

Angiogenic, Neurotrophic, and Inflammatory System SNPs Moderate the Association between Birth Weight and ADHD Symptom Severity

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Abstract:

Low birth weight is associated with increased risk for Attention-Deficit/Hyperactivity Disorder (ADHD); however, the etiological underpinnings of this relationship remain unclear.

This study investigated if genetic variants in angiogenic, dopaminergic, neurotrophic, kynurenine, and cytokine-related biological pathways moderate the relationship between birth weight and ADHD symptom severity.

A total of 398 youth from two multi-site, family-based studies of ADHD were included in the analysis. The sample consisted of 360 ADHD probands, 21 affected siblings, and 17 unaffected siblings. A set of 164 SNPs from 31 candidate genes, representing five biological pathways, were included in our analyses. Birth weight and gestational age data were collected from a state birth registry, medical records, and parent report. Generalized Estimating Equations tested for main effects and interactions between individual SNPs and birth weight centile in predicting ADHD symptom severity.

SNPs within neurotrophic (NTRK3) and cytokine genes (CNTFR) were associated with ADHD inattentive symptom severity. There was no main effect of birth weight centile on ADHD symptom severity. SNPs within angiogenic (NRP1 & NRP2), neurotrophic (NTRK1 & NTRK3), cytokine (IL16 & S100B), and kynurenine (CCBL1 & CCBL2) genes moderate the association between birth weight centile and ADHD symptom severity. The SNP main effects and SNP birth weight centile interactions remained significant after adjusting for multiple testing.

Genetic variability in angiogenic, neurotrophic, and inflammatory systems may moderate the association between restricted prenatal growth, a proxy for an adverse prenatal environment, and risk to develop ADHD.

Key words:

Attention Deficit Hyperactivity Disorder; birth weight; gene-environment interaction; neurotrophin; Developmental Origins of Health and Disease

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by persistent, pervasive, and developmentally inappropriate levels of inattention, hyperactivity-impulsivity, or both. ADHD arises from the complex interplay between genetic and environmental factors [Thapar et al., 2013]. Consequently, there are likely to be multiple etiological pathways leading from early risk to the development of the disorder [Sonuga-Barke and Halperin, 2010; Thapar et al., 2013]. In particular,

environmental insults during prenatal development have the potential to have lasting effects on neurodevelopmental risk for ADHD [Lou, 1996; Toft, 1999; Lou et al., 2004; Mill and Petronis, 2008]. Although multiple prenatal environmental risk factors for ADHD have been identified [Banerjee et al., 2007; Nigg et al., 2010; Froehlich et al., 2011], specific developmental mechanisms that contribute to the emergence of ADHD are poorly understood.

Restricted fetal growth phenotypes, like low birth weight (<2,500 g) and small

for gestational age, are among the strongest risk factors for ADHD and lead to 1.5 to 3-fold increase in ADHD risk [Breslau et al., 1996; Mick et al., 2002; Indredavik et al., 2004; Linnert et al., 2006; Boulet et al., 2009]. The strength of this association, however, varies across studies [Nigg, 2006] and is not always replicated [Cornforth et al., 2012]. Consistent with the dimensional nature of ADHD [Levy et al., 1997; Coghill and Sonuga-Barke, 2012], the association between lower birth weight and ADHD-related phenotypes is continuous and extends into the normal birth weight range [Boulet et al., 2009; Phua et al., 2012; Qiu et al., 2012; Walhovd et al., 2012]. Lower birth weight is also associated with reduced anterior cingulate cortex, caudate nucleus, and total brain volumes [Peterson et al., 2003; Tolsa et al., 2004; de Kieviet et al., 2012; Walhovd et al., 2012], which are linked with ADHD behavioral symptomatology [Frodl and Skokauskas, 2012; Hart et al., 2013]. Identifying biological mechanisms that contribute to the association between lower birth weight and ADHD may further elucidate early developmental pathways to ADHD.

Similar to ADHD [Thapar et al., 2013], birth weight has multifactorial origins and a substantial heritability estimate [Mook-Kanamori et al., 2012]. This allows for the possibility that birth weight and ADHD share a common genetic liability. Twin studies, however, demonstrate that prenatal environmental factors, rather than shared genetic factors, largely account for the relationship between birth weight and ADHD symptoms [Lehn et al., 2007; Groen-Blokhuis et al., 2011; Ficks et al., 2013; Sharp et al., 2003] or

externalizing behavior [van Os et al., 2001; Wichers et al., 2002]. This suggests that environmental determinants of lower birth weight contribute to the development of ADHD.

Suboptimal maternal-placental-fetal nutrient and oxygen transport (e.g., placental insufficiency) is associated with restricted fetal growth in most cases [Ghidini, 1996; Hendrix et al., 2008]. Prenatal ischemia-hypoxia is considered the primary pathway to lower birth weight, especially in well-nourished populations [Henriksen et al., 2002]. Placental insufficiency and fetal growth restriction are associated with altered angiogenic [Conde-Agudelo et al., 2013], dopaminergic [Vucetic et al., 2010], neurotrophic [Malamitsi-Puchner et al., 2007], and inflammatory responses [Amarilyo et al., 2011], and numerous poor neurodevelopmental outcomes [Baschat, 2011]. Prenatal ischemia-hypoxia is a common element to multiple early risk factors for ADHD including maternal smoking [Bush et al., 2000] and maternal alcohol use during pregnancy [Bosco and Diaz, 2012] as well as ischemia-hypoxia related obstetric complications [Pineda et al., 2007; Rennie et al., 2007; Getahun et al., 2013]. Consistent with the Developmental Origins of Health and Disease (DOHaD) framework [Gluckman et al., 2004; Mill et al., 2008; Swanson and Wadhwa, 2008; Swanson et al., 2009; Wadhwa et al., 2009], the association between lower birth weight and ADHD may arise from prenatal ischemia-hypoxia. Prenatal ischemia-hypoxia may directly disrupt or delay development or lead to structural or functional adaptations to the adverse

intrauterine environment. Such adaptations, however, may leave the individual ill-equipped to function in a nutrient and oxygen rich postnatal environment. For example, in response to prenatal ischemia-hypoxia some fetuses preferentially redistribute blood flow to the brain, known as the “brain-sparing effect” [Roza et al., 2008]. Fetuses that demonstrate “brain-sparing” circulation may be better protected from the immediate adverse effects of ischemia-hypoxia, however, these fetuses may exhibit decreased cerebral vascular plasticity [Fu et al., 2006] and increased behavioural problems [Roza et al., 2008; Figueras et al., 2011]. Genetic variability in key ischemia-hypoxia related developmental systems may further alter susceptibility to ADHD, following an adverse intrauterine environment.

Few studies have investigated how the interplay between fetal growth and genetic variability contributes to ADHD’s complex pathophysiology. Langley et al. (2008) found that “classic” candidate neurotransmitter gene (DAT1, DRD4, DRD5, and SLC6A4) variants did not moderate the association between birth weight and ADHD. Another study reported that ADHD youth who also had low birth weight were at increased risk for early-onset antisocial behavior if they possessed the COMT Val/Val genotype [Thapar et al., 2005]. This finding, however, was not replicated in a separate ADHD clinical sample [Sengupta et al., 2006]. To examine mechanisms linking fetal growth with ADHD, it may be important to broaden the search to genes implicated in the response to prenatal ischemia-hypoxia, a main determinant of restricted

fetal growth.

Prenatal ischemia-hypoxia impacts multiple neurodevelopmental systems [Schmidt-Kastner et al., 2012; Zhang et al., 2012; Wang et al., 2013]. Of the many systems implicated in the ischemia-hypoxia response, dopaminergic [Levy, 1991; Swanson et al., 2007], neurotrophic [Ribases et al., 2008; Sanchez-Mora et al., 2009], angiogenic [Kim et al., 2002; Jesmin et al., 2004], kynurenine [Oades, 2011] and cytokine systems [Oades, 2011] are also implicated in the development of ADHD and related conditions. Therefore, genetic variants within these five systems were the focus of this study. Variability in genes regulating these systems may alter vulnerability to the effects of prenatal ischemia-hypoxia leading to the neurodevelopmental deficits that mediate the ADHD behavioural phenotype [Toft, 1999; Shaw et al., 2006; Rapoport and Gogtay, 2008]. To address this hypothesis, we examined interactions between genetic variants within ischemia-hypoxia response systems and birth weight centile, adjusted for gestational age, to predict ADHD symptom severity. We predicted that: (i) lower birth weight centile would be associated with increased ADHD symptomatology; and (ii) SNPs within dopaminergic, neurotrophic, angiogenic, kynurenine and cytokine system genes would moderate the association between birth weight centile and ADHD symptom severity.

MATERIALS AND METHODS

Subjects

Participants were drawn from two larger studies - the North Carolina Genetics of ADHD Project [NCGAP; Kollins et al., 2008; Anastopoulos et al., 2011] and the

International Multisite ADHD Genetics Project [IMAGE; Brookes et al., 2006; Kuntsi et al., 2006; Neale et al., 2008b], the latter including 12 enrolment sites within Europe and Israel. The current analysis was conducted on a subset of the NCGAP and IMAGE samples who were singleton births and had birth weight, gestational age, and genome-wide single nucleotide polymorphism (SNP) data. Birth weight and gestational age data were only available for IMAGE study sites in the United Kingdom, Ireland and the Netherlands. Furthermore, we only included Caucasian participants due to genotype imputation procedures (described below). Of the 398 youth in the final sample (Table I), 86% met criteria for

TABLE I. Sample Size by Site

Site	n	% of total sample
Ireland	33	8.3
Netherlands - Amsterdam	101	25.4
Netherlands - Nijmegen	73	18.3
United Kingdom	84	21.1
IMAGE Subtotal	291	73.1
Duke	65	16.3
UNCG	42	10.6
NCGAP Subtotal	107	26.9
Total Sample	398	100

DSM-IV ADHD Combined Type (n=327), 11% met for ADHD Inattentive Type (n=42), 3% met for ADHD Hyperactive-Impulsive Type (n=12), and 4% were unaffected (n=17). For NCGAP [Anastopoulos et al., 2011] and IMAGE [Neale et al., 2008a], DSM-IV ADHD diagnoses were based on parental responses to a clinical interview as well as teacher and/or parent responses to behavior rating scales. This study was approved by the affiliated institutional

review boards and conducted in accordance with human subjects guidelines.

Measures

Conners' parent rating scale (CPRS; Conners, 1997). Parent responses to the CPRS 18-item DSM-IV ADHD total subscale, as well as 9-item Inattentive and Hyperactive-Impulsive subscales were summed and converted to t-scores adjusting for age and gender of each participant [Conners et al., 1998]. Parents were instructed to rate their child's ADHD symptoms when not taking medication prescribed for ADHD. The resulting scores were continuous measures of ADHD symptom severity and served as outcomes in this study. The CPRS ADHD Total (skewness = -0.81; SE = 0.12), Inattentive (skewness = -0.50; SE = 0.12), and Hyperactive-Impulsive (skewness = -0.85; SE = 0.12) scores were non-normally distributed. Therefore, transformed CPRS ADHD Total (square root of reflected score transformation; skewness = -0.03; SE = 0.12), Inattentive (squared transformation; skewness = <0.01; SE = 0.12), and Hyperactive-Impulsive scores (square root transformation; skewness = -0.07; SE = 0.12) were selected for analysis based on normality.

Birth weight centile range. Birth weight centiles were calculated for each participant adjusting for gestational age and sex, based on separate normative samples for the Netherlands, United Kingdom/Ireland, and United States participants.

NCGAP. Birth weight and gestational age for the NCGAP sample was retrieved through medical records, parental report, and state birth registry. Birth weight

centiles for NCGAP were created using all singleton births from 2000xps12004 from the CDC National Vital Statistics natality files. For consistency, individual centiles were then converted to the centile ranges described below.

IMAGE. For the Dutch sample, birth weight and gestational age were obtained through retrospective parent report. The Netherlands Perinatal Registry reference curves were used to calculate birth weight centiles for the Dutch sample [Visser et al., 2009]. The Netherlands Perinatal Registry reference curves provide 11 normative references at 2.3, 5, 10, 16, 20, 50, 80, 84, 90, 95, and 97.7 centiles [Visser et al., 2009]. Therefore, 12 birth weight centile ranges were created (0–2.29, 2.3–4.9, 5–9.9, 10–15.9, 16–19.9, 20–49.9, 50–79.9, 80–83.9, 84–89.9, 90–94.9, 95–97.6, 97.7–100). Lower scores on the resulting ordinal severity scale of birth weight centile ranges represented higher levels of fetal growth restriction.

Birth weight and gestational age for samples from Ireland and the UK were obtained from retrospective parent report. The UK reference curves [Pan et al., 2010; Cole et al., 2011] were used to calculate birth weight centiles for the UK and Ireland samples, based on birth weight, gestational age, and sex. For consistency, individual birth weight centiles were converted to birth weight centile ranges identical to those created in the Dutch sample.

Genotyping. SNP genotyping for the NCGAP subsample was performed using the Illumina Infinium HumanHap300 duo (Illumina, Inc., San Diego, CA) at the Center for Human Genetics at Duke University Medical School. Two Centre

d’Etude du Polymorphisme Humain (CEPH) controls and blinded duplicates were used for every 94 samples and required to match 100%. Additional quality checks of the genotyping data were examined using PLINK [Purcell et al., 2007]. Call rates exceeded 98% for all individuals. Individuals were excluded due to gender discrepancy and if per-family Mendelian errors were in excess of 1%. SNPs were excluded from analysis if they had Mendelian errors in >4 families or deviated from Hardy-Weinberg Equilibrium (HWE; $P < 0.000001$).

SNP genotyping for the IMAGE subsample was performed at Perlegen Sciences (Mountain View, CA) on a microarray designed for the Genetic Association Information Network (GAIN). Quality checks were completed by the National Center for Biotechnology Information (NCBI) using GAIN QA/QC, version 0.7.4 [Abecasis Gopalakrishnana]. Individuals were excluded due to gender discrepancy and if per-family Mendelian errors were in excess of 2%. SNPs were excluded if the: (i) call rate was <95%; (ii) heterozygosity was >32%; (iii) discrepancy in SNP call was <10% in whole sample; or (iv) HWE $P < 0.000001$.

Candidate genes were selected based of literature review of candidate signalling pathways [Reichardt, 2006; Shibuya, 2008], ischemia–hypoxia response genes [Schmidt-Kastner et al., 2006], ADHD etiological studies [Gizer et al., 2009; Oades et al., 2010; Oades, 2011] and genotyping platform coverage. SNPs within dopaminergic (COMT, DAT1, DRD2, DRD3, and DRD5), neurotrophic (BDNF, NGF, NT3, NGFR, NTRK1, NTRK2, and NTRK3), angiogenic (VEGFA, VEGFR1,

VEGFR2, NRP1, NRP2, HIF1A, and HIF1AN), kynurenine (CCBL1, CCBL2, and KYNU) and cytokine related genes (CNTF, CNTFR, CRLF1, IL6, IL13, IL16, LIF, LIFR, and S100B) that passed quality control measures were considered for inclusion in the analysis. To increase genetic overlap across NCGAP and IMAGE, genotype data were imputed with the use of the phased data from the HapMap samples (CEU; build 36, release 22) and MACH [<http://www.sph.umich.edu/csg/abecasis/MaCH/download>; Li et al., 2009, 2010]. Imputed SNPs with an R² value <0.3, indicating poor imputation quality, were excluded from analysis (see Supplementary Table SI for SNP imputation quality). Note that not all SNPs attributed to candidate genes in this build are attributed to the same genes in NCBI build 37.

A total of 2,014 dopaminergic, neurotrophic, angiogenic, kynurenine and cytokine SNPs were available for this study and submitted for quality checks. The majority of these SNPs were not functional. To reduce the number of statistical tests conducted, remaining SNPs with a: (i) minor allele frequency (MAF) < 0.1; (ii) genotype frequency below seven; or (iii) in linkage disequilibrium (LD; R² ≥ 0.64) were eliminated. A total of 164 SNPs in dopaminergic, neurotrophic, angiogenic, kynurenine, and cytokine systems remained.

Data Analysis

Bivariate correlations and Pearson product-moment correlation coefficients examined the associations among demographic, perinatal risk, and ADHD variables. In addition, t-tests and ANOVAs were used to test for differences between demographic groups on perinatal and

ADHD variables. Alpha was set at 0.01 for these analyses.

Generalized Estimating Equations (GEEs) tested for main effects of SNP genotype and birth weight centile range, and the interaction between SNP and birth weight centile range in predicting ADHD symptom severity. Given that within family data are more correlated than between family data, GEEs account for the family correlation among siblings within the sample. An independent working correlation matrix and the model-based robust estimator covariance matrix were selected, which provides a reliable covariance estimate even when the correlation matrix is not correctly specified.

Linear GEEs were employed to test the SNP and birth weight centile range main effects on ADHD symptom severity after adjusting for research site, age, and sex as covariates. Next, to test the hypothesis that SNP genotype moderates the association between birth weight centile and ADHD symptom severity, the covariates of site, age, and sex and main effects of SNP genotype and birth weight centile range were entered into the model, followed by the SNP x birth weight centile range interaction. Wald chi-square tests calculated with Type III sums of squares tested the significance of main and interactive effects. In addition, continuous variables were centered to ease the interpretation of model effects. No specific genetic model was assumed in the primary analysis, as the genetic model could differ depending on the genetic variant. Additive, dominant, and recessive genetic models were tested on a secondary basis.

In the GEEs, alpha was set at .01 for

nominally significant findings. A total of 164 independent GEEs were calculated. The Benjamini–Hochberg False Discovery Rate (FDR) test [Benjamini and Hochberg, 1995] was used to adjust for multiple comparisons. The FDR q -value threshold was set at 0.05 to determine statistical significance. This study is adequately powered to detect reasonably sized SNP \times birth weight centile interactions on ADHD without accounting for multiple testing and is underpowered to detect interactions after FDR correction (Supplementary Table SII). Exploratory Sobel tests were conducted to examine if birth weight centile mediated the effect of SNPs on ADHD symptom severity. All analyses were completed using SAS.

RESULTS

Demographic, Perinatal, and ADHD Variables

A total of 398 youth participated in the current study (see Table I for sample size by site), including 360 ADHD probands, 21 affected siblings, and 17 unaffected siblings. The sample had a mean age of 10.7 years ($SD = 3.02$ years; range 5–17 years) and was 83% male. In terms of birth characteristics, the samples' mean birth weight ($M = 3,389.25$ g; $SD = 565$ g) and gestational age ($M = 39.56$ weeks; $SD = 1.94$ weeks) were in the normal range.

Table II gives a summary of the relationships between continuous demographic, perinatal, and ADHD variables. Older youth had lower birth weight centile range scores and higher CPRS ADHD Total scores. There were no differences between females and males in birth weight centile range ($t(396) = 0.67$, $p = 0.50$),

birth weight ($t(396) = -0.707$, $p = 0.48$), or gestational age ($t(396) = 0.72$, $p = .47$).

Birth weight centile range scores, varied across data collection sites, $F(5, 397) = 8.34$, $P < 0.01$ (Duke, $M = 6.92$, $SD = 0.28$; UNCG, $M = 7.98$, $SD = 0.34$; Ireland, $M = 6.26$, $SD = 0.24$; Netherlands–Amsterdam, $M = 5.77$, $SD = 0.22$; Netherlands–Nijmegen, $M = 5.88$, $SD = 0.26$; UK, $M = 7.24$, $SD = 0.39$). In addition, CPRS ADHD Total scores varied across data collection sites, $F(5, 397) = 4.09$, $P < 0.01$. In general, IMAGE samples had higher CPRS ADHD Total scores compared to the NCGAP samples (Duke, $M = 74.24$, $SD = 13.96$; UNCG, $M = 75.19$, $SD = 14.49$; Ireland, $M = 79.27$, $SD = 9.26$; Netherlands–Amsterdam, $M = 76.35$, $SD = 8.22$; Netherlands–Nijmegen, $M = 78.32$, $SD = 7.82$; UK, $M = 81.58$; $SD = 8.33$).

Analysis of SNP main effects on ADHD symptom severity.

After controlling for site, age, sex, and multiple testing, three out of 164 SNPs had a significant main effect on the CPRS Inattentive score (see Table III and Supplementary Tables SVII and SVIII for SNP main effects from each statistical model). In the cytokine system, rs10758268 (CNTFR; $q = 0.005$) and rs7044318 (CNTFR; $q = 0.021$) genotypes were associated with the CPRS Inattentive score. In the neurotrophic system, rs3825885 (NTRK3; $q = 0.021$) genotype predicted the CPRS Inattentive score. SNP main effects on ADHD Total Score and Hyperactivity–Impulsivity were not significant after adjusting for multiple testing (Table III).

Main effect of birth weight centile range on ADHD symptom severity.

Contrary to the first hypothesis, birth weight centile range was not associated with ADHD Total ($b = 0.26$; $SE = 0.21$; 95% $CI = -0.15-0.68$; $P = 0.21$), Inattentive ($b = 0.28$; $SE = 0.20$; 95% $CI = -0.11-0.67$; $P=0.16$) or Hyperactive-Impulsive ($b = 0.14$; $SE = 0.23$; 95% $CI = -0.30-0.59$; $P = 0.53$) scores. Note for interpretative purposes the above statistics are from non-transformed ADHD subscale models (P -values are consistent with transformed ADHD subscale models)

Interactions between SNPs and birth weight centile on ADHD symptom severity. Out of the 164 interaction effects tested below without assuming a specific genetic model (Supplementary Table SIII), multiple SNP \times birth weight centile interactions predicted ADHD symptom severity after multiple testing correction (Table IV). Significant interactions included SNPs within angiogenic, neurotrophic, kynurenine, and cytokine systems. Specifically, for ADHD Total symptom severity, interactions between SNPs within the CCBL1, NTRK1, and NTRK3 genes and birth weight centile range were significant (Fig. 1). The interaction between a CCBL2 SNP and birth weight centile range predicted Inattentive symptom severity (Fig. 2). Finally, eleven SNPs in the CCBL1, CCBL2, IL16, NRP1, NRP2, NTRK1, NTRK3, and S100B genes moderated the

association between birth weight centile range and Hyperactive-Impulsive symptom severity (Fig. 2). Interactions involving dopaminergic SNPs were no longer significant after the multiple testing correction.

Exploratory analyses were conducted assuming additive, dominant, and recessive genetic models. Dominant genetic models produced five interactions predicting ADHD total score, two interactions predicting Inattentive symptom severity, and eleven interactions predicting Hyperactive-Impulsive score after multiple testing corrections (Supplementary Table SIV). Fewer interactions were observed for additive and recessive genetic models (Supplementary Tables SV and SVI, respectively). Finally, Sobel tests did not provide evidence that the relationship between individual SNPs and ADHD symptom severity was mediated by birth weight centile for any of the models (results not shown).

DISCUSSION

Examining biologically informed gene by environment interactions in ADHD may aid in the identification of novel genes associated with ADHD and further the search for neurodevelopmental mechanisms underlying vulnerability for ADHD.

TABLE II. Correlations Between Selected Demographic, Perinatal, and ADHD Variables

	Age	CPRS ADHD total	Birth weight centile range	Birth weight (g)
Age	—			
CPRS ADHD Total	0.21*	—		
Birth Weight Centile Range	-0.14*	0.02	—	
Birth Weight (g)	-0.08	0.04	0.76a	—
Gestational Age	0.08	0.10	-0.09	0.50*

Note: $N=398$. CPRS, Conners' Parent Rating Scale. *Correlation is significant at the 0.01 level (2-tailed).

TABLE III.**Summary of SNP Main Effects (P<0.01) on CPRS ADHD Total, Inattentive, and Hyperactive-Impulsive T-Scores**

Phenotype	System	Gene	SNP	n	MAF	<u>Minor Allele Count Mean (SD)</u>			<u>SNP Main Effect</u>	
						0	1	2	p-value	q-value
ADHD Total	CYTK	CNTFR	rs10758268	397	(T) 0.43	79.90 (8.94)	76.94 (11.61)	75.28 (8.78)	0.001	0.083
	DA	DRD3	rs324035	396	(A) 0.19	77.73 (10.18)	76.76 (11.17)	84.43 (2.88)	0.001	0.083
	CYTK	CNTFR	rs7044318	395	(T) 0.19	78.54 (10.15)	75.85 (10.93)	68.00 (6.66)	0.002	0.093
Inattentive	CYTK	IL16	rs7171540	387	(G) 0.46	78.96 (9.76)	75.88 (11.39)	79.17 (9.37)	0.003	0.142
	CYTK	CNTFR	rs10758268	397	(T) 0.43	74.75 (9.16)	71.19 (10.79)	69.28 (8.73)	3.1E-05	0.005
	NT	NTRK3	rs3825885	395	(C) 0.32	71.48 (10.57)	73.76 (8.77)	67.26 (11.64)	3.4E-04	0.021
	CYTK	CNTFR	rs7044318	395	(T) 0.19	73.02 (9.92)	70.25 (10.27)	61.00 (7.28)	3.9E-04	0.021
	CYTK	CNTFR	rs6476455	391	(C) 0.49	70.36 (8.75)	71.69 (10.92)	74.30 (9.41)	0.002	0.074
	DA	DAT1	rs420422	385	(C) 0.44	71.66 (10.34)	70.96 (9.62)	74.85 (9.89)	0.009	0.231
	CYTK	LIFR	rs2731960	393	(T) 0.37	70.85 (10.53)	73.47 (9.01)	70.70 (11.39)	0.009	0.231
Hyperactive-Impulsive	ANG	VEGFR2	rs2067951	397	(C) 0.48	73.93 (8.52)	70.23 (10.83)	73.55 (9.64)	0.010	0.231
	CYTK	IL6	rs10266564	397	(C) 0.1	78.37 (11.53)	79.47 (10.96)	87.67 (3.61)	0.001	0.162
	CYTK	IL16	rs7171540	387	(G) 0.46	79.94 (10.99)	76.97 (12.04)	81.26 (10.26)	0.002	0.179
	NT	NTRK3	rs1017757	390	(G) 0.15	79.13 (11.15)	77.11 (11.92)	86.29 (4.86)	0.004	0.202

Note. MAF, minor allele frequency; CYTK, cytokine; DA, dopaminergic; NT, neurotrophic; ANG, angiogenic; p-value, nominal p-value; q-value, FDR corrected p-value.

TABLE IV.

Summary of SNP and Birth Weight Centile Range Interactions (P<0.01) Predicting the Transformed CPRS ADHD Total, Inattentive, and Hyperactive-Impulsive T-Scores

Phenotype	System	Gene	SNP	NCBI	n	MAF	<u>SNP Main Effect</u>		<u>Interaction</u>	
							p-value	q-value	p-value	q-value
ADHD total	NT	NTRK1	rs962879	155113379	397	(C) 0.14	0.889	0.979	3E_06	4E_04*
	KYN	CCBL1	rs10793967	130642111	397	(A) 0.15	0.805	0.949	1E_04	0.009*
	NT	NTRK3	rs8037291	86308935	380	(G) 0.18	0.021	0.274	3E_04	0.016*
	NT	NTRK3	rs17755717	86426100	377	(A) 0.18	0.454	0.852	0.003	0.088
	KYN	CCBL2	rs4656076	89190875	389	(C) 0.23	0.261	0.697	0.003	0.088
	NT	NTRK3	rs1017757	86355556	390	(G) 0.15	0.097	0.507	0.006	0.161
Inattentive	ANG	NRP2	rs17682318	206285589	391	(C) 0.3	0.998	0.998	0.008	0.188
	KYN	CCBL2	rs4656076	89190875	389	(C) 0.23	0.195	0.669	3E_04	0.049*
	CYTK	IL16	rs11634770	79383455	397	(T) 0.13	0.785	0.953	6E_04	0.051
	NT	NTRK3	rs8037291	86308935	380	(G) 0.18	0.048	0.426	0.003	0.159
	NT	NTRK3	rs17755717	86426100	377	(A) 0.18	0.36	0.773	0.007	0.262
	ANG	NRP1	rs2273466	33551053	397	(C) 0.19	0.269	0.689	0.008	0.262
Hyperactive-impulsive	CYTK	IL16	rs931963	79263756	393	(T) 0.15	0.706	0.926	0.01	0.264
	NT	NTRK3	rs8037291	86308935	380	(G) 0.18	0.153	0.719	4E_06	7E_04*
	NT	NTRK1	rs962879	155113379	397	(C) 0.14	0.979	0.989	9E_06	E_04*
	KYN	CCBL2	rs10922552	89212813	387	(G) 0.11	0.422	0.793	8E_05	0.003*
	NT	NTRK3	rs1017757	86355556	390	(G) 0.15	0.004	0.202	6E_05	0.003*
	KYN	CCBL1	rs10793967	130642111	397	(A) 0.15	0.983	0.989	8E_05	0.003*
	ANG	NRP1	rs2065364	33634008	395	(T) 0.29	0.809	0.982	2E_04	0.005*
	ANG	NRP2	rs13419677	206266851	395	(C) 0.15	0.301	0.788	5E_04	0.013*
	ANG	NRP1	rs2073320	33593263	396	(A) 0.4	0.883	0.988	0.001	0.021*
	NT	NTRK3	rs2114251	86465797	384	(A) 0.15	0.868	0.988	0.001	0.023*
	CYTK	IL16	rs8039027	79343327	393	(A) 0.24	0.628	0.917	0.002	0.026*
	CYTK	S100B	rs2839361	46848617	395	(C) 0.14	0.875	0.988	0.003	0.037*
	ANG	NRP1	rs3780867	33587815	397	(A) 0.47	0.879	0.988	0.005	0.069
	NT	NTRK2	rs11141486	86522947	396	(G) 0.31	0.862	0.988	0.008	0.099
	DA	DRD3	rs963468	115345577	397	(A) 0.39	0.909	0.988	0.009	0.102

Note. MAF, minor allele frequency; KYN, kynurenine; CYTK, cytokine; DA, dopaminergic; NT, neurotrophic; ANG, angiogenic.

Lower birth weight is commonly associated with ADHD [Nigg et al., 2010]; however, it is unclear what accounts for the phenotypic overlap between restricted fetal growth and ADHD. Therefore, this study examined whether SNPs within ischemia-hypoxia responsive systems interact with birth weight centile to predict ADHD symptom severity.

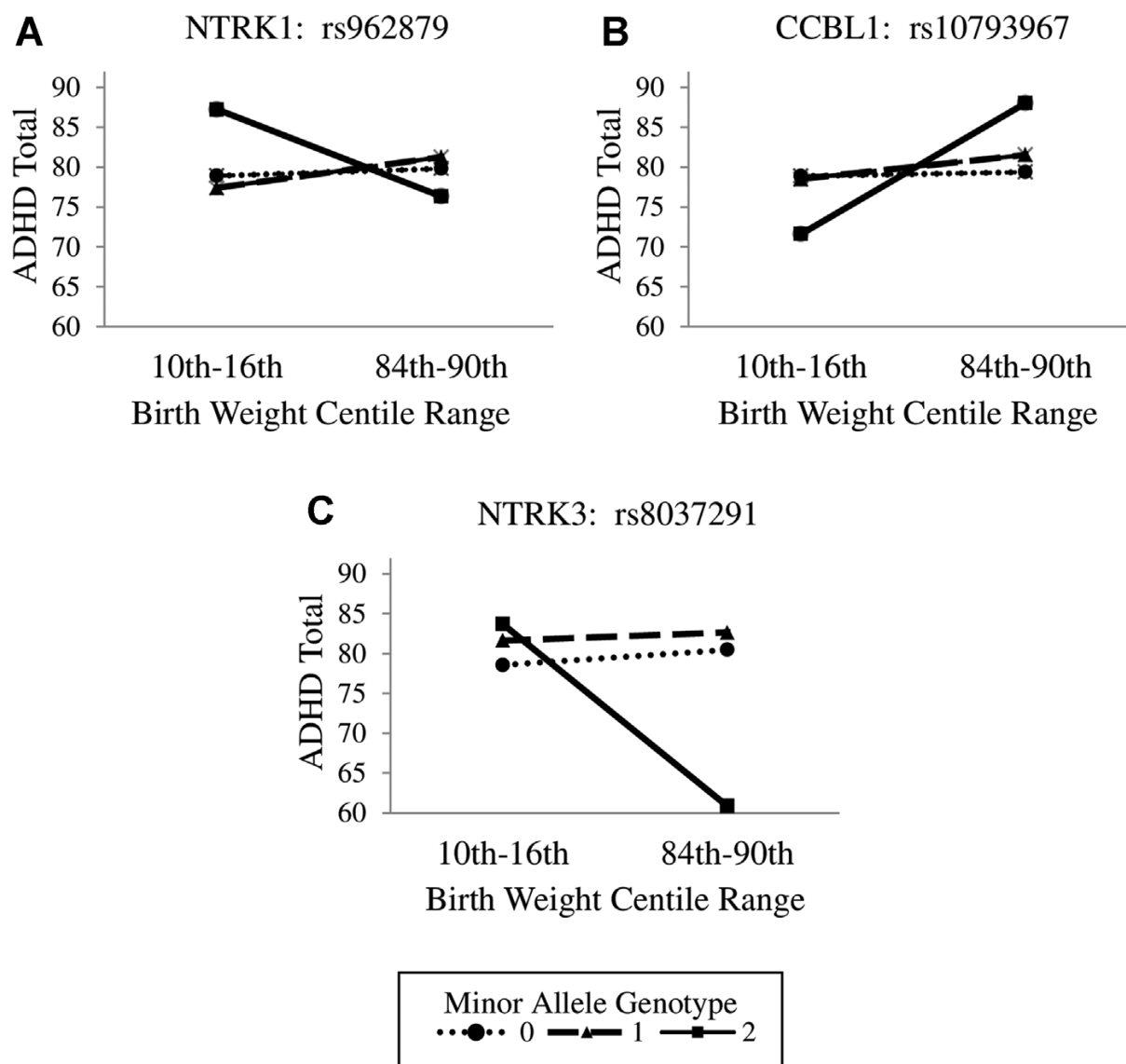
Contrary to previous work, lower birth weight centile was not independently associated with increased ADHD symptom severity in our data set. In general, literature demonstrates there is an association between restricted fetal growth and ADHD symptom severity [Bhutta et al., 2002; Indredavik et al., 2004; Lahti et al., 2006], however, null findings have also been reported [Cornforth et al., 2012]. In this sample largely consisting of ADHD cases, levels of inattention and hyperactivity-impulsivity were elevated and represented the upper end of the ADHD risk spectrum. Thus, reduced variability in ADHD symptom severity in case-only [Langley et al., 2007] or family-based designs may have made the relationship between lower birth weight and ADHD more difficult to detect. These results emphasize the heterogeneity in the relationship between lower birth weight and ADHD risk.

Regarding genetic main effects, one SNP within NTRK3 (described below) and two SNPs within CNTFR were associated with ADHD inattentive symptom severity, after adjusting for multiple testing. CNTFR encodes for ciliary neurotrophic factor receptor and is implicated in neurodevelopment and neuron survival [De Chiara et al., 1995]. In independent

samples of children and adults, a three-marker CNTFR haplotype was associated with ADHD [Ribases et al., 2008]. Taken together, these findings suggest that CNTFR may be implicated in the development of ADHD. SNPs within angiogenic, neurotrophic, kynurenine, and cytokine genes moderated the association between birth weight centile and ADHD symptom severity. In the neurotrophic pathway, NTRK1 and NTRK3 SNPs moderated the association between birth weight centile and ADHD total and hyperactive-impulsive symptom severity. NTRK1 and NTRK3 encode for tyrosine kinase receptors TrkA and TrkC, respectively. Nerve growth factor (NGF) preferentially binds to TrkA whereas neurotrophin-3 (NT3) binds at high affinity to TrkC to promote neuron survival and synaptic plasticity [Lamballe et al., 1991; Reichardt, 2006], including in hypoxic conditions [Lee et al., 2003; Lin et al., 2006; Ishitsuka et al., 2012]. TrkA is expressed in various neuronal populations including cholinergic neurons in the basal forebrain and striatum [Holtzman et al., 1995]. TrkC is expressed throughout the brain and is most abundant in the hippocampus [Ernfors et al., 1992]. A previous molecular genetic study has implicated neurotrophic factors, especially, NT3, in ADHD risk, though not NTRK1 or NTRK3 [Ribases et al., 2008]. Additionally in the present study, one SNP within NTRK2 moderated the relationship between birth weight centile and ADHD hyperactive-impulsive symptoms at a trend level. Together these findings support the notion that neurotrophic receptor genotype is implicated in the development of ADHD and this

FIG. 1.

Significant SNP x birth weight centile interactions predicting ADHD total symptom severity



relationship may depend on prenatal environmental influences, such as ischemia-hypoxia.

The angiogenic system regulates the formation of new blood vessels. In the angiogenic system, NRP1 and NRP2 SNPs interacted with birth weight centile to predict hyperactive-impulsive symptom severity. NRP1 and NRP2 encode for neuropilin-1 and neuropilin-2, co-receptors for the vascular endothelial growth factor (VEGF) and semaphorin

families [Pellet-Many et al., 2008]. NRP1 and NRP2 are expressed in the central nervous system and endothelial cells and play an essential role in vascular development and axonal guidance [Polleux et al., 2000; Rossignol et al., 2000; Gu et al., 2003; Pellet-Many et al., 2008]. Following cerebral ischemia, NRP1 disrupts axonal guidance near the ischemic area [Hou et al., 2008]. Further, NRP1 plays a central role coordinating neuronal migration and guidance of axons

that project from the thalamus to the cortex [Lopez-Bendito et al., 2006], which has been implicated in the development of ADHD [Ivanov et al., 2010; Shaw, 2010] and externalizing behavior problems [Arcos-Burgos et al., 2012].

Cytokines are implicated in inflammatory, immune, and oxidative stress responses [Capuron et al., 2011]. Genetic variation in IL16 and S100B interacted with birth weight centile to predict hyperactive-impulsive symptom severity. IL16 encodes for interleukin-16 and regulates the inflammatory response [Cruikshank et al., 2008]. IL16 is expressed in T-cells, macrophages, and microglia [Cruikshank et al., 2008; Jana et al., 2009]. S100B, a calcium binding protein, is a glial cytokine with neurotrophic properties [Steiner et al., 2007]. S100B is released in astrocytes following a restricted nutrient and oxygen supply [Gerlach et al., 2006]. Similar to the current findings, IL16 and S100B serum levels are associated with hyperactive-impulsive symptom severity within ADHD cases, and ADHD total symptom severity across cases and controls [Oades et al., 2010]. Within ADHD cases, S100B and IL16 serum levels have also been linked to pre- and perinatal risk factors including birth weight, gestational age, and maternal smoking during pregnancy [Oades, 2011], which makes them good candidates for a role in disease etiology.

The kynurenine pathway metabolizes tryptophan and plays a role in glial and dopaminergic functioning, as well as inflammatory and immune responses [Steiner et al., 2012; Vecsei et al., 2013]. SNPs within CCBL1 and CCBL2 moderated the relationship between ADHD total,

inattentive, and hyperactive-impulsive symptom severity. CCBL1 and CCBL2 encode kynurenine amino-transferase I and II, respectively, which transaminate kynurenine into the neuroprotective kynurenic acid [Guillemin et al., 2007; Myint et al., 2007; Vecsei et al., 2013]. Kynurenic acid is an antagonist at the N-methyl D-aspartic acid (NMDA) and $\alpha 7$ nicotinic acetylcholine ($\alpha 7$ nACh) receptors that are implicated in learning [Hilmas et al., 2001]. In rats, kynurenic acid in the prefrontal cortex is inversely related to glutamate, acetylcholine and dopamine levels, a relationship that has been detected even with minor changes in kynurenic acid [Wonodi et al., 2010]. In youth with ADHD, kynurenic acid in serum was positively associated with adverse events during the third trimester, at a trend level [Oades, 2011]. In light of these findings, prenatal ischemia-hypoxia may put individuals with susceptible CCBL1 and CCBL2 genotypes at risk for ADHD by leading to suboptimal expression of kynurenine aminotransferase I and II. Thus, variability in cytokine and kynurenine genes may alter risk for ADHD following exposure to pre- and perinatal risk, potentially by affecting glial functioning [Todd and Botteron, 2001; Russell et al., 2006; Oades et al., 2010].

We are encouraged by the promising findings of this study, but also recognize there are some study limitations. First, this study had a modest sample size and therefore, replication studies of these results are warranted. Second, youth in the study were either diagnosed with ADHD or at genetic risk for ADHD by nature of having a sibling with ADHD. This resulted in constrained variability in ADHD

FIG. 2.

Significant SNP x birth weight centile interactions predicting inattentive and hyperactive-impulsive symptom dimensions.

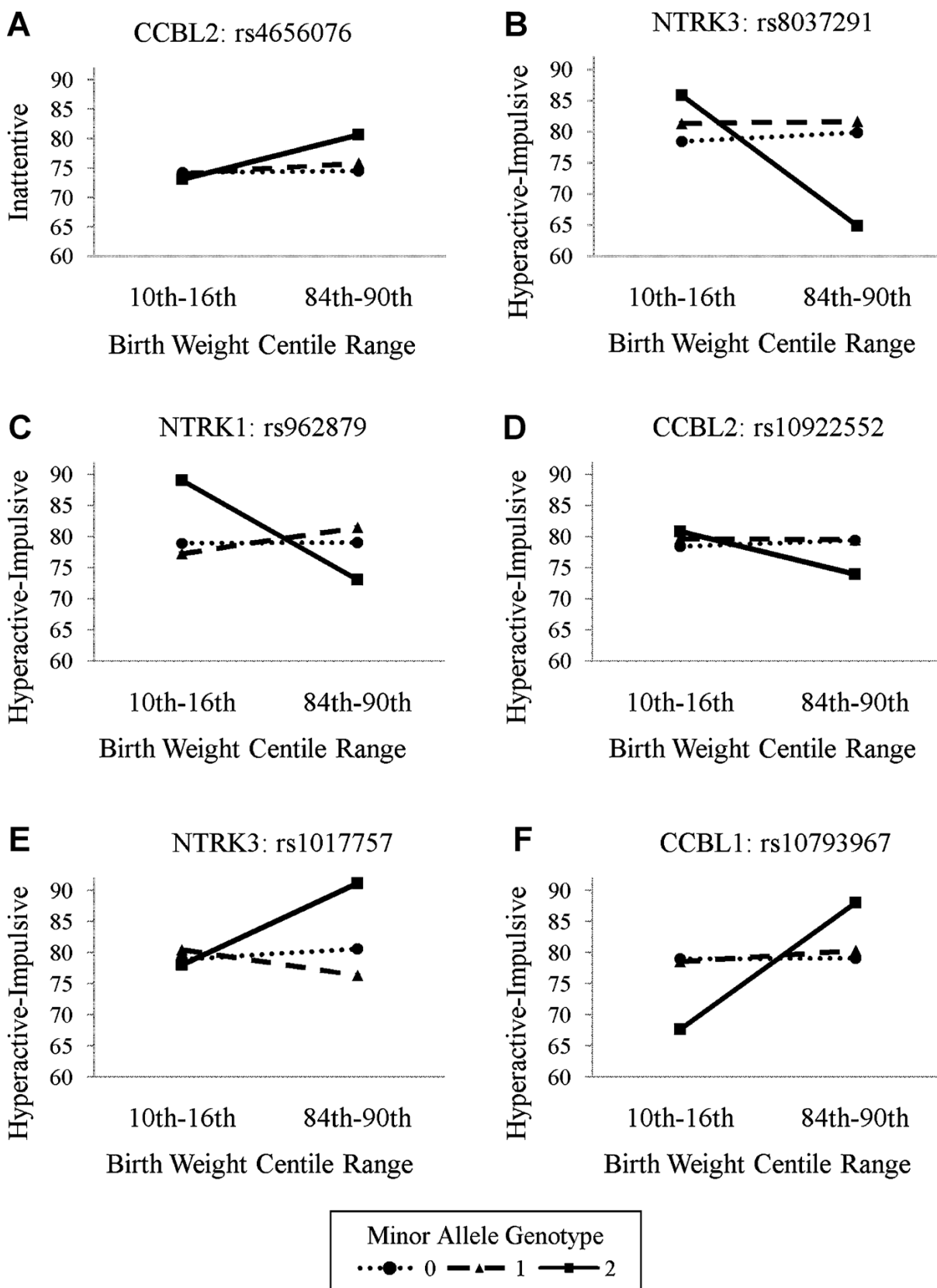
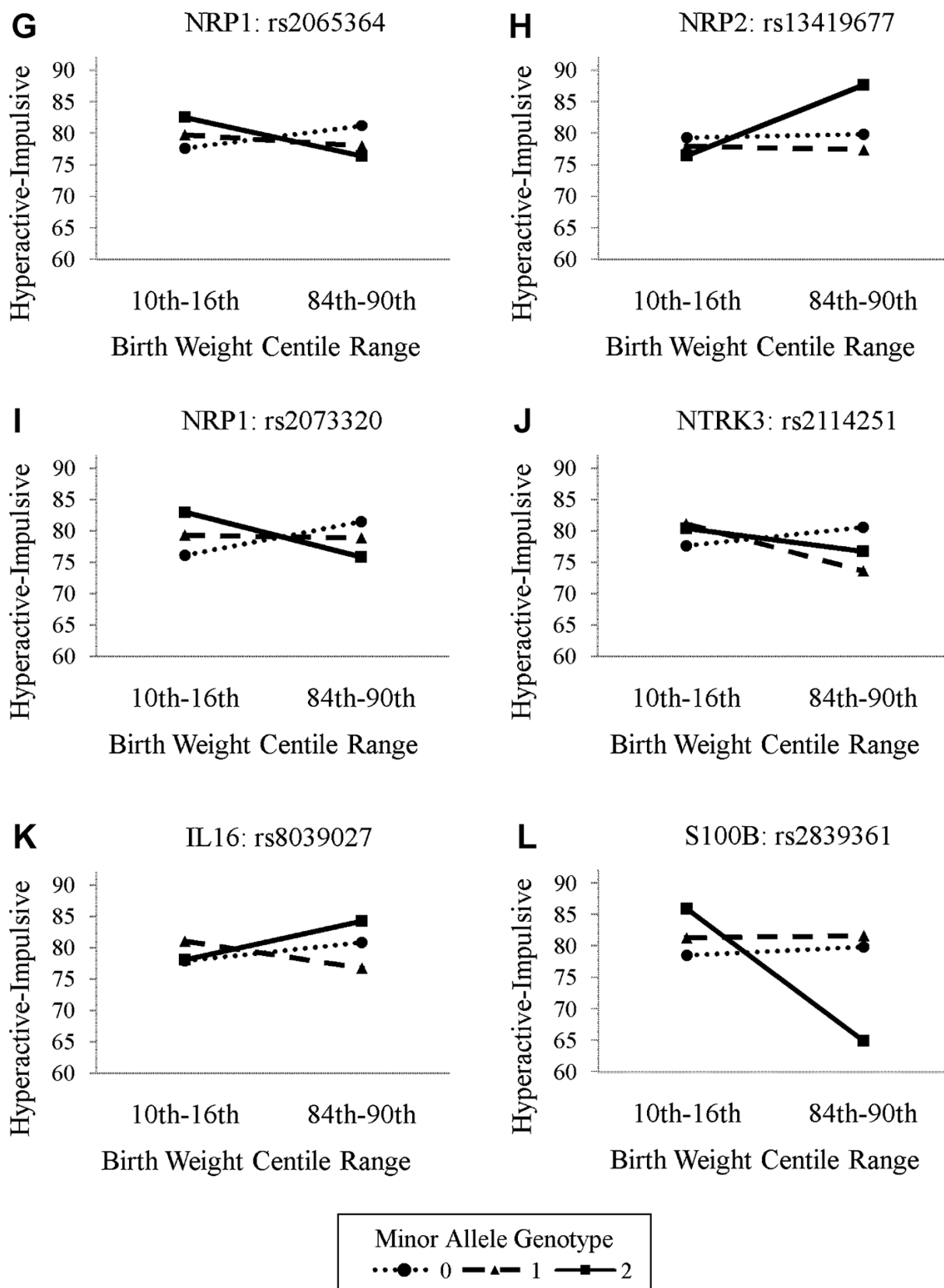


FIG. 2. (Continued)



symptom severity compared with the general population which could have reduced statistical power and the

likelihood of significant findings. Third, birth weight centile range served as a proxy measure for an adverse intrauterine

environment as no direct measure was available. Therefore, inferences about the underlying environmental pathogen were made in this study. Fourth, this design is unable to methodologically control for genetic determinants of birth weight. This allows for the possibility that that genetic, rather than environmental determinants of birth weight are interacting with SNPs to predict the ADHD phenotype. Fifth, we also acknowledge that we used an earlier NCBI build of the genome and as a result, some of the SNPs that we analyzed are now attributed to other genes. For example, SNPs identified in significant interactions which are no longer attributed to the same gene include: rs962879 (NTRK1 to CD1B), rs10793967 (CCBL1 to ABL1), rs4656076 (CCBL2 to GBP3), rs10922552 (CCBL2 to intergenic region) and rs13419677 (NRP2 to PARD3B). Thus, it is possible that the association signals we detected are in LD with a genetic variant in a neighboring gene. Finally, the design of this study was unable to rule-out the effect of maternal genotype on the observed SNP x birth weight centile range interactions [Waldman, 2007]. Future research should include both maternal and child genotype when investigating the developmental origins of ADHD.

Taken together, this study raises the possibility that angiogenic, neurotrophic, cytokine and kynurenine genetic variants moderate the association between birth weight and ADHD symptom severity. To our knowledge, this is the first study to support the involvement of CCBL1, CCBL2, IL16, NRP1, NRP2, NTRK1, NTRK3, and S100B genes in the development of ADHD which highlights the importance of

including measures of environmental risk when searching for novel genetic variants associated with ADHD. Although overall the pattern of results is consistent with expectations, we are pursuing replication datasets to further elucidate the relationships between these SNPs, birth weight centile, and ADHD risk. If replicated, these results provide a basis for future targeted gene methylation investigations. Findings also support the use of the DOHaD framework [Gluckman et al., 2004] in conceptualizing the etiological underpinnings of the association between lower birth weight and ADHD. Further application of this framework may aid in isolating specific prenatal environmental pathogens and genetic/epigenetic pathways implicated in the development of ADHD.

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The IMAGE site Principal Investigators are Philip

Asherson, Tobias Banaschewski, Jan Buitelaar, Richard P. Ebstein, Stephen V. Faraone, Michael Gill, Ana Miranda, Fernando Mulas, Robert D. Oades, Herbert Roeyers, Aribert Rothenberger, Joseph Sergeant, Edmund Sonuga-Barke, and Hans-Christoph Steinhausen. Senior co-investigators are Margaret Thompson, Pak Sham, Peter McGuffin, Robert Plomin, Ian Craig and Eric Taylor. Chief Investigators at each site are Rafaela Marco, Nanda Rommelse, Wai Chen, Henrik Uebel, Hanna Christiansen, Ueli Mueller, Cathelijne Buschgens, Barbara Franke, and Lamprini Psychogiou. We thank all the families who kindly participated in this research. In the last 24 months Professor Sonuga-Barke has received speaker fees from Janssen Cilag, Shire, Medice and QBtech and consultancy, grant funding, advisory board fees and conference support from Shire. Dr. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Novartis, Roche and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Dr. Oades has received research funding and conference attendance support from Shire. In the past year, Dr. Faraone received consulting income and/or research support from Akili Interactive Labs, VAYA Pharma, and SynapDx and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*.

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