CLYBL	Encodes citrate lyase beta like protein of unknown function. Expression in many tissues including brain. The finding lies within/near linkage regions for bipolar disorder (Detera-Wadleigh et al. 1999) and schizophrenia (Blouin et al. 1998)	

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
Hyperactive-impulsive symptom count	rs11590090	Recessive	2.51E-06	1	113115086	Within 60 kb downstream of FAM19A3	Encodes 'family with sequence similarity 19 [chemokine (C–C motif)-like], member A3'. This gene is a member of the TFAFA family which encode small secreted proteins. These proteins are distantly related to MIP-1alpha, a member of the CC-chemokine family. The TFAFA proteins are predominantly expressed in specific regions of the brain, and are postulated to function as brain-specific chemokines or neurokines, that act as regulators of immune and nervous cells (Tom et al. 2004). The finding lies within/near linkage regions for schizophrenia from primary and meta-analysis studies (Arinami et al. 2005; Lewis et al. 2003)	Site known for CNVs
	rs1202199	Dominant	8.52E-06	6	20264153	In intron of MBOAT1	MBOAT1 shares structural similarity with a superfamily of membrane-bound O-acetyltransferases that transfer organic compounds, usually fatty acids (e.g., cholesterol, diacylglycerol, palmitoyl), onto hydroxyl groups of membrane-embedded targets. By this way MBOAT1 is essential for membrane asymmetry and diversity. Expression in many tissues including brain. The finding lies within/near linkage regions for schizophrenia from meta-analysis (Lewis et al. 2003)	
	rs7816032	Recessive	2.25E-06	8	19831171	Within 15 kb upstream of LPL	Encodes lipoprotein lipase, a protein which has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake. Expressed in many tissues including brain. Gene has shown association with many different lipid-related disorders	
	rs8041675	Additive	3.98E-06	15	35129894	In intron of MEIS2	Encodes a homeobox protein belonging to the TALE ('three amino acid loop extension) family of homeodomain-containing proteins. TALE homeobox proteins are highly conserved transcription regulators, and several members have been shown to be essential contributors to developmental programs. Expression in multiple tissues including brain. The finding lies within/near linkage region for ADHD from a primary study and meta-analysis (Bakker et al. 2003; Zhou et al. 2008c)	

Table 2 continued

Phenotype	SNP	Genetic model	P value	Chr	Base pairs	Position	Gene function ^a	Additional remarks
	rs13353224	Additive	8.54E-06	16	63551405	Intergenic	Encodes aurora kinase C, a serine/threonine protein kinase, which may play a role in organizing microtubules in relation to centrosome/spindle function during mitosis. The gene is expressed in many tissues including brain	
	rs2014572	Additive	7.32E-06	19	62451830	Within 15 kb downstream of AURKCI		
	rs10421632	Additive	9.68E-06	19	62456582	Within 25 kb downstream of AURKCI		
Inattentive symptom count	rs10227331	Recessive	3.79E-06	7	156987699	Within 40 kb of PTPRN2	Encodes protein tyrosine phosphatase, receptor type, N polypeptide 2, a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. PTPRN2 shows especially high expression in brain. Lies within linkage region for autism observed in meta-analysis (Trikalinos et al. 2006). In addition, the gene showed association in GWAS of schizophrenia (Sullivan et al. 2008) and of bipolar disorder (Sklar et al. 2008) at $P = 10^{-4}$	
	rs2769967	Recessive	3.63E-06	9	81079178	Intergenic	Close to meta-analytic suggestive linkage region for ADHD (Zhou et al. 2008c)	
	rs1471225	Additive	8.09E-06	15	27675688	Within 30 kb downstream of KIAA0574	Encodes protein of unknown function expressed in brain and other tissues. Finding lies within meta-analytic suggestive linkage region for ADHD (Zhou et al. 2008c). The gene is found in CNV regions in 3 studies of autism (Christian et al. 2008; Marshall et al. 2008; Sebat et al. 2007)	Site known for CNVs
	rs7172689	Additive	3.86E-06	15	79320750	Within intron of IL16	Encodes interleukin 16. The protein is a pleiotropic cytokine that functions as a chemoattractant, a modulator of T cell activation, and an inhibitor of HIV replication. The gene is expressed in many tissues including brain	Also found in GWAS by Neale et al. (2008a)
	rs7172689	Dominant	1.50E-06	15	79320750			
	rs4128767	Dominant	1.28E-06	15	79330462			

Values indicated in bold are SNPs that appear in the list more than once

^a Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ± 5 Mb for genome-wide linkage scans, ± 5 kb for GWAS, microarray and CNV studies, and ± 50 kb for signposts)

[#] These findings were derived using the PBAT screening procedure prior to association testing

Structured Clinical Interview of DSM-IV axis I disorders (SCID-I; Jacob et al. 2007), supported by ratings from the Wender Utah Rating Scale and an ADHD diagnostic checklist applying DSM-IV criteria categorically and dimensionally (ADHD-DC) (Rosler et al. 2004). Comorbidity along the entire spectrum was analyzed using SCID-I and SCID-II, the latter assessing axis II disorders. Lifetime comorbidity with major depression was 44.7%, with substance use disorders it was 44.1% (of which 32.0% for cannabis use, 40.6% for alcohol use). Of the 304 controls only 54 were screened for psychiatric disorders prior to inclusion. Genotyping was on the Affymetrix GeneChip Human Mapping 500K sets. Importantly, instead of genotyping individual samples, pools were constructed of the 343 cases and 304 controls, respectively. For each pool nine technical replicates were analyzed. After data cleaning the authors ended up with allele frequencies for 504,219 SNPs, of which the autosomal SNPs were ranked based on the mean of rankings performed using ANOVA, rank sums and silhouette scores. Whereas the other ADHD GWAS reports relied strictly on statistical rankings to describe their results, Lesch and coworkers used additional criteria for further prioritization of SNPs for follow up, one being localization within or near genes (± 100 kb flanking region), a second being presence in clusters of at least three SNPs located in regions of genes, a third being the comparison with a family-based association study performed in a dataset from a recently published linkage paper by the same group, or being present in a suggestive linkage region from this analysis in adult ADHD patients (Romanos et al. 2008). In addition, expression in brain, as well as earlier findings suggesting involvement in complex traits and neuropsychiatric disorders (especially substance use disorders) were taken into consideration.

Although none of the findings were genome-wide significant, interesting candidate genes for ADHD are reported in this paper, too. Of the 80 top-ranked SNP findings, 30 fall into genes, of which nearly all are known to be expressed in brain (see Table 3). A second list, containing the top-10 of those genes with 3 or more SNPs among the 1,000 highest-ranking findings contains the genes *KALRN* (15 SNPs), *ZNF354C* (15 SNPs), *WRNIP1* (14 SNPs), *GRB10* (10 SNPs), *DPP6* (7 SNPs), *ARHGAP22* (11 SNPs), *RAB38* (11 SNPs), *FAT3* (8 SNPs), *DA259379* (13 SNPs), *NT5DC3* (20 SNPs). A third list summarizes all findings that show overlap with the linkage analysis in adult ADHD patients published earlier by the same group (Romanos et al. 2008), and in some instances also a family-based GWAS based on the 50 K linkage dataset (Table 3 in Lesch et al. 2008). Of the 30 genes listed there, 8 genes (*CTNNA2*, *MOBP*, *MAP1B*, *REEP5*, *ASTN2*, *ATP2C2*, *CDH13* and *ITGAE*) overlap with the list of the 80 top-ranked SNP findings, as indicated in Table 3. The authors

highlight the findings for *ASTN2*, *CSMD2*, *ITGA11*, *CTNNA2* and *CDH13* in their discussion. All of these genes have earlier shown association with substance use disorders and related phenotypes, which is interesting in the light of the frequent comorbidity with such disorders in (adult) ADHD (44.1% in the current study). The five genes encode proteins involved in cell adhesion and/or cell–cell communication in development and maturation of the brain. Also the *UNC5B* (Table 3) and *KALRN* genes fit into this category. The latter encodes a protein present in the post-synaptic density which regulates dendritic spine development and is important for the neuronal plasticity underlying memory and learning (Lesch et al. 2008; Penzes and Jones 2008).

Comparing this list with the findings from the other two GWAS, very little overlap is seen (which might be expected, given power limitations of the studies, see below), except for one finding on chromosome 16, which falls into *CDH13*. As indicated above, this gene was also among the top-findings from both GAIN/IMAGE GWAS studies, as well as many genome-wide studies of addiction related phenotypes, recently reviewed by Uhl et al. (2008a). An additional similarity to be noted is for two *TLL* genes, *TLL1* found among the top-ranks of the analysis based in the categorical ADHD phenotype and showing nominal association in the quantitative analyses by Lasky-Su et al. (see Table V in Lasky-Su et al. 2008b), *TLL2* present among the top-30 SNPs in gene regions in the analysis by Lesch et al. Both genes encode metalloproteases that cleave collagen and are expressed in multiple tissues including brain. A specific role in brain development or functioning has not been reported for either of these genes, though. Additional genes modulating the extracellular matrix are found in all three studies, including *HAS3* (Lasky-Su et al. 2008b), *SPOCK3* (Neale et al. 2008a), *MAN2A2*, *GPC6* and *MMP24* (Lesch et al. 2008). A third interesting overlap is for genes related to potassium-channel function, like the *KCNK1* gene reported by Lesch et al. (2008), the *KCNIP1* and *KCNIP4* genes observed by Neale et al. (2008a) and the *DPP10* finding for total ADHD symptom count (Lasky-Su et al. 2008b).

An exploratory analysis based on the GAIN/IMAGE sample made use of the age of onset of hyperactive–impulsive and inattentive symptoms, as assessed with a question from the PACS interview, each, as an informative phenotype for a GWAS (Lasky-Su et al. 2008a). Earlier work of the authors had suggested that environmental exposure outside the womb were less likely to contribute significantly to the development of ADHD with a very early age of onset (Lasky-Su et al. 2007). The number of children included in the analysis was 930 with a mean age of 10.86 years, 810 of them being males. The average age at onset of ADHD symptoms was 2.67 years; for the

Table 3 Top 30 single SNPs located in gene regions (including 100 kb of flanking sequences) ranked according to the mean rank calculated across three statistics as reported by Lesch et al. (2008) for association with persistent ADHD in adults

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs11243897	1	5.63E-08	9q34.13	134608104	In intron of <i>C9orf98</i>	Encodes chromosome 9 open reading frame 98, a putative adenylate kinase-like protein of unknown function expressed in brain and other tissues	
rs2587695	2	2.73E-07	2q14.2	120038287	In intron of <i>PCDPI</i> = <i>MGC33657</i>	Encodes primary ciliary dyskinesia protein 1, a protein playing an important role in ciliary and flagellar biogenesis and motility of (among others) the cilia of respiratory epithelial cells and brain ependymal cells in both mice and humans. Finding lies within linkage region for schizophrenia from meta-analysis (Lewis et al. 2003)	
rs864643	4	1.30E-08	3p22.2	39530584	In 3'UTR/intron of <i>MOBP</i>	Encodes myelin-associated oligodendrocyte basic protein. The gene shows altered expression in several areas of the brain of patients with substance use disorders (Albertson et al. 2004; Mitkus et al. 2008). Finding lies close to a linkage region for schizophrenia from meta-analysis (Lewis et al. 2003)	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008)
rs2199161	11	1.62E-06	5q13.2	71446112	In intron of <i>MAP1B</i>	Encodes microtubule-associated protein 1B, a member of a protein family thought to be involved in microtubule assembly, which is an essential step in neurogenesis. Gene knockout studies of the mouse microtubule-associated protein 1B gene suggested an important role in development and function of the nervous system. Finding lies within linkage region for ADHD from meta-analysis (Zhou et al. 2008c)	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008)
rs16928529	12	3.90E-06	10q22.1	72652991	In intron of <i>UNC5B</i>	Encodes unc-5 homolog B (<i>C. elegans</i>), which belongs to a family of netrin-1 receptors thought to mediate the chemorepulsive effect of netrin-1 on specific axons. Finding lies in linkage region for bipolar disorder (1997)	
rs2677744	13	9.69E-07	15q26.1	89251445	In intron of <i>MAN2A2</i>	Encodes mannosidase, alpha, class 2A, member 2, expressed in brain and many other tissues. The protein is involved in N-glycan synthesis. The finding lies close to linkage regions for autism (Szatmari et al. 2007b) and major depressive disorder (Holmans et al. 2007)	
rs7175404	14	6.03E-07	15q26.1	91837692	In intron of <i>AK094352</i>	Gene of unknown function. The finding lies close to linkage region for major depressive disorder (Holmans et al. 2007)	

Table 3 continued

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs10983238	15	1.37E-07	9q33.1	118373504	In intron of <i>ASTN2</i>	Encodes astrotactin 2, a membrane protein expressed in multiple tissues including brain. It is critically involved in neuron-glia binding during the developmental periods of glial-guided cell migration and assembly into neuronal layers in the developing brain (Lesch et al. 2008). A homologue of the gene, <i>ASTN</i> , is involved in neuronal migration (Vrijenhoek et al. 2008). The gene was found disrupted by rare CNVs in schizophrenia patients (Vrijenhoek et al. 2008) and patients with autism (Marshall et al. 2008) shows association in GWAS of multiple addition-related traits (Uhl et al. 2008a), as well as of schizophrenia (Sullivan et al. 2008)	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008). Association also observed in the 50 K GWAS in the same publication. Three SNPs in the gene are among the highest-ranking 260 in the analysis
rs2281597	18	5.41E-07	1p35.1	34132445	In intron of <i>CSMD2</i>	Encodes CUB and Sushi multiple domains 2, a protein with a potential role in cell adhesion and neurogenesis. Intermediate expression in fetal brain, adult brain, spinal cord, and all specific adult brain regions examined. Lower levels were detected in spleen, lung, and testis, and little to no expression was detected in the other tissues examined. The protein product is enriched in axonal growth cones and is involved in neuronal outgrowth during formation of neuronal circuits (Lesch et al. 2008). <i>CSMD2</i> and its homologue <i>CSMD1</i> have been found associated with addition-related phenotypes in multiple GWAS (Uhl et al. 2008a)	
rs2502731	19	1.58E-06	9q34.11	130016378	In intron of <i>DNMI</i>	Encodes dynamin 1, a GTPase involved in clathrin-mediated endocytosis and other vesicular trafficking processes, especially during high levels of neuronal activity. The finding lies close to linkage regions for autism (Szatmari et al. 2007b).	

Table 3 continued

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs412050	23	5.83E-06	22q11.22	20637519	Immediately downstream of <i>PPM1F</i>	The protein encoded by this gene is a member of the PP2C family of Ser/Thr protein phosphatases. PP2C family members are known to be negative regulators of cell stress response pathways. Calcium/calmodulin-dependent protein kinase II gamma (CAMK2G/CAMK-II) is found to be one of the substrates of this phosphatase. Expressed in brain and other tissues. Finding lies in linkage region for schizophrenia from meta-analysis (Lewis et al. 2003) and close to linkage finding for smoking (Saccone et al. 2007)	Site known for CNVs
rs515910	24	4.36E-06	10q25.1	105956394	In intron of <i>C10orf79</i>	Gene/protein of unknown function expressed in brain and other tissues	
rs220470	28	1.34E-07	17p13.2	3611724	<i>ITGAE</i>	Encodes integrin alpha E. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. Expressed in multiple tissues including brain. Finding lies within linkage region for ADHD from meta-analysis (Zhou et al. 2008c)	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008). Another integrin alpha, encoded by <i>ITGAI1</i> , also is listed at rank 50
rs4964805	32	4.74E-06	12q23.3	102716954	In intron of <i>NTSDC3</i>	Encodes 5'-nucleotidase domain containing 3, a potential oncogene. Expression is found in brain and several other tissues. Finding lies close to linkage regions for the personality trait neuroticism (Fullerton et al. 2003) and a neuropsychological ADHD endophenotype (Rommelse et al. 2008c)	19 additional SNPs in the gene showed association with ADHD
rs2242073	40	8.27E-06	2q33.3	208702290	In intron of <i>CRYGC</i>	Encodes crystallin gamma C. Crystallins constitute the major proteins of vertebrate eye lens and maintains the transparency and refractive index of the lens. No reports of expression in brain	Site known for CNVs (Kidd et al. 2008)
rs1555322	49	3.60E-06	20q11.22	33312595	In intron of <i>MMP24</i>	Encodes matrix metalloproteinase 24 (membrane-inserted). Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling. Expression is found in brain and several other tissues. Finding lies in linkage region for autism (Allen-Brady et al. 2008)	

Table 3 continued

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs7164335	50	1.30E-07	15q23	66502086	<i>ITGA11</i>	Encodes integrin alpha 11. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. Expressed in multiple tissues including brain. The finding lies close to linkage regions for autism (Szatmari et al. 2007b)	Site known for CNVs. Another integrin-encoding gene <i>ITGAE</i> , also is listed under rank 28
rs11594082	52	1.00E-05	10q22.1	72969259	In intron of <i>CDH23</i>	Encodes cadherin-like 23, a member of the cadherin superfamily, whose genes encode calcium dependent cell–cell adhesion glycoproteins. Expressed in the neurosensory epithelium, the protein is thought to be involved in stereocilia organization and hair bundle formation; also expressed in brain. The gene is involved in deafness. Finding lies close to linkage region for bipolar disorder (1997). Gene shows association with schizophrenia at <i>P</i> values of 10^{-4} (Sullivan et al. 2008)	
rs7995215	53	1.35E-08	13q31.3	93206507	In intron of <i>GPC6</i>	Encodes glypican 6. The glypicans comprise a family of glycosylphosphatidylinositol-anchored heparan sulfate proteoglycans. The glypicans have been implicated in the control of cell growth and division. Glypican 6 is a putative cell surface coreceptor for growth factors, extracellular matrix proteins, proteases and anti-proteases. Expressed in multiple tissues including brain. SNPs in the close vicinity of this finding showed association at 10^{-4} in GWAS for bipolar disorder (Sklar et al. 2008). Gene shows association with schizophrenia (Sullivan et al. 2008) and bipolar disorder (Sklar et al. 2008) at $P = 10^{-4}$ and CNVs in the gene have been noted in a study on autism (Marshall et al. 2008)	
rs2241685	54	8.11E-06	2p25.3	1905000	In intron of <i>MYT1L</i>	Encodes myelin transcription factor 1-like, a protein of unknown function, which shows expression in brain and other organs. The gene was found disrupted by rare CNVs in schizophrenia patients (Vrijenhoek et al. 2008)	
rs469727	55	7.54E-06	5q22.2	112270867	In intron of <i>REEP5</i>	Encodes the receptor accessory protein 5, expressed in many tissues including brain. The protein may be involved in the transport of G-protein-coupled receptors to the cell membrane	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008). Association also observed in the 50 K GWAS in the same publication

Table 3 continued

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs13395022	57	9.68E-06	2p12	79735768	In intron of <i>CTNNA2</i>	Encodes catenin alpha 2, expressed in brain and other tissues. The activity of cadherins, which mediate homophilic cell–cell Ca(2+)-dependent association, depends on their anchorage to cytoskeleton via catenins. Catenin alpha 2 functions as a critical agent to regulate the stability of synaptic contacts. Cell-adhesion complexes of catenin alpha 2 with cadherin are likely most important in cerebellar and hippocampal lamination. Finding lies within a linkage region for schizophrenia from meta-analysis (Lewis et al. 2003). Gene shows association with schizophrenia (Sullivan et al. 2008) at <i>p</i> -values of 10 ⁻⁵ and bipolar disorder (Wellcome Trust Case Control Consortium 2007) at 10 ⁻⁴	Gene also shows association with ADHD at 10 ⁻⁴ in GWAS of Neale et al. (2008a)
rs10786284	61	1.96E-06	10q24.1	98125495	In intron of <i>TLL2</i>	Encodes tollid-like 2, an astacin-like zinc-dependent metalloprotease and is a subfamily member of the metzincin family. Its function is not clear, but it shows expression in brain	The homologue TLL1 shows association with ADHD and related quantitative traits in the GWAS of Neale et al. (2008a) and Lasky-Su et al. (2008b)
rs12453316	62	1.72E-05	17q25.1	69027654	Within 83 kb of <i>SDK2</i>	Encodes sidekick homologue 2, a member of the immunoglobulin superfamily. Chicken Sdk2 mediates homophilic adhesion and direct laminar targeting of neurites	
rs2237349	64	4.63E-06	7p15.1	28729488	<i>CREB5</i>	Encodes cAMP-responsive element binding protein 5, which belongs to the cAMP response element (CRE)-binding protein family. Members of this family contain zinc-finger and bZIP DNA-binding domains. The encoded protein specifically binds to CRE as a homodimer or a heterodimer with c-Jun or CRE-BP1, and functions as a CRE-dependent trans-activator. Expressed in brain, especially fetal brain and prefrontal cortex, and other tissues. Finding is close to linkage region for neuroticism (Fullerton et al. 2003), and in a region associated with bipolar disorder in a GWAS at 10 ⁻⁴ (Wellcome Trust Case Control Consortium 2007). Gene shows association with schizophrenia in GWAS (Sullivan et al. 2008) at <i>P</i> = 10 ⁻⁴	

Table 3 continued

SNP	Mean of ranks	ANOVA <i>P</i> value	Locus	Physical position	Position	Gene function ^a	Additional remarks
rs10514604	69	8.06E-07	16q24.1	83003885	<i>ATP2C2</i>	Encodes Ca ²⁺ -transporting ATPase type 2C member 2, potentially involved in cellular detoxification of Mn ²⁺ ions (Xiang et al. 2005). Shows expression predominantly in brain and testis. Finding falls into the significant linkage region for ADHD as observed in meta-analysis (Zhou et al. 2008c)	Also lies within suggestive linkage region for ADHD reported in the same publication (Lesch et al. 2008). Association also observed in the 50 K GWAS in the same publication
rs2842643	70	3.28E-06	6p21.1	41758714	Immediately upstream of <i>TFEB</i>	Encodes transcription factor EB of unknown function. The gene is expressed in brain and many other tissues. The finding lies within/close to regions of suggestive linkage to ADHD (Zhou et al. 2008c) and schizophrenia (Lewis et al. 2003) from meta-analyses	Site known for CNVs
rs3893215	73	2.56E-05	11p15.1	17721406	In intron of <i>KCNK1</i>	Encodes potassium voltage-gated channel Shaw-related subfamily member 1, a protein belonging to the delayed rectifier class of channel proteins and an integral membrane protein that mediates the voltage-dependent potassium ion permeability of excitable membranes. The finding is present close to/within regions of (suggestive) linkage to autism from meta-analysis (Trikalinos et al. 2006) and primary studies (Duvall et al. 2007; Szatmari et al. 2007b)	
rs11646411	79	7.40E-06	16q23.3	81304438	In intron of <i>CDH13</i>	Encodes cadherin 13, a member of the cadherin superfamily. The encoded protein is a calcium-dependent cell–cell adhesion glycoprotein. This particular cadherin is a putative mediator of cell–cell interaction in the heart and may act as a negative regulator of neural cell growth. Lies within the only significant linkage region for ADHD as determined in met-analysis (Zhou et al. 2008c). Has earlier shown association with metamphetamine dependence in GWAS (Uhl et al. 2008b) as well as multiple other addiction related phenotypes (Uhl et al. 2008a)	Most significant finding in quantitative GWAS by Lasky-Su et al. (2008b), and shows association in the GWAS in adult ADHD by Lesch et al. (2008)
rs3799977	80	4.90E-06	6p21.1	44945334	In intron of <i>SUPT3H</i>	Encodes suppressor of Ty 3 homolog, expressed in brain and other tissues, with a potential role in transcription. The finding lies within/close to regions of suggestive linkage to ADHD (Zhou et al. 2008c) and schizophrenia (Lewis et al. 2003) from meta-analyses	

^a Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ± 5 Mb for genome-wide linkage scans, ± 5 kb for GWAS, microarray and CNV studies, and ± 50 kb for signposts)

hyperactive–impulsive symptoms this age was 2.77, for the inattentive symptoms it was 4.31 years. The study investigated 429,784 autosomal SNPs using the FBAT-logrank algorithm (Lange et al. 2004a) to identify genetic variants that could predispose children to an earlier age of onset of disease symptoms. Additive, dominant and recessive genetic models were tested. A total of 16 SNPs reached P values for association $<10^{-5}$ including 14 unique findings (Table 4). There is no overlap with the results from the other GWAS. Although potentially due to chance it is remarkable to see that this list contains a number of genes that are involved in the response of the body to environmental exposures and/or are regulated by the environment, like the inflammation related *ADAMTS2*, the stress regulator *MAP3K7* or the vitamin A-responsive *NAV2* gene.

An interesting new approach in GWAS is represented by the exploratory study by Sonuga-Barke et al. (2008). The author and his colleagues evaluated gene–environment interactions ($G \times E$) in ADHD in a genome-wide analysis. Specifically, they investigated the effects of maternal warmth and criticism on ADHD severity in the GAIN/IMAGE dataset (also, a $G \times E$ analysis for conduct disorder symptoms is reported in the publication, but is not reviewed here). ADHD symptoms were derived from the PACS interview in IMAGE, maternal expressed emotion was assessed using the Camberwell Family Interview. Maternal warmth and criticism were coded, separately; warmth was assessed by tone of voice, spontaneity, sympathy and/or empathy toward the child. Criticism was coded from statements that criticized or found fault with the child based on the tone of voice and critical phrases (Sonuga-Barke et al. 2008). Statistical analysis made use of the FBAT-Interaction methodology (Vansteelandt et al. 2008). In total, 430,060 autosomal SNPs were included in the analysis, as were 909 patients (87% males) from complete trios. Mean age of the participants was 10.88 years, the average number of ADHD symptoms was 16.1, the mean overall measure for mother's warmth was 1.43 (range from 0 to 3) and for maternal criticism it was 1.74 (range from 0 to 4). Additive, dominant and recessive genetic models were tested for the phenotype and the two environmental factors.

The analysis did not produce any genome-wide significant findings, the highest P value reaching 9.08×10^{-7} . Nineteen SNPs showed interaction association P values below 10^{-5} in the presence of main genetic effects (at $P \leq 10^{-5}$), of which five showed association under two genetic models (Table 5). Only two findings were related to maternal criticism. Most of the genes interacting with maternal warmth clustered in three distinct regions on chromosomes 6, 11 and 13. The regions on chromosomes 6 and 11 fall into genes, *KIF6* and *PIWIL4*, respectively. The region of 58 kb on chromosome 13 includes 8 association

findings for 4 unique SNPs, and although it does not contain genes, it shows extensive LD extending proximally to the *SLC46A3* gene, the function of which is unknown. Interestingly, the *KIF6* gene has repeatedly been shown to respond to environmental stimuli (Jakoubova et al. 2008b; Jakoubova et al. 2008a; Shiffman et al. 2008). In the referenced studies, a coding variant in *KIF6* altered the response to statins in cardiovascular disease. The gene's role in moderating the influence of mother's warmth on ADHD severity will have to be investigated in further detail. An additional six interaction associations at P values of 10^{-4} were observed in the absence of genetic main effects (Table V in Sonuga-Barke et al. 2008). Interestingly, all but one finding were observed under a recessive genetic model, which strongly limited the number of informative families. Of these associations, only one was for mother's warmth. This finding falls into the *BCAS1* gene on chromosome 20, which is a potential oncogene with high expression in brain. Of the five association findings interacting with mother's criticism, especially a finding on chromosome 2 is interesting, as it falls into the *MTA3* gene, which has two additional SNPs associated with ADHD in the GWAS for quantitative phenotypes (Lasky-Su et al. 2008b). The authors also tested potential $G \times E$ effects for the list of ADHD candidate genes defined earlier (Brookes et al. 2006). Interaction association P values are most significant for *DDC* (mother's warmth and criticism), *HTR2A* and *SLC9A9* (warmth) at 10^{-4} .

The interpretation of the analytical strategy used in this study is difficult. First of all, the direction of causation is not clear: it could be that maternal expressed emotion influences ADHD severity in the child, on the other hand, a child with severe ADHD might also elicit more pronounced criticism and less warmth from parents. Furthermore, explaining the biological effects of the environmental moderators of ADHD severity is not straightforward. The authors discuss epigenetic effects (like DNA methylation) as possible mechanisms. This might indeed be supported by at least one of their findings: *PIWIL4* plays a role in chromatin-modification, another epigenetic regulator of gene expression (Szyf et al. 2007, 2008).

Taking together all results from the GWAS performed in ADHD, the following is to be remarked: none of the findings so far show genome-wide significant association with ADHD according to the thresholds currently handled (Dudbridge and Gusnanto 2008; Pe'er et al. 2008; van Steen and Lange 2005). Nevertheless, the most high-ranking findings from the different studies contain interesting new candidates for further study. Little overlap is observed between studies, except for *CDH13*, which is found in three studies (Lasky-Su et al. 2008b; Lesch et al.

Table 4 Findings from genome-wide analysis of ADHD age of onset by Lasky-Su et al. (2008a), including genes in or near which the association finding is present

SNP	Genetic model	Direction of effect	P value	Chromosome, base pairs	Position	Gene function ^a	Additional remarks
rs1517484	Additive	Earlier onset	5.42E-07	chr2:225945904	Within 28 kb of KIAA1486	Gene of unknown function, expressed in brain and other tissues	
rs9845475	Dominant	Later onset	3.95E-06	chr3:32817105	Within 20 kb upstream of TRIM71	Gene of unknown function, expressed in brain and other tissues. Potentially plays an important role in development. Finding lies within linkage region for schizophrenia from meta-analysis (Lewis et al. 2003)	
rs3892715	Dominant	Earlier onset	6.46E-06	chr3:196239299	Within 31 kb upstream of C3orf21	Gene of unknown function, codes for membrane protein expressed in brain and other tissues	
rs9687070	Additive	Earlier onset	9.34E-06	chr5:178501755	In intron of ADAMTS2	Encodes ADAM metalloproteinase with thrombospondin type 1 motif 2, a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family. The enzyme encoded by this gene excises the N-propeptide of type I, type II and type V procollagens. May also play a role in development that is independent of its role in collagen biosynthesis. Expressed at high levels in skin, bone, tendon and aorta and at low levels in thymus and brain. Lies in suggestive linkage region for smoking (Duggirala et al. 1999)	
rs9687070	Recessive	Earlier onset	2.98E-06	chr5:178501755			
rs10039254	Additive	Later onset	7.87E-06	chr5:178503520			
rs3776816	Recessive	Earlier onset	4.64E-06	chr5:178507474			
rs806276	Additive	Later onset	3.38E-07	chr6:91264072	Within 20 kb upstream	Encodes mitogen-activated protein kinase kinase kinase 7. The protein encoded by this gene is a member of the serine/threonine protein kinase family. This kinase mediates the signaling transduction induced by TGF beta and morphogenetic protein (BMP), and controls a variety of cell functions including transcription regulation and apoptosis. It plays a role in the cell response to environmental stresses and is expressed in brain at multiple other tissues. Lies within suggestive linkage region for ADHD from meta-analysis (Zhou et al. 2008c)	
rs806276	Dominant	Later onset	1.02E-07	chr6:91264072	Within 20 kb upstream of MAP3K7		
rs9451437	Additive	Later onset	3.08E-06	chr6:91266607	Within 15 kb of MAP3K7		
rs6968385	Recessive	Earlier onset	1.61E-06	chr7:109834707	Intergenic	Lies within linkage region for autism spectrum disorder (Trikalinos et al. 2006), and falls into CNV found in study on schizophrenia (Walsh et al. 2008)	
rs17658378	Additive	Later onset	9.15E-06	chr8:116463251	Within 30 kb upstream of TRPS1	Encodes trichorhinophalangeal syndrome I, a zinc finger transcription factor that represses GATA-regulated genes and binds to a dynein light chain protein. Ubiquitously expressed in the adult. Found in fetal brain, lung, kidney, liver, spleen and thymus	

Table 4 continued

SNP	Genetic model	Direction of effect	P value	Chromosome, base pairs	Position	Gene function ^a	Additional remarks
rs1325154	Dominant	Later onset	4.75E-06	chr9:12572565	Intergenic	Falls into linkage region for nicotine dependence (Li et al. 2008)	Site known for CNVs
rs874426	Recessive	Earlier onset	3.75E-06	chr11:19526139	In intron of NAV2	Encodes neuron navigator 2, an retinoic acid-responsive gene that seems to play a role in neuronal development. It is highly expressed in fetal and adult brain. Lies within/close to linkage region for autism from primary studies and meta-analysis (Duvall et al. 2007; Szatmari et al. 2007b; Trikalinos et al. 2006). Gene is associated with bipolar disorder in GWAS at P values of 10^{-4} (Sklar et al. 2008)	Also associated with ADHD at 10^{-4} in GWAS of Neale et al. (2008a)
rs1335515	Dominant	Earlier onset	7.76E-06	chr14:57455118	Intergenic		
rs4810685	Dominant	Earlier onset	6.51E-06	chr20:45834120	In intron of SULF2	Encodes heparan sulfatase 2. Heparan sulfate proteoglycans (HSPGs) act as coreceptors for numerous heparin-binding growth factors and cytokines and are involved in cell signaling. SULF2 can change properties of the coreceptors by removing sulfate moieties. The gene is essential for mammalian development and survival, it shows ubiquitous expression. Lies close to linkage region for autism (Allen-Brady et al. 2008)	Site known for CNVs

Values indicated in bold are SNPs that appear in the list more than once

^a Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ± 5 Mb for genome-wide linkage scans, ± 5 kb for GWAS, microarray and CNV studies, and ± 50 kb for signposts)

Table 5 Summary of the GxE interaction association P values $<10^{-5}$ using total ADHD symptoms as the phenotype (Sonuga-Barke et al. 2008)

Environmental variable	SNP	Genetic model	Main genetic effect P value	Interaction effect estimate	Interaction P value	SNP position	Position	Gene function ^a	Additional remarks
Mother's criticism	rs2825388	Recessive	3.27E-05	1.06	7.82E-06	chr21:19458520	Intergenic		Site known for CNVs
	rs2827093	Additive	3.37E-05	0.72	4.78E-06	chr21:22142959	Intergenic		Site known for CNVs
Mother's warmth	rs2212361	Dominant	6.96E-06	-0.97	9.08E-07	chr11:93951971	In intron of PIWIL4	Encodes piwi-like 4, a protein expressed in brain and other tissues. PIWIL4 plays an important role in the chromatin-modifying pathway in human somatic cells.	
	rs2212361	Additive	2.53E-05	0.69	5.78E-06	chr11:93951971			
	rs7126782	Dominant	2.12E-05	-0.95	2.42E-06	chr11:93963488			
	rs1792040	Dominant	1.74E-05	0.99	2.33E-06	chr13:28274943	Within 60-120 kb of SLC46A3	Encodes solute carrier family 46, member 3, a gene expressed in many tissues including brain. The substrate of the transporter is not known	
	rs1792040	Additive	1.75E-05	-1.25	3.05E-06	chr13:28274943			
	rs1161453	Additive	2.26E-06	-1.47	2.33E-06	chr13:28315484			
	rs1161453	Dominant	5.05E-05	0.82	5.53E-06	chr13:28315484			
	rs1161463	Dominant	3.18E-05	0.84	3.34E-06	chr13:28329338			
	rs1161463	Additive	1.20E-06	-1.72	1.45E-06	chr13:28329338			
	rs1161457	Additive	8.34E-06	-1.41	2.14E-06	chr13:28332854			
rs1161457	Dominant	2.41E-05	0.95	2.75E-06	chr13:28332854				
	rs11752175	Dominant	1.17E-05	0.99	4.65E-06	chr6:39625468	Within intron of KIF6	Encodes kinesin family member 6, a member of the superfamily of molecular motors that are involved in intracellular transport. Several kinesins have been implicated in the pathogenesis of chronic diseases, including neurodegenerative diseases, type 2 diabetes, and Alzheimer's disease. The finding falls into a suggestive linkage region for schizophrenia from meta-analysis and several primary studies (Lewis et al. 2003), as well as being close to a suggestive linkage finding from meta-analysis in ADHD (Zhou et al. 2008c). KIF6 also shows association with schizophrenia in GWAS (Sullivan et al. 2008) at P values of 10^{-4}	
	rs2360997	Additive	6.32E-05	-1.30	7.79E-06	chr14:75882244	Within 25 upstream of ESRRB	Encodes estrogen-related receptor beta, a protein with similarity to the estrogen receptor, expressed in brain and other tissues. Mutations in the gene cause non-syndromal hearing loss (Collin et al. 2008). Was also found in CNV study in autism (Marshall et al. 2008)	
	rs10049246	Additive	3.25E-05	0.60	8.09E-06	chr3:187169435	Within intron of AK309325	Hypothetical gene of unknown function. Finding lies in linkage region for autism (Allen-Brady et al. 2008)	
	rs4875598	Dominant	1.31E-05	-0.94	8.91E-06	chr8:5449161	Intergenic	Finding lies in suggestive linkage region for ADHD from meta-analysis (Zhou et al. 2008c)	Site is known for CNVs

Values indicated in bold are SNPs that appear in the list more than once

^a Where not indicated otherwise, the information is derived from the UCSC Browser, NCBI's OMIM, Gene and Unigene databases, and the Sullivan Lab Evidence Project website (location of SNP expanded by ± 5 Mb for genome-wide linkage scans, ± 5 kb for GWAS, microarray and CNV studies, and ± 50 kb for sigposts)

2008; Neale et al. 2008a). None of the ‘classic’ candidate genes for ADHD are found among the top-findings of either study, although two more recently reported genes, *NOS1* and *CNRI*, are observed at least once. In the candidate gene analyses reported for the GAIN/IMAGE sample, most evidence is repeatedly found for involvement of *SLC9A9* in ADHD. For all studies discussed here, overlap with results from linkage studies reported in ADHD and linkage as well as GWAS in other psychiatric disorders is multiple.

Looking at the processes potentially involved in the etiology of ADHD, little evidence (as yet) points to a direct involvement of neurotransmitters (at least the classic dopaminergic, noradrenergic and serotonergic pathways) or regulators of neurotransmission (except for *DNMI*). Some suggestions are found for involvement of ‘new’ neurotransmission and cell–cell communication systems, though, like glutamate, vasopressin, and TFAA proteins. Also, the potential involvement of potassium channel subunits and regulators definitely warrants further investigation. However, more basic processes also seem involved, like cell division, adhesion (especially via cadherin and integrin systems), neuronal migration, and neuronal plasticity, as well as related transcription, cell polarity and extracellular matrix regulation, and cytoskeletal remodeling processes. Our conclusion is consistent with and extends the conclusion drawn by Lesch and coworkers based on the findings from their GWAS, in which they suggest that neuronal spine formation and plasticity may underlie the pathophysiology of ADHD. Finding inflammatory genes (*IL16* and *ADAMTS2*) is somewhat surprising, although inflammation is already known to be involved in different psychiatric disorders, like major depression and Alzheimer’s disease (Anisman 2009; Bazar et al. 2006; Garcia-Bueno et al. 2008; Serretti et al. 2007). The analysis of age of onset of ADHD revealed a number of environmentally regulated genes (Lasky-Su et al. 2008a), which may suggest a particularly important influence of the environment in this aspect of the disorder. However, all of these biological hypotheses must be tempered by the limited knowledge of the genetic architecture of ADHD at this point. Currently, we do not have sufficient information to draw strong conclusions about the relative impact of the biological pathways and genetic influences, aside from likely knowing that the genetic effects are modest in size.

In the last 2 years, much progress has been made in identifying genes for psychiatric disorders through GWAS. From the studies so far it has become apparent that early power estimates have been far too optimistic and at least several thousands of samples will be needed for the design of an optimal study (Burton et al. 2008). Genetic heterogeneity appears even more extensive than previously expected, with relative risks due to single genetic variants

in the range of 1.05–1.1 or even smaller (Ferreira et al. 2008; Neale et al. 2008a; O’Donovan et al. 2008; Sklar et al. 2008). ADHD is no exception to this, and so all of the ADHD GWAS performed to date are highly underpowered. In addition, Lesch and colleagues used a pooling design, which reduces power by about 70% and puts limitations to the genetic models that can be investigated (Lesch et al., 2008). Furthermore, using controls unscreened for the presence of psychiatric disorders can be expected to reduce power, though the effect of this is modest, given that the prevalence is at most 5% (McCarthy et al. 2008). The X-chromosome was not analyzed in most of the studies, due to a limitation of the FBAT-program. As a clear difference in prevalence of ADHD exists between genders, this might still be an interesting target to look at.

An important issue in psychiatric disorders in general and ADHD in particular is phenotypic heterogeneity. First, psychiatric diagnosis must rely on clinical symptoms that, without external validators, cannot be expected to reflect biologically relevant concepts that are closely linked to genes (Kuntsi et al. 2006; Thapar et al. 2006). Although the instruments used to define psychiatric GWAS phenotypes are generally chosen for high reliability, they have no proven biological validity and will therefore (at best) result in a more ‘noisy’ phenotype definition than most biological tests (Craddock et al. 2008). More importantly, however, the classical nosological approaches identify phenotypically distinct diseases, such as ADHD, substance abuse, affective disorder and schizophrenia, though these exhibit considerable overlap in symptomatology, clinical course, and long-term outcome. ADHD is hardly ever the only disorder a patient suffers from, comorbidity is the rule rather than the exception. For example, reported frequencies of depression and substance use disorders were also high in the GWAS sample used by Lesch et al. (2008). These factors severely hamper the power of genetic association studies and might explain why psychiatric genetics has had an extremely modest track record in pinpointing and characterizing susceptibility loci, even using the GWAS approaches.

That said, what are the perspectives for genome-wide association studies in ADHD? The results of the first studies—though most not genome-wide significant—are already very exciting and change the way in which we think about genetic factors involved in ADHD etiology. For now, GWAS holds the greatest promise for understanding the genetic architecture of ADHD! However, we need to improve the design of these studies by increasing sample size for more power and by further improving/extending phenotypic assessment to better reflect and partition the phenotypic complexity of the disorder. The former will only become possible through collaboration. As a field, ADHD has the good fortune of having several

thousand samples collected world-wide, with collaborative efforts supported by the National Institute of Mental Health. Investigators with ADHD GWAS datasets are also participating in the Psychiatric GWAS Consortium (PGC), a confederation of 101 scientists from 11 countries and 48 institutions having GWAS datasets on ADHD, autism, bipolar disorder, schizophrenia and major depression (Psychiatric GWAS Consortium Steering Committee 2009). The PGC investigators have agreed to participate in coordinated mega-analyses both within and across disorders. Within 1 year, it is to be expected that a collaborative GWAS with more than 4,000 cases can be carried out via the PGC for ADHD. It is this spirit of collaboration that we believe will be needed to achieve the breakthroughs in genetic research that will ultimately help us discover new pathophysiological pathways and targets for treatment.

Improving GWAS design through extension of phenotypic assessment could be done by taking characteristics into consideration that we already know or suspect to play a role in genetic susceptibility. Given the limits of the nosological systems, subdividing ADHD according to subtype will probably not be sufficient, as there is already evidence of shared genetic factors between subtypes (Faraone et al. 2000a; Thapar et al. 2006). Taking into account comorbidity might deal with some of the limits of the phenotypes, as a number of studies have suggested that ADHD plus a specific comorbidity may constitute a distinct subtype of ADHD (Faraone et al. 2000b; Faraone 2000; Faraone and Doyle 2001; Fliers et al. 2009; Rasmussen et al. 2004; Smalley et al. 2000; Willcutt et al. 2000). A recent study in IMAGE can be used as an example that this affects association findings: Zhou et al. (2008b) showed that *SLC6A3/DATI* was only associated with ADHD in the absence of conduct disorder. Another example is gender; given the difference between sexes, certain genetic risk factors can be expected to affect males and females differently. That this affects association studies has already been shown in ADHD (Biederman et al. 2008; Guimaraes et al. 2007; Rommelse et al. 2008b) as well as other (related) psychiatric disorders (Craig et al. 2004; Diamond 2007; Haefner et al. 2008; Kendler 1998; Lang et al. 2008; Okamura et al. 2007; Rucci et al. 2009). An additional potentially important factor is age at diagnosis. It is well established that age influences cognitive performance, with children performing worse in neuropsychological tests than adolescents and adults (Addamo et al. 2007) on tasks that are relevant to ADHD (Rommelse et al. 2008a). We and others have presented evidence that age can modulate the association of *SLC6A3/DATI* with ADHD, with different haplotypes of the gene being associated with ADHD in childhood and adulthood (Barkley et al. 2006; Elia and Devoto 2007; Franke et al. 2008).

A more radical way of dealing with the shortcomings of the nosological system is to look deeper into the possibilities of using (ADHD) endophenotypes for GWAS. Endophenotypes, or intermediate phenotypes, represent heritable phenotypic constructs that are, presumably, more directly affected by genes than clinical symptoms or disease categories (Gottesman and Gould 2003; Szatmari et al. 2007a; Walters and Owen 2007). This should result in a stronger association between causal genes and the endophenotype than the clinical disease phenotype. The success of an endophenotype strategy requires either a higher heritability of the endophenotype compared to the disease phenotype (which is generally not generally observed, Szatmari et al. 2007a) or a reduced complexity of the genetic architecture of the endophenotype due to the involvement of less genes (see Fig. 1). Endophenotypes for ADHD have been proposed at different levels, e.g. those based on neuropsychological performance (Doyle et al. 2005; Rommelse 2008) and those based on neuroimaging (Castellanos and Tannock 2002), i.e. brain activity and structure. Recent genome-wide linkage studies of neuropsychological endophenotypes for ADHD indeed suggest that these measure offer increased power for finding loci compared to clinical phenotypes (Doyle et al. 2008; Rommelse et al. 2008c). A pooled GWAS on memory performance also suggests this (Papasotiropoulos et al. 2006). ‘Imaging genetics’ studies would be thought to be particularly powerful, requiring even smaller sample sizes (Dreher et al. 2008; van Haren et al. 2008). Studies using such ADHD endophenotypes for GWAS are currently ongoing.

An additional aspect to be taken into consideration in GWAS is the potential role of $G \times E$ and gene–gene ($G \times G$) interactions in the etiology of ADHD. As the exploratory analysis by Sonuga-Barke et al. (2008) shows, this type of analysis will help to further delineate mechanisms moderating disease severity and those leading to disease.

A last aspect to be discussed relates to the genetic models currently used in ADHD research. Up to now, we work under the assumption that the ‘common disease, common variant’ model will hold for ADHD. This model suggests that ADHD is caused by multiple variants that are common in the population and each contribute a small amount of disease risk. However, experience from GWAS in other multifactorial disorders now challenges this view and postulates the existence of rare genetic variants contributing to disease, that are not captured by GWAS (see also McCarthy et al. 2008 for a more elaborate discussion of this subject). This case of the ‘missing heritability’ might imply that private or low-frequency variants of large effect size exist and actually explain most of the heritability of a multifactorial disorder in individual patients. Copy number variants (CNVs) might contribute a part of

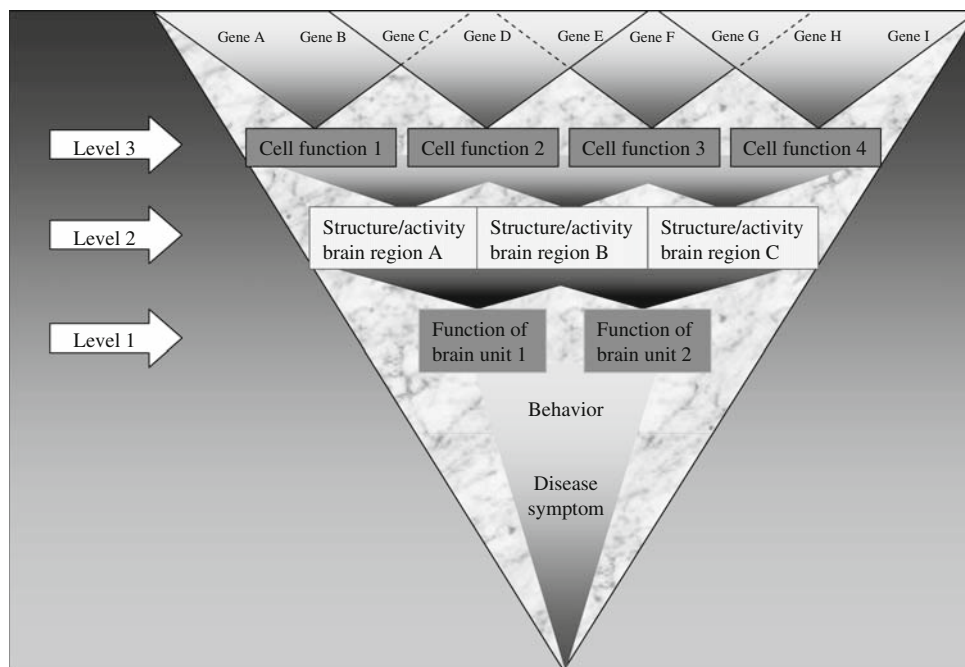


Fig. 1 Simplified schematic representation of the endophenotype concept in psychiatric genetics. Many genes (depicted in an oversimplified way as gene A to I) are involved in causing a disease symptom and the categorical disease phenotype. A reduced number of genes is involved in disease related endophenotypes, like ‘Function of a brain unit’ (Level 1), as assessed through performance on

neuropsychological tests; even less genes play a role if an endophenotype at levels 2 or 3 is used for genetic association studies. On level 2, endophenotypes measured through (structural and functional) neuroimaging are shown, on level 3 cellular behavior, assessed through e.g. assays measuring migration, apoptosis or cell division rates are shown

this puzzle. CNVs include insertions, deletions and duplications and encompass relatively large genomic segments of 1 kb to several Mb in size (Redon et al. 2006; Sebat et al. 2004). Although they are a frequent class of polymorphism in the human genome, most CNVs are rare. Many reports indeed now suggest involvement of CNVs in psychiatric disorders (Lachman et al. 2007; Marshall et al. 2008; Sebat et al. 2007; Stefansson et al. 2002, 2008; Szatmari et al. 2007b; Ullmann et al. 2007; Vrijenhoek et al. 2008; Walsh et al. 2008; Weiss et al. 2008). The role of CNVs in ADHD has not been studied, yet.

In conclusion, the GWAS performed so far in ADHD, though far from conclusive, provide a first glimpse at genes for the disorder. Many more (much larger studies) will be needed. For this, collaboration between researchers as well as standardized protocols for phenotyping and DNA-collection will become increasingly important. Furthermore, understanding how the genes identified by GWAS contribute to ADHD risk, will require smart biological experiments facing the challenge of an organ as inaccessible and complex as the human brain.

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