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Genome-Wide Association Study of the Child Behavior Checklist Dysregulation Profile

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Abstract

Objective—A potentially useful tool for understanding the distribution and determinants of emotional dysregulation in children is a Child Behavior Checklist profile comprised of the Attention Problems, Anxious/Depressed, and Aggressive Behavior clinical subscales (CBCL-DP). The CBCL-DP indexes a heritable trait that increases susceptibility for later psychopathology, including severe mood problems and aggressive behavior. We have conducted a genome-wide association study of the CBCL-DP in children with attention-deficit/hyperactivity disorder (ADHD).

Method—Families were ascertained at Massachusetts General Hospital and University of California, Los Angeles. Genotyping was conducted with the Illumina Human1M or Human1M-Duo BeadChip platforms. Genome-wide association analyses were conducted with the MQFAM multivariate extension of PLINK.

Results—CBCL data were available for 341 ADHD offspring from 339 ADHD affected trio families from the UCLA (N=128) and the MGH (N=213) sites. We found no genome-wide statistically significant associations but identified several plausible candidate genes among findings at p<5E-05: *TMEM132D*, *LRRC7*, *SEMA3A*, *ALK*, and *STIP1*.

Conclusions—We found suggestive evidence for developmentally expressed genes operant in hippocampal dependent memory and learning with the CBCL-DP.

Keywords

ADHD; Emotional Dysregulation; CBCL; GWAS

Introduction

Decades of research demonstrate that individuals with attention-deficit/hyperactivity disorder are at increased risk of additional psychiatric morbidity with mood, anxiety, behavioral, or substance use disorders [1,2]. While the mechanism underlying this spectrum of psychiatric morbidity is not known, it has been hypothesized that these disorders reflect impaired self-regulation of affect, cognition and behavior [3]. One of the most well-studied clinical and research tools for indexing dysregulation across these three domains is the Child Behavior Checklist Dysregulation Profile (CBCL-DP) [4,5] defined from the Anxious/Depressed (A/D), Attention Problems (AP) and Aggression (AGG) scales. Referred children with elevated CBCL-DP scores are at an increased risk of psychopathology, psychiatric hospitalization, and suicidality [6–10]. In the general community, impairment on the CBCL-DP is observed in 1–5% [11–13] of children and it is associated with a similarly elevated risk

of anxiety, mood, disruptive behavior, and drug abuse disorders 14 years later in adulthood [3].

Several lines of evidence suggest that the susceptibility conveyed by the CBCL-DP may be strongly influenced by genetic factors. For example, the CBCL-DP is highly heritable with additive genetic effects consistently explaining up to 67% of its variance [11–14]. Candidate gene association studies of the CBCL-DP have suggested possible association with genes coding the dopamine transporter (*SLC6A3*) and brain-derived neurotrophic factor (*BDNF)* [13,15]. Genome-wide linkage scans have implicated potential loci (LOD scores>2.5) on chromosome 2q23 [16] and 1p21.1, 6p21.3 and 8q21.13 [17]. The suggestive linkage findings are noteworthy as they partially overlap loci implicated in bipolar spectrum disorders (2q22-2q24 and 6q23-6q24) [18] that are associated with dysregulation of affect, behavior, and cognition, as well.

To extend this small literature, we conducted a genome-wide association study of the CBCL-DP in an affected offspring trio study of ADHD [19]. We also focused on loci at previously identified linkage signals for the CBCL-DP itself (2q23, 1p21.1, 6p21.3, and 8q21.13), those from meta-analyses of bipolar disorder (8q24 and 6q21) and, owing to the association between the CBCL-DP and ADHD [7,9,11,13,16,20], ADHD (16q23.1) [21].

Method

All study procedures were reviewed and approved by the subcommittee for human subjects of each respective institution. All subjects' parents or guardians signed written permission forms and children older than 7 years of age signed written assent forms.

ADHD families were ascertained at Massachusetts General Hospital (MGH, N=309 trios) and University of California, at Los Angeles (UCLA, N=156 trios) [19]. Children were 6–17 years of age at initial assessment and met criteria for DSM-IV-TR attention-deficit hyperactivity disorder. Psychiatric assessment of ADHD criteria was made with the Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version (K-SADS-E) at MGH and with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) at UCLA.

Genotyping was conducted by Genizon BioSciences Inc. with funding from Pfizer Inc. Genomic DNA samples from the MGH were genotyped using the Illumina Human1M BeadChip (N=1,057,265 SNPs) while the UCLA samples were genotyped using the Illumina Human 1M-Duo array (N=1,151,846 SNPs). Genotyping calls were generated after clustering all available data within platform at Genizon and then merged into a single file of 1,172,613 SNPs. To generate a data set of markers common to all sites, we removed SNPs that were either not included on both arrays (N=128,718 SNPs) or failed preliminary quality-control (QC) procedures conducted at Genizon (99% call rate for all samples and for all SNPs, gender check, Mendelian errors) on both the 1M and 1M-Duo arrays (N=9,500 SNPs), the 1M array only (N=39,753 SNPs) or the 1M-Duo array only (N=11,201 SNPs). For association analyses we included only SNPs with $0.01 \leq MAF < 0.05$ and call rate >99%; $0.05 \leq MAF < 0.1$ and call rate >97%, $MAF \geq 0.1$ and call rate >95% (N=142,386 SNPs excluded). Any SNPs found to be out of Hardy-Weinberg Equilibrium ($p<1.0E-6$) were excluded from further consideration (N=5,908 SNPs excluded). We checked for sample duplication by examining identity-by-state for all pairs of individuals and found none. After applying quality control filters, the final sample of ADHD trios across all three sites was 835,136 SNPs in 735 DSM-IV-TR ADHD trios from 732 families.

The Child Behavior Checklist-Parent Form (CBCL) [4] is a standardized assessment of child behavior problems and social competence. The CBCL records, in standardized format, the behavioral problems and competencies of children ages 6 to 18, as reported by their parents. A T-score above 70 is considered to be a clinically meaningful indicator of childhood psychopathology. The CBCL-DP [10] is comprised of the Attention Problems (AP), Aggressive Behavior (AGG), and the Anxious/Depressed (A/D) clinical subscales.

Statistical Analysis

We selected a family-based, quantitative, multivariate test of association for this GWAS of the component subscales of the CBCL-DP. A family-based test was necessary to account for background genetic heterogeneity in the sample. We focused on a quantitative trait analysis because the sample size was small and prohibited a categorical analysis of CBCL-DP classes. A multivariate test of association was preferable because the CBCL-DP is a composite of multiple (N=3) correlated subscales (r2 ranged from 0.41 – 0.57). We wished to maintain the information contained in the covariation amongst the AP, A/D, and AGG subcomponents (rather than testing a summation of the scales) and to avoid the additional number statistical tests required to test each sub-scale separately. Therefore, we used the MQFAM multivariate extension of PLINK [22,23] on the Genetic Cluster Computer (http://www.geneticcluster.org) which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003).

This multivariate test is described in detail in the original publication [23] but we describe it here briefly. MQFAM uses canonical correlation analysis (CCA) to identify correlation between two sets of correlated variables: X containing one variable (the bi-allelic SNP), and Y containing the three correlated CBCL-DP subscales. For each test conducted, CCA finds the linear combination of X and Y that maximizes correlation between the SNP and all traits simultaneously. This is an additive test of association but is flexible as the CBCL-DP subscales are not restricted to the same linear combination for each SNP tested. Because the phenotype loadings produced are not inherently interpretable, we also estimated the change of each component subscale with univariate linear regression to generate beta coefficients that convey direction and magnitude of effect.

Multiple, within-family permutation was used to conduct association tests that are robust to population stratification [24,25]. Because this is computationally intensive, we employed adaptive permutation to maintain family structure of the data and the permuted p-values do not adjust for multiple comparisons. To control for the number of SNPs tested, we adopted the conservative recommendation of Dudbridge et al and Pe'er et al [26,27] and considered p-values less than 5.0E-08 to be statistically significant genome-wide.

Because the power to detect a genome-wide significant associations in our sample, is quite low at 11% (assuming a quantitative trait locus explaining 2.5% of the variance) [28], we anticipate that many false negative findings will be observed amongst our top hits. Functional annotation clustering and gene enrichment tests were conducted online with the Database for Annotation, Visualization and Integrated Discovery (DAVID v6.7; http://david.abcc.ncifcrf.gov/home.jsp) clustering algorithm [29,30] in an attempt to distinguish falsely negative from falsely positive findings. Genes were submitted to DAVID if at least one SNP located within that gene (i.e., 3′ UTR, 5′ UTR, intron or exon) was nominally significant at $p<0.001$. Each cluster is assigned an EASE (Expression Analysis Systematic Explorer) score representing the statistical significance of gene enrichment in the selected gene list (i.e., -log10 of the p-value). This p-value is calculated by comparing the percent of submitted genes associated with a particular functional category against the percent of genes associated with that functional category in the relevant genomic background (i.e., the human genome). Although any EASE score ≥1.3 is nominally statistically significant at $p<0.05$, we

applied a sequential Bonferroni correction [31] to the EASE scores to account for the number of clusters identified.

Results

CBCL data were available for 341 ADHD offspring of 339 ADHD affected trio families from UCLA (N=128) and MGH (N=213). Children were 10.8±3.2 years of age at ascertainment and predominantly male (64%, N=219). Most children met DSM-IV criteria for ADHD combined type (64%, N=212), followed by ADHD inattentive (30%, N=99) and hyperactive/impulsive (6%, N=22) subtypes. The mean T-score for the Anxious/Depressed (A/D; 62.2±10.5), Aggressive Behavior (AGG; 63.8±11.6), and Attention Problems (AP; 67.9±9.6) components of the CBCL-DP were of borderline clinical significance; 11% (N=39) of ADHD children scored above 70 on all three subscales.

Because we used family-based tests, the lambda statistic (defined as the observed median F statistic divided by the expected median F statistic) was 1.0008 indicating that there was no evidence of bias associated with population genetic heterogeneity. As illustrated in the Manhattan plot of association results, however, the smallest p-value observed (Figure 1, p=1.0E-06) was not statistically significant genome-wide. Also highlighted in Figure 1 are SNPs within 1Mb of suggestive leakage peaks for the CBCL-DP (1p21.1, 2q23, 6p21.3, 8q21.13) and meta-analyses of bipolar disorder (6q21 and 8q24.22) or ADHD (16q23.1). Association results under these loci were generally unremarkable with the exception of the ADHD loci on 16q23.1 with 2 SNPs at p≤5E-04.

Six CNS expressed genes were implicated in the top 50 genome-wide associations or within 1Mb of prior linkage peaks at p<0.001 (full results presented in Table S1, available online; regional association results presented in Figure 2). Although the strongest signal for association on chromosome 11q13.1 was driven by rs12575642 (p=1.0E-6; Table S1, available online), the most functionally relevant gene at this locus is *STIP1* (stress-inducible protein 1). STIP1 is a ligand for the cellular prion protein [32] that is highly expressed in the brain and mediates astrocyte differentiation, survival, and proliferation [33]. LRRC7 (also referred to as Densin-180) is a brain-specific intracellular membrane-bound protein involved in cell adhesion, dendritic branching and neuronal excitability [34]. SEMA3A is a secreted axonal guidance protein that demonstrates increased neuronal transcription during postnatal development [35] and functions as a chemo-repellant collapsing neuronal growth cones [36]. ALK is a receptor tyrosine kinase associated with several forms of cancer [37] but also plays an important role in brain development and function. Not much is known about the function of TMEM132D, but it is a novel candidate for anxiety-related behavior [38]. CDH13 (cadherin 13, heart) on chromosome 16q24 is a calcium dependent cell-cell adhesion glycoprotein and may act as a negative regulator of neural cell growth. [39]

For each of the CNS expressed candidate genes implicated in the top genome-wide results, the Bonferonni corrected p-value for the sentinel SNP (i.e. the smallest p-value, see Table 1) was <0.05 after correcting for the number of SNPs genotyped for that gene. Of these, *LRRC7* was associated with the most clinically relevant impact on the CBCL-DP: a 10-point increase in each of the A/D, AGG, and AP subscales. *TMEM132D* SNP was associated with a similar but more moderate increase in each the components of the CBCL-DP, but *STIP1* (increased A/D and AGG scores) and *ALK* (lower A/D scores only) affected more specific behavioral domains (Table 1).

Of the 835,136 SNPs tested for association, 928 (0.11% 95%CI [0.105%-0.118%]) in 506 genes were nominally statistically significant at p<0.001 and were clustered into 18 non-mutually exclusive functional categories nominally significant at p<0.05 (i.e. EASE score

≥1.3) (for details on the top-ranked categories see Table S2, available online). Using a sequential Bonferroni correction for the number of clusters identified, two were had corrected $p<0.05$. The enrichment cluster identified by the DAVID algorithm with the smallest p-value (p=5.7E-04) was for genes involved with neuron development/ differentiation and the second cluster surviving correction for the number of clusters identified was for membrane lipoproteins. The sentinel SNP and associated gene for these top two categories are presented in Table 1.

Discussion

The "dysregulatory syndrome" measured by the CBCL-DP encompasses affective, behavioral, and cognition-related behaviors that are impaired across several psychiatric diagnoses of childhood. The CBCL-DP is attractive for genetic research because it is heritable and indexes underlying susceptibility for a severe phenotype (explosive and emotionally dysregulated) with a poor prognosis (serious psychopathology, suicidality, psychiatric hospitalization). In study of the CBCL-DP in children with ADHD, we failed to identify any genome-wide statistically significant associations. However, results from the top-ranked, suggestive findings or via gene enrichment analysis support the hypothesis that the CBCL-DP captures a heritable neurodevelopmental syndrome in children. In particular, a number of the top-ranked genes are involved in hippocampal dependent learning and memory.

Of the top ranked findings from the genome-wide association results, SNPs in *LRRC7* were associated with largest clinical impact on CBCL-DP subscales. LRRC7 is scaffolding protein expressed in the post-synaptic density [40] and is used as postsynaptic marker of hippocampal glutamatergic synapse integrity. In the post-synaptic membrane LRRC7 anchors a calcium dependent protein kinase (CAMK2A) that is critical for the initiation of early long-term potentiation [34]. Furthermore, the tyrosine kinase receptor gene (*NTRKB2*) activated by BDNF was included in the neuronal differentiation/development gene enrichment category. NTRKB2 activation in the hippocampus initiates intra-cellular signaling cascades that partially rely on LRRC7-anchored CAMK2A activity to mediate calcium release required for long-term potentiation [41]. The possible involvement of this signaling pathway is consistent with prior research suggesting association with BDNF and both bipolar disorder [42–44] and the CBCL-DP [15]. Additional research suggests that the BDNF-NTRKB2-CREB pathway may interact with childhood adversity to impact depressive symptoms in adulthood [45] and anti-depressant induced suicidality [46].

We also found nominal evidence of association with several SNPs in *STIP1* on chromosome 11q13.1. STIP1 is highly expressed in the brain and is a ligand for cellular prion protein (PRPN; included the lipoproteins/integral to membrane enrichment category listed in Table 1). STIP1-PRPN binding mediates astrocyte differentiation and survival through ERK activation and the PKA signaling pathway, respectively [32,33]. Direct infusion of polyclonal antibodies against the STIP1-PRPN binding site into the dorsal hippocampus blocked memory consolidation during an inhibitory avoidant step-down paradigm in rats [47].

A third gene implicated amongst our top-ranked association results has been implicated in brain development and hippocampal neurogenesis [37]. Several SNPs on chromosome 2p23.1 in the *ALK* gene were nominally associated with the CBCL-DP. Loss of ALK function is associated with improved performance on hippocampal-dependent learning tasks and an anti-depressant behavioral profile on the tail suspension and Porsolt swim tests [48]. The anti-depressant effects demonstrated with inhibition of ALK activity in animal models mirrors our study in which we observed a 5-point reduction with each minor allele of the *ALK* SNP

(Table 1) for the CBCL-AD T-score but no appreciable effect for either the AP or AGG T-scores.

The pathophysiology underlying dysregulated affect, cognition and behavior is unknown and the small extant literature has not specifically addressed hippocampal dependent memory and learning [49]. Nonetheless, the hypotheses generated from these genome-wide data are consistent with a learning-disordered/transactional model of explosive behavior in which lagging higher-order cognitive skills interfere with a child's ability to comply with authoritarian demands [50,51]. Specific deficits in learning and memory could contribute to explosive reactivity through inefficient encoding of previous consequences of noncompliance, thereby interfering with the ability to anticipate consequences of potential actions [51].

Although preliminary, the genetic enrichment analysis suggests that the CBCL-DP phenotype may be associated with genes mediating developmental neuromorphology, as well. For example, *SEMA3A* was one of our top-ranked association results and was included in the neuron developmental/differentiation enrichment category. SEMA3A is a secreted axonal guidance protein that demonstrates increased neuronal transcription during postnatal development [35] and functions as a chemo-repellant collapsing neuronal growth cones [36]. Additional neurodevelopmental candidate genes in this category include EPHA7 that is amongst the earliest markers of subcortical parcellation of the neocortex [52] and cerebral volume [53]. *DLX2* also regulates subcortical development in the telencephalon and has previously been associated with autism [54].

It may also be noteworthy, however, that these and other neurodevelopmental candidates from this category also mediate synaptic plasticity and memory/learning. DLX2, for example, interacts with the promoter region of the NTRKB2 gene in the mouse retina [55]. Although EPHA7 is widely expressed during embryonic development, it is also expressed postnatally and has been hypothesized to impact ongoing synaptic plasticity [52]. SEMA3A is highly expressed in in the entorhinal cortex [56] and SEMA3A induced neuronal growth cone collapse is significantly reduced in hippocampal neurons in the FMR1 knock-out model of Fragile X syndrome [57]. Additionally, NRXN1 is a cell membrane protein that regulates calcium triggered neurotransmitter release and has been associated with both schizophrenia and developmental disorders [58–61].

This collaborative effort improves upon our earlier linkage studies [16,17] by utilizing the Illumina Human1M array and improving the genomic coverage afforded by our prior linkage studies. Despite pooling samples from the two previous CBCL-DP linkage studies [16,17], we failed to identify any nominally significant candidate genes under the suggestive linkage peaks reported. While this clearly could be due to small sample size, additional differences may explain the lack of replication of prior findings. Because the inclusion criteria for the primary ADHD genome-wide study [19] required independent ADHD trios and substantial quantities of DNA for genotyping, many children from the UCLA (N=412) and MGH (N=235) linkage analyses were not included in the current study while additional (N=129) trios from MGH were included. Thus, the current report is neither an independent replication nor a focused follow-up of the previous work.

Rather, our results represent the next step in trying to understand genes contributing to dysregulated affect, cognition, and behavior measured with the CBCL-DP. Clearly, larger independent samples are needed to test the hypotheses that developmentally expressed genes operant in hippocampal-dependent learning and memory may be associated with the CBCL-DP. If replicated, these findings may be useful for identifying children at risk for severe

psychopathology and developing novel interventions for this impairing dysregulatory syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Manhattan Plot of Association Results. Note: Single Nucleotide Polymorphisms (SNPs) within 1 million base-pairs of suggestive leakage peaks for the Child Behavior Checklist – Dysregulation Profile (CBCL-DP) (1p21.1, 2q23, 6p21.3, 8q21.13) and meta-analyses of bipolar disorder (6q21 and 8q24.22) or ADHD (16q23.1) are highlighted in red.

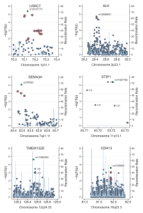

Figure 2.

Regional Association Plots for Genes Implicated in the Top 50 Associations. Note: The sentinel Single Nucleotide Polymorphism (SNP) (i.e. with the smallest p-value) is indicated by the green square. Any SNPs in linkage disequilibrium (LD) (r2≥0.8) with the sentinel SNP are marked with a red border. For SNPs with no additional SNPs in linkage disequilibrium (STIP1, TMEM132D) the r2 values available are depicted with text. Estimated recombination rates from the latest HapMap download (build 36) are depicted in light blue. Additional SNPs in *LRRC7* and *SEMA3A* were also nominally significantly associated with the Child Behavior Checklist – Dysregulation Profile (CBCL-DP), but were in strong LD (r2≥0.8) with the sentinel SNPs (rs12037173 and rs797820, respectively) and likely represent single regions of association within these genes. Additional nominally significant SNPs in *ALK*, *STIP1*, and *TEMEM132D*, however, were not in strong LD with the sentinel SNPs (rs12996631, rs11607165, and rs11060369, respectively) as indicated by the r2 values. Although *STIP1* was covered with only seven SNPs in our data, all but two were nominally statistically significant. Few additional SNPs in *CDH13* were nominally associated with the CBCL-DP, and two of the three in LD (r2≥0.8) with rs1035569 were not statistically significant.

Table 1

Candidate Genes from the Top Genome-Wide Association Results and from Gene Enrichment Analysis

Chromsome		SNP	A1	Position	MAF	HWE p-value	AD	AGG	AP	p-value	Gene	Size (bp)	SNP (N)	Bonferroni p-value
Top GWAS Findings														
1	p31.1	rs12037173	C	70,128,569	0.05	0.255	10.2	12.0	10.3	4.0E-06	LRRC7	1,002,328	33	0.0001
2	p23.1	rs12996631	C	29,425,803	0.40	0.247	−4.8	−0.9	−0.2	1.9E-05	ALK	844,608	235	0.005
7	q21.11	rs797820	G	83,446,975	0.25	0.635	2.4	−3.2	2.5	8.0E-06	SEMA3A	768,248	74	0.0006
11	q13.1	rs11607165	G	63,720,523	0.18	0.864	6.0	7.2	1.3	4.0E-06	STIP1	20,400	4	0.00002
12	q24.33	rs11060369	C	128,526,150	0.35	0.379	5.8	3.2	3.6	2.3E-05	TMEM132D	981,144	323	0.007
Gene Enrichment: Neuron Development/Differentiation														
1	q21.3	rs4845552	G	151,746,622	0.15	0.482	−3.5	2.4	1.6	2.2E-04	S100A6	34,752	4	0.0009
2	p16.3	rs7571753	C	50,587,462	0.40	0.462	2.8	4.3	−0.6	2.4E-04	NRXN1	1,280,896	247	0.06
2	q31.1	rs6717347	A	172,825,756	0.27	0.704	4.5	4.8	4.1	6.5E-04	DLX2	166,320	42	0.03
3	p26.3	rs4234555	G	2,887,699	0.10	0.675	5.2	−1.6	−0.8	5.2E-04	CNTN4	1,058,541	456	0.2
3	q22.2	rs4072181	C	135,351,487	0.04	0.111	−8.8	−13.6	−4.8	1.9E-04	RYK	202,944	18	0.003
5	q11.2	rs10051973	G	51,299,258	0.05	0.008	3.3	10.4	6.1	7.0E-04	ISL1	696,056	69	0.048
6	p21.32	rs3830041	A	32,299,317	0.09	0.648	7.0	5.9	5.9	7.9E-04	NOTCH4	44,120	61	0.048
6	p21.2	rs747158	A	37,832,391	0.17	0.363	3.5	7.0	2.5	9.4E-05	MDGA1	169,496	79	0.007
6	p21.1	rs6458486	T	46,115,804	0.24	0.102	−5.4	−3.3	−2.0	7.4E-04	CLIC5	341,772	103	0.08
6	q16.1	rs493340	C	93,813,605	0.36	0.230	−0.6	0.3	3.6	8.4E-05	EPHA7	1,946,928	320	0.03
7	q31.1	rs7788778	C	107,388,759	0.31	0.598	−2.6	−0.7	−4.2	5.6E-04	LAMB1	78,024	21	0.01
9	q21.13	rs11144062	A	76,489,560	0.18	0.207	3.9	2.8	5.9	3.7E-04	RORB	624,696	82	0.03
9	q21.33	rs4578034	G	86,777,602	0.45	0.839	1.6	4.9	2.5	4.0E-04	NTRK2	760,688	147	0.06
11	q25	rs7129456	T	132,027,753	0.04	0.546	−7.0	−10.7	−3.9	9.6E-04	OPCML	1,278,504	344	0.3
12	p12.1	rs12371851	T	24,336,029	0.17	0.471	−1.8	−2.1	−6.3	6.2E-04	SOX5	1,451,484	383	0.2
12	q24.13	rs11066321	C	111,393,779	0.02	1.000	−4.7	−13.6	−8.6	4.6E-04	PTPN11	205,312	22	0.01
13	q22.3	rs700363	T	76,473,397	0.09	1.000	−4.7	−6.1	1.7	9.0E-05	CLN5	46,800	5	0.0005
14	q13	rs7157863	C	27,869,620	0.11	0.074	5.1	8.8	1.4	6.1E-05	FOXG1	537,492	74	0.005
14	q24.3	rs12880418	A	78,239,581	0.35	0.243	−0.8	1.6	3.5	3.0E-04	NRXN3	1,694,640	352	0.1
15	q11.2	rs6606810	C	20,499,465	0.26	0.115	−3.3	1.1	0.2	9.1E-04	CYFIP1	118,148	34	0.03
15	q26.3	rs7174918	T	97,068,879	0.32	0.107	−1.5	−3.0	2.3	3.6E-04	IGF1R	379,256	115	0.04
16	q23.3	rs1035569	G	81,906,325	0.32	0.730	−3.0	−5.7	−1.5	2.5E-04	CDH13	1,403,424	765	0.2

Chromsome		SNP	A1	Position	MAF	HWE p-value	AD	AGG	AP	p-value	Gene	Size (bp)	SNP (N)	Bonferroni p-value
21	q21.1	rs10482920	G	22,293,822	0.03	1.000	10.2	14.4	9.0	1.9E-04	NCAM2	1,746,048	347	0.06
21	q21.3	rs2829983	C	26,206,976	0.11	1.000	7.9	2.5	3.1	9.5E-05	APP	490,344	101	0.01
Gene Enrichment: Lipoproteins / Integral to Membrane														
1	p35.1	rs648718	C	32,183,069	0.42	0.837	1.8	−2.1	2.4	9.7E-04	PTP4A2	102,136	14	0.01
1	q42.13	rs11585386	T	227,085,771	0.08	1.000	−1.2	−7.4	−4.9	3.4E-04	RHOU	349,440	42	0.01
2	q37.3	rs7609518	C	240,945,709	0.24	0.731	4.6	3.2	−0.1	7.9E-04	GPC1	183,248	48	0.04
3	p24.3	rs12490991	G	16,432,099	0.35	0.657	0.3	−1.2	−3.5	5.3E-04	RFTN1	236,443	80	0.04
3	q24	rs2587028	T	147,725,651	0.12	0.562	0.7	−5.0	2.2	7.2E-04	PLSCR1	43,344	17	0.01
5	p15.33	rs2289827	C	1,032,148	0.22	0.335	5.6	2.2	1.8	6.8E-04	NKD2	76,855	21	0.01
8	q24.3	rs7461733	A	144,299,103	0.05	0.588	−0.3	3.5	7.2	7.5E-04	LY6H	54,992	15	0.01
9	p13.3	rs10814119	G	34,540,295	0.33	1.000	4.3	−0.2	1.9	2.6E-04	CNTFR	44,692	14	0.004
9	q31.3	rs9696126	T	111,949,957	0.18	0.433	−5.7	−1.4	−3.9	2.1E-04	PALM2-AKAP2	474,560	86	0.02
10	q23.31	rs1274409	A	92,352,777	0.23	0.361	0.4	−4.4	0.6	7.6E-04	HTR7	498,072	74	0.06
11	p13	rs262421	G	35,994,935	0.47	0.724	3.7	4.0	3.2	4.2E-04	LDLRAD3	337,892	122	0.05
11	q13.2	rs3736228	A	67,957,871	0.14	0.174	−3.4	−2.3	−6.2	7.8E-04	LRP5	151,392	18	0.01
11	q14.1	rs7125165	T	83,048,044	0.29	0.162	5.0	2.2	3.3	6.5E-04	DLG2	1,882,608	345	0.2
11	q22.1	rs11217465	T	98,278,107	0.28	0.215	1.2	4.6	−0.7	5.3E-04	CNTN5	2,804,208	659	0.3
12	q12	rs776893	A	39,790,611	0.47	0.801	−1.6	−1.0	2.6	4.5E-04	CNTN1	613,804	83	0.04
13	q31.3	rs9556365	G	93,815,239	0.24	0.889	−4.7	−3.2	0.1	3.7E-04	GPC6	1,364,712	268	0.1
14	q32.2	rs878077	A	99,684,876	0.03	0.705	1.7	−10.0	5.9	3.2E-04	DEGS2	48,896	10	0.003
19	q13.33	rs3786776	C	53,242,659	0.42	1.000	2.5	4.1	3.4	7.2E-04	PLA2G4C	66,180	29	0.02
20	p13	rs6084754	G	4,392,161	0.44	0.475	4.2	−0.1	2.1	4.6E-04	ADRA1D	253,469	91	0.04
20	p13	rs6139516	G	4,597,276	0.22	0.553	−2.5	−2.7	−5.4	5.6E-04	PRNP	241,770	68	0.04
21	q21.1	rs2300508	A	18,762,467	0.48	0.512	4.9	1.6	1.9	4.9E-04	PRSS7	358,200	101	0.049

Note: Due to linkage disequilibrium (LD) between Single Nucleotide Polymorphisms (SNPs), the number of independent statistical comparisons made is fewer than the total number of genotyped for each gene. The LD-based pruning was used to identify SNPs in linkage equilibrium to correct nominal p-values by the number of independent tests conducted in each gene. AD = Child Behavior Checklist (CBCL) Anxious/Depressed T-Score beta; AGG = CBCL Aggressive Behavior T-Score beta; AP = CBCL Attention Problems T-Score beta; GWAS = genome-wide association study; HWE = Hardy-Weinburg Equilibrium p-value; MAF = Minor Allele Frequency.