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Genome-Wide Association Study of Inattention and Hyperactivity–Impulsivity Measured as Quantitative Traits

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Genome-wide association studies (GWAS) of attention-deficit/hyperactivity disorder (ADHD) offer the benefit of a hypothesis-free approach to measuring the quantitative effect of genetic variants on affection status. Generally the findings of GWAS relying on ADHD status have been non-significant, but the one study using quantitative measures of symptoms found SLC9A9 and SLC6A1 were associated with inattention and hyperactivity–impulsivity. Accordingly, we performed a GWAS using quantitative measures of each ADHD subtype measured with the Strengths and Weaknesses of ADHD and Normal Behaviour (SWAN) scale in two community-based samples. This scale captures the full range of attention and kinetic behavior; from high levels of attention and appropriate activity to the inattention and hyperactivity–impulsivity associated with ADHD within two community-based samples. Our discovery sample comprised 1,851 participants (mean age = 22.8 years [4.8]; 50.6% female), while our replication sample comprised 155 participants (mean age = 26.3 years [3.1]; 68.4% females). Age, sex, age × sex, and age^2 were included as covariates and the results from each sample were combined using meta-analysis, then analyzed with a gene-based test to estimate the combined effect of markers within genes. We compare our results with markers that have previously been found to have a strong association with ADHD symptoms. Neither the GWAS nor subsequent meta-analyses yielded genome-wide significant results; the strongest effect was observed at rs2110267 (4.62×10^{-7}) for symptoms of hyperactivity–impulsivity. The strongest effect in the gene-based test was for GPR139 on symptoms of inattention (6.40×10^{-5}). Replication of this study with larger samples will add to our understanding of the genetic etiology of ADHD.

■ **Keywords:** ADHD, inattention, hyperactivity–impulsivity, SWAN, GWAS, meta-analysis

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by developmentally inappropriate activity and deficiencies in attention span. ADHD symptoms typically manifest in 4% to 7% of children and continue into adulthood for around 50% of those affected during childhood (Biederman et al., 2010; Ebejer et al., 2012). Heritability estimates of the inattentive and hyperactive–impulsive subtypes range between 70% and 80% (Derks et al., 2008; Hudziak et al., 2005; Martin et al., 2002), indicating that genetic effects largely account for the variation we see in symptoms. In adulthood, ADHD is associated with comorbidity and ongoing difficulties, for example, substance use, anxiety, mood and disruptive behavior disorders, unemployment, multiple marriages, reduced income, low social support, and poor health (Das et al., 2012; Kessler et al., 2006). Of most relevance, 6.2% Australian adults have reported impairment in their lives due to ADHD symptoms that do not necessarily meet the diagnostic threshold outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) — Fourth Edition (DSM-IV) (Das et al., 2012; Faraone & Biederman, 2005;

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Kooij et al., 2005). Understanding the genetic etiology of symptoms will provide a step toward more directed and appropriate treatment for people affected by symptoms.

Research largely indicates that ADHD symptoms are expressed quantitatively within populations (Levy et al., 1997) and are affected by multiple genetic and environmental factors that provide either risk or protection for developing symptoms (Thapar et al., 2007). A liability to ADHD becomes evident when enough risk factors accumulate to outweigh the factors protective against symptom expression and is probably the sum of the multi-factorial effects (Gottesman & Shields, 1967). The point at which liability becomes pathological is arbitrary and is generally based on DSM-IV or the International Classification of Diseases 2010 (World Health Organization, 1992) criteria, excluding those people with subthreshold ADHD who report that these symptoms cause problems in their lives.

Linkage and association studies of ADHD have mainly focused on specific genetic regions. The results of these studies are mixed (Banaschewski et al., 2010), but several genes from the dopamine system are frequently implicated in symptom expression: dopamine transporter DAT1, dopamine receptor DRD4, and dopamine receptor DRD5 (Li et al., 2006). Genome-wide association scans provide the benefit of a hypothesis-free approach to measuring the quantitative effect of specific markers across the whole genome. However, to date, meta-analyses of GWAS using case-control methodology have found no significant genetic effects (Mick et al., 2011; Neale et al., 2010). The only prior GWAS using symptom count as a quantitative measure of ADHD found markers in the region of SLC6A1 and SLC9A9 that were associated with inattention and hyperactivity–impulsivity (Lasky-Su et al., 2008).

For our purpose, liability is considered to be an underlying continuous distribution of risk on which a diagnosis threshold has been imposed. In the current study we extend the use of a quantitative measure of ADHD symptoms, ranging from high levels of attention and appropriate motor inhibition to the inattention and hyperactivity–impulsivity associated with ADHD, to increase the power to detect genes associated with ADHD symptoms at varying degrees of expression. As an additional boost to power, we combine GWAS for two samples into a meta-analysis and run a gene-based test to estimate the independence of marker effects within associated genes. We also compare our findings to a previous genome-wide association scan meta-analysis of ADHD (Neale et al., 2008), testing the generalization of quantitative symptoms of ADHD to qualitative diagnosis-based phenotypes.

Methods

Participants

The data used in this study were drawn from two community-based substudies of the Brisbane Longitudinal Twin Study: a twin study of Melanocytic Naevi (MN; for details, see Figure 1 and Wright and Martin, 2004), and the Nineteen-Up study — examining neurobiological changes associated with mental health (NU; additional study details are provided in Gillespie et al., 2012). From an initial sample of 3,236 participants within the MN study, 1,851 family members from 735 families for whom genotype and phenotype data were available comprised our discovery sample. The sample included 266 monozygotic (MZ) twin pairs and 9 single twins from an MZ pair (251 males and 290 females), 216 same sex dizygotic (DZ) twin pairs and 26 single twins from the same sex DZ pair (239 males and 219 females), 214 opposite sex DZ twin pairs and 26 single twins from an opposite sex DZ pair (224 males and 230 females), and 398 siblings of twins (189 males and 209 females). The age of these participants ranged from 13 to 40 years ($M = 22.8$, $SD = 4.8$).

The data collected within the NU study provided our replication sample, initially comprising 953 participants. These data were collected in two waves; the first included 374 individuals and the second wave included 711, with 132 people who participated in both waves and 477 who had contributed data for both MN and NU studies. Of the initial replication sample, 155 people from 100 families had phenotype and genotype data available and their age ranged from 19 to 36 years ($M = 26.3$, $SD = 3.1$). This group comprised 21 complete and 21 incomplete MZ twin pairs (17 males and 46 females), 18 paired, and 10 unpaired same-sex DZ twin pairs (12 males and 34 females), 8 complete opposite-sex DZ twin pairs and 17 unpaired twins (16 males and 17 females), and 13 siblings of twins (4 males and 9 females). All participants were fully informed of study procedures and they gave consent to participate online. Ethics approval for this study was provided by QIMR Human Research and Ethics Committee (HREC) and Virginia Commonwealth University Institutional Review Board (IRB).

Measures

Data collection for ADHD-related behaviors began in 2010 and were collected from mothers of all twins who had participated in the Brisbane Longitudinal Twin study since 1992. In the MN study the mother-reported data were used, and in the NU study these data were collected directly from the twins (self-reported). Both studies used the Strengths and Weaknesses of ADHD and Normal-Behavior Scale (SWAN; Swanson et al., 2005) for data collection. Within MN, 1,822 mothers reported ADHD symptoms for the twins and each of their siblings as one component of a 60- to 90-min online questionnaire assessing several health phenotypes: (A) physique, (B) complexion and sun exposure, (C) handedness, (D) to (G) ancestral and family information, (H) migraine headache, (I) asthma and eczema, (J) women's health, and (K) behavior. If the children were older than 20 years, parents were asked what their child's behavior was like in primary school. If the child

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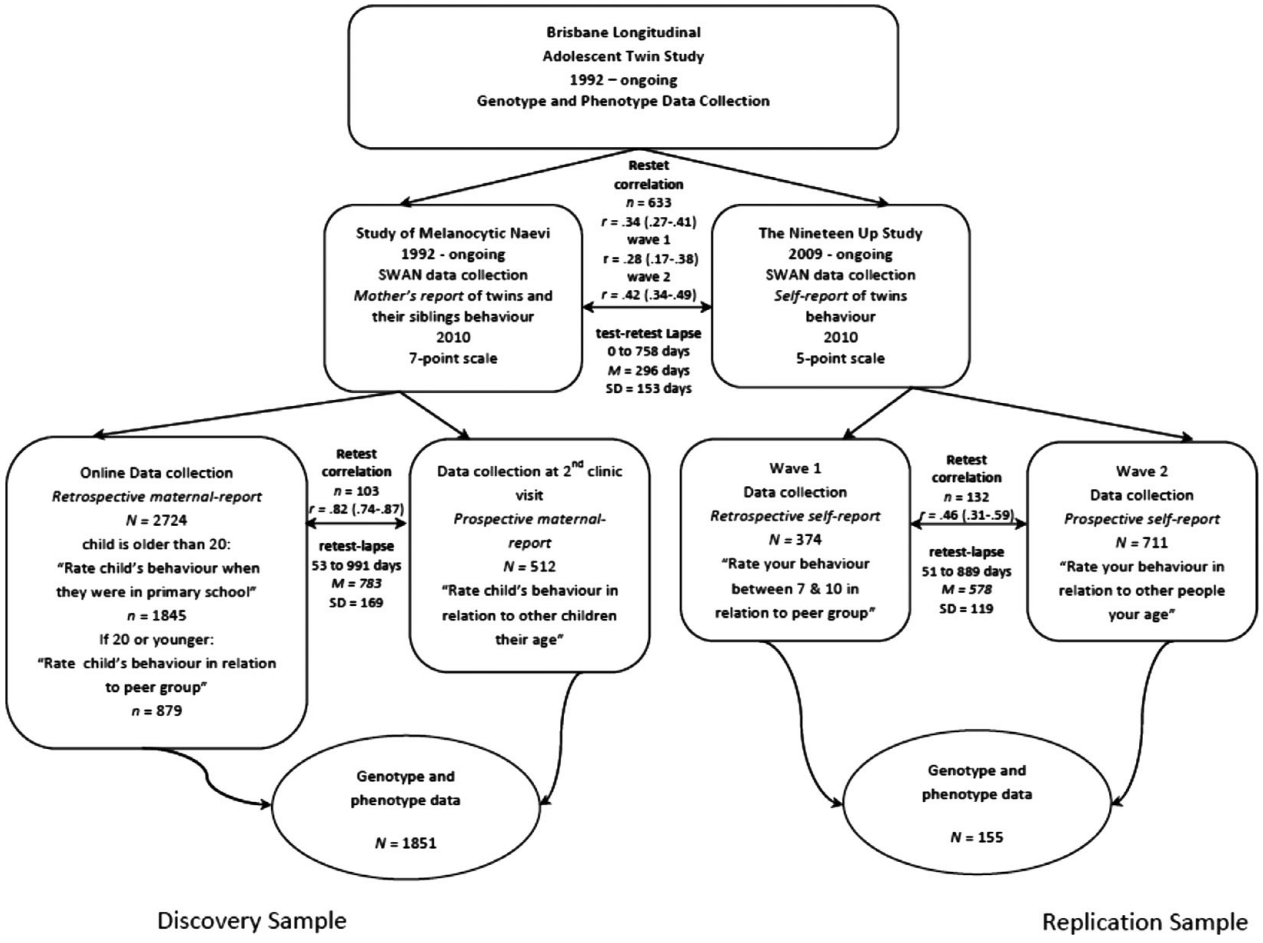

FIGURE 1

Recruitment process leading to collection of SWAN measured ADHD data used in this study.

was 20 or younger, their behavior was rated in relation to their peer group. The remaining 28 parents completed the questionnaire during their child's second clinic visit (at age 14 years). This scale was similarly directed toward the twins and each of their siblings and comprised 30 items: 1 to 18 addressed ADHD symptoms, 19 to 27 were specific to oppositional defiant disorder, and 28 to 30 measured cognitive tempo.

The inattention and hyperactivity–impulsivity subscales of the SWAN demonstrate retest reliabilities of 0.72 to 0.90 and a Cronbach's alpha of 0.80 (Arnett et al., 2013). Each of the 18 SWAN items addresses criterion A of DSM-IV (text revision), but is worded to reflect normal behavior as indicated in Table 1, along with the probability of endorsing a positive symptom by sex. The scale used for both the versions of the questionnaire in the MN study was 7-point scale and coded with high scores reflecting problem behaviors: -3 (*far above average*), -2 (*above average*), -1 (*slightly above average*), 0 (*average*), 1 (*slightly below average*), 2 (*below average*), and 3 (*far below average*).

The SWAN data collected for the NU study were self-reported by twins and were also completed as a component of an online questionnaire similarly addressing health phenotypes: (A) general health, (B) relationships, (C) migraine and headaches, (D) SWAN items, (E) hair loss, (F) sleep and wake, (G) activity schedule, (H) personality, (I) romantic preferences, and (J) flexibility loss. This questionnaire also took approximately 60–90 min to complete and respondents could go back and modify their answers or discontinue completion at any time. Within the first wave of the study, twins were asked to report on their behavior between the age of 7 and 10 years 'in relation to their peer group'. In the second wave, twins rated their current behavior 'in relation to their current peer group'. The scale of this questionnaire ranged from -2 to 2: -2 (*far above average*), -1 (*above average*), 0 (*average*), 1 (*below average*), and 2 (*far below average*) and was coded again, so high scores reflected symptom expression. For questionnaires in both studies, the mean of the first 9 items was used as our measure of inattention, the mean of items

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TABLE 1

Endorsement Probabilities for Listed SWAN Scale Items Within the Melanocytic Naevi (MN) and Nineteen-Up (NU) Studies

	MN		NU			MN		NU	
Inattention	Female	Male	Female	Male	Hyperactivity	Female	Male	Female	Male
1. Give close attention to details and avoid careless mistakes.	.10	.26	.09	.17	1. Sits still (control movement of hands and feet or control squirming).	.08	.22	.19	.45
2. Sustain attention on tasks or other activities.	.09	.21	.08	.20	2. Stay seated (when required by class rules workplace or social convention).	.04	.14	.07	.15
3. Listens when spoken to directly.	.07	.13	.05	.08	3. Modulate motor activity	.05	.14	.10	.16
4. Follows through on instructions and finishes work/chores/schoolwork.	.11	.28	.06	.16	4. Works/plays quietly (keep noise level reasonable).	.06	.15	.06	.15
5. Organizes activities and tasks.	.10	.26	.08	.20	5. Settles down and rests/relaxes (control of constant activity)	.07	.15	.09	.15
6. Engages in tasks that require sustained mental effort.	.11	.21	.08	.17	6. Modulates verbal activity (control excess talk).	.14	.18	.15	.16
7. Keeps track of things necessary for activities.	.10	.26	.08	.13	Impulsivity				
8. Ignores extraneous stimuli	.14	.31	.14	.26	1. Reflects on questions (control blurting out answers).	.09	.15	.10	.19
9. Remembers daily activities.	.07	.19	.06	.10	2. Awaits turn (standing in line and taking turns).	.04	.09	.05	.07
					3. Enters into conversation and activities (control interrupting and intruding).	.08	.14	.13	.14

Note: These probabilities were calculated using full samples (MN: 1,572 males and 1,664 females and NU: 392 males and 561 females).

TABLE 2

Descriptive Statistics for SWAN Scale Data Collected During the Twin Study of Melanocytic Naevi (MN) and Nineteen-Up (NU) Studies

	n	Mean age (years)	*SD*	Age range (years)	Combined mean (*SD*)	Inattention mean (*SD*)	Hyperactivity–impulsivity mean (*SD*)
MN							
Males	914	22.68	4.78	13–40	-0.55 (1.10)	-0.46 (1.21)	-0.64 (1.15)
Females	937	22.94	4.83	13–38	-1.11 (1.03)	-1.13 (1.11)	-1.10 (1.09)
Clinic	29	14	0	0	-1.00 (1.03)	-0.93 (1.18)	-1.08 (1.19)
Online	1,822	22.95	4.71	13–40	-0.83 (1.10)	-0.79 (1.21)	-0.87 (1.14)
Skewness	—	—	—	—	0.18	0.26	0.18
Sample Size	**1,851**						
NU							
Males	49	26.33	2.97	21–31	-0.29 (0.55)	-0.28 (0.64)	-0.30 (0.66)
Females	106	26.33	3.14	19–36	-0.47 (0.61)	-0.50 (0.67)	-0.44 (0.70)
Wave 1	50	25.04	3.35	19–30	-0.46 (0.46)	-0.54 (0.54)	-0.38 (0.63)
Wave 2	105	26.94	2.75	21–36	-0.39 (0.65)	-0.38 (0.72)	-0.41 (0.71)
Skewness	—	—	—	—	-0.16	0.19	-0.10
Sample Size	**155**						

Note: SWAN scale in MN is coded from -3 to 3 and in NU from -2 to 2. In both studies scores >1 represent positive symptoms. Clinic = data collected within MN from mothers during twin's second clinic visit. Online = data collected within MN from online questionnaire completed by mothers.

10 to 18 provided our measure of hyperactivity–impulsivity, and the mean of all 18 items provided our measure of combined ADHD symptom expression, as presented in Table 2, with descriptive statistics for the SWAN metrics across studies.

Genotyping

In both samples participants were genotyped using the Illumina single-nucleotide polymorphism (SNP) Human610-Quad platform and 592,392 SNPs were genotyped; 8,447 of these had a call rate < 0.95, and 2,841 had Hardy–Weinberg equilibrium (HWE) p-value < 10^{-6}. There were 33,347 SNPs with one allele frequency <0.01 or only one observed allele, and these SNPs were removed from the dataset. After cleaning, 529,379 SNPs remained and of these, 274,604 were common to additional waves of data collection as described in Medland et al. (2009). These SNPs were imputed to Hapmap II (build 36, release 22) using the Utah residents with ancestry from northern and western Europe references (CEU) with MACH 1.0 (Li & Abecasis,

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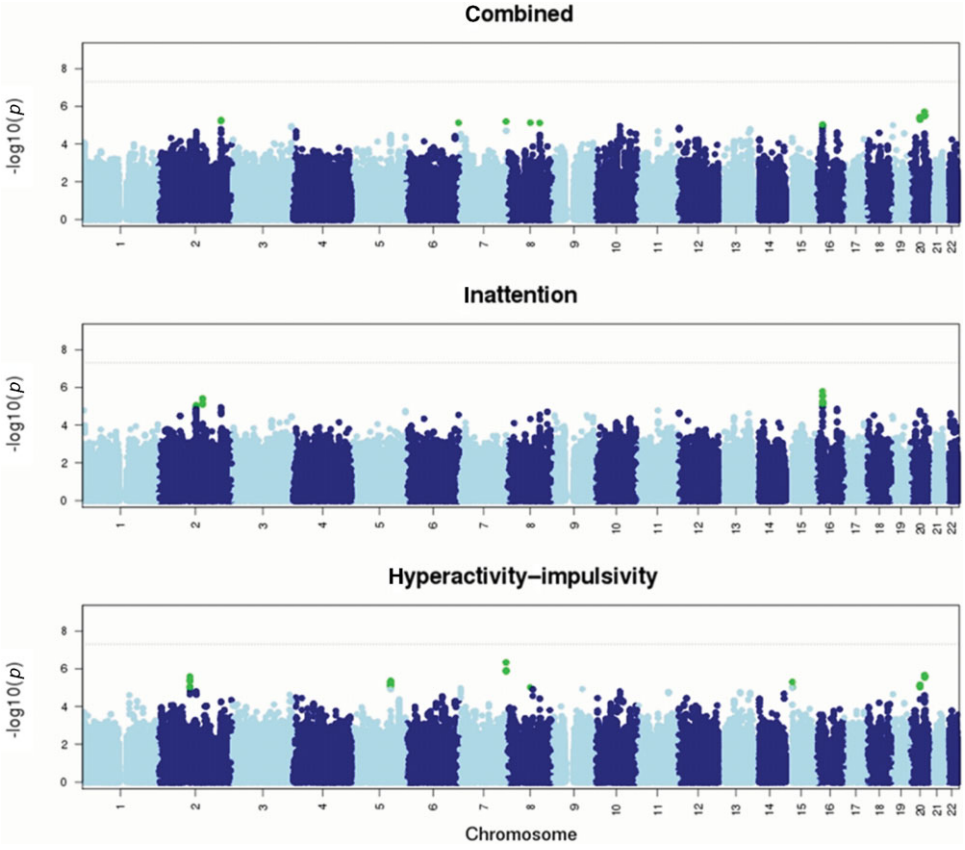

FIGURE 2

(Colour online) Manhattan plot for MN and NU data meta-analysis indicating the strongest associations between the 22 autosomes and combined symptoms, inattention, and hyperactive–impulsive behaviors.

2006) and imputation resulted in 2,373,249 SNPs with an $r_{sq} > .3$.

Statistical Analyses

Genome-wide association studies were conducted to examine genetic associations for the quantitative measures of inattention, hyperactivity–impulsivity, and combined behaviors separately for the MN and NU studies, including sex, current age, sex × age, and age^2 as covariates. Within the MN study, the method of form completion (online or clinic) was included as a covariate to correct for any variation across the method of data collection. In the NU study we ran structural equation models using OpenMx (Boker et al., 2010) to estimate the similarity of genetic effects across waves of data collection due to the difference in time to which the questions were directed. There was no significant difference in genetic and environmental parameters between waves of data collection, $p > .05$, $h^2 = 0.42$ (0.19–0.56), so all data for NU were combined and analyzed with wave as a covariate. Data were screened for ancestry outliers and SNP-based association was conducted across the genome using family-based association analysis in Merlin-offline (Chen & Abecasis, 2007) under an additive model. This method models family structure and the additive genetic effect of each genotype onto inattention, hyperactivity–impulsivity, and combined behaviors.

The results of individual GWAS for inattention, hyperactivity–impulsivity, and combined symptoms within each study were combined in a meta-analysis using Meta-Analysis Helper (Metal; Abecasis & Willer, 2007). Within Metal, *z*-scores are calculated from the *p*-values and direction-of-effect within each sample and weighted according to the inverse of the sample size. This method characterizes the magnitude and direction of additive genetic effects relative to the same reference allele across samples. The results of the meta-analysis were examined for gene-based association using Versatile Gene-based Association Study (VEGAS; Liu et al., 2010) to estimate the combined effect of all markers within ±50 kb of 5' and 3' untranslated regions of a gene. The significance level required for the gene-based test is $p < 2.8 \times 10^{-6}$ (.05/17,787 autosomal genes). Finally, we compare the top 50 SNPs from a meta-analysis of ADHD case-control studies (Neale et al., 2010) with the effect for the same SNPs within our meta-analysis. The alleles at each of these markers were aligned

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TABLE 3

Top 25 Markers for MN and NU Data Meta-Analysis of Combined Symptoms, Inattention, and Hyperactivity–Impulsivity

Combined					Inattention					Hyperactivity–Impulsivity				
Chr	Marker	Al1:Al2	*z*-score	*p*-value	Chr	Marker	Al1:Al2	*z*-score	*p*-value	Chr	Marker	Al1:Al2	*z*-score	*p*-value
20	rs910191	a:g	4.76	1.95e-06	5	rs7448069	t:c	-4.84	1.27e-06	7	rs2110267	c:g	5.04	4.62e-07
20	rs4458264	t:c	-4.68	2.94e-06	16	rs12919130	a:g	4.80	1.60e-06	7	rs2192271	t:c	-4.85	1.22e-06
20	rs4402823	t:c	4.67	2.95e-06	16	rs12596252	a:g	-4.69	2.75e-06	7	rs6947495	a:t	4.85	1.24e-06
20	rs4810796	a:g	-4.66	3.12e-06	16	rs1902813	c:g	-4.69	2.77e-06	7	rs12671878	a:c	-4.83	1.37e-06
20	rs13043694	a:g	-4.65	3.29e-06	16	rs12926725	t:c	-4.69	2.80e-06	20	rs910191	a:g	4.74	2.16e-06
20	rs6057648	a:c	-4.63	3.75e-06	2	rs11687420	a:t	-4.62	3.87e-06	20	rs4458264	t:c	-4.70	2.56e-06
20	rs6119285	t:c	-4.62	3.80e-06	2	rs1822881	a:g	-4.61	4.13e-06	20	rs4402823	t:c	4.70	2.58e-06
20	rs6057651	a:g	-4.61	3.98e-06	16	rs12931939	t:c	-4.54	5.57e-06	2	rs6758152	t:g	4.70	2.59e-06
20	rs6057652	a:c	4.61	3.99e-06	16	rs6497436	t:c	-4.54	5.62e-06	20	rs4810796	a:g	-4.69	2.72e-06
20	rs7270085	a:g	-4.61	4.04e-06	6	rs9364220	a:g	4.54	5.72e-06	20	rs13043694	a:g	-4.68	2.87e-06
20	rs6119286	a:g	-4.59	4.38e-06	16	rs2608200	a:g	-4.54	5.74e-06	2	rs2119507	t:c	-4.62	3.90e-06
20	rs6057659	a:g	-4.57	4.93e-06	16	rs11642377	a:g	-4.50	6.68e-06	2	rs11903187	a:g	-4.60	4.23e-06
20	rs8123073	a:g	4.57	5.00e-06	16	rs12926729	a:g	-4.50	6.79e-06	2	rs10193430	a:t	-4.60	4.30e-06
20	rs17123726	a:g	4.56	5.03e-06	16	rs11647507	a:c	4.49	7.07e-06	2	rs12613775	t:c	-4.60	4.32e-06
2	rs11681930	a:g	-4.55	5.35e-06	2	rs10180522	a:c	-4.49	7.14e-06	2	rs1036736	t:c	4.60	4.33e-06
2	rs10153620	c:g	-4.52	6.07e-06	16	rs7185264	a:g	-4.49	7.19e-06	5	rs1515641	a:g	-4.59	4.38e-06
7	rs2110267	c:g	4.51	6.43e-06	16	rs12924103	t:c	4.48	7.33e-06	5	rs7722425	t:c	4.58	4.64e-06
6	rs9364220	a:g	4.51	6.62e-06	16	rs7201408	a:g	4.48	7.44e-06	5	rs10463833	a:g	-4.58	4.70e-06
8	rs11994034	t:c	4.48	7.38e-06	16	rs10521115	a:g	-4.47	7.86e-06	15	rs7164923	t:c	-4.57	5.00e-06
6	rs4708431	a:g	4.48	7.45e-06	16	rs10521114	a:g	-4.47	7.90e-06	5	rs10463832	a:c	-4.55	5.40e-06
8	rs6983777	a:g	4.48	7.58e-06	2	rs13407123	t:c	-4.46	8.09e-06	5	rs12523164	t:c	4.52	6.29e-06
16	rs12596252	a:g	-4.43	9.60e-06	2	rs13006237	a:g	-4.44	8.81e-06	5	rs12513840	a:g	4.51	6.60e-06
16	rs1902813	c:g	-4.43	9.61e-06	2	rs2670605	a:g	4.43	9.66e-06	5	rs4835929	t:g	4.49	7.00e-06
16	rs12926725	t:c	-4.43	9.64e-06	2	rs4848873	c:g	-4.43	9.66e-06	20	rs6057652	a:c	4.49	7.15e-06
19	rs1077667	t:c	-4.42	1.00e-05	2	rs2256248	a:g	-4.42	9.90e-06	20	rs6057651	a:g	-4.49	7.19e-06

across studies and samples were entered into an additional meta-analysis using Metal.

Results

We first discuss results for the two separate substudies and three core phenotypes — combined symptoms, inattention, and hyperactivity–impulsivity — and present these results in Appendix A. The lambda values within each substudy (quantile–quantile [qq] plots) shown in Figure A1 provide no evidence for population stratification or technical artifact for the data collected during the MN study, but they do indicate low power for data collected within the NU study. Within each sample there were no SNP effects that reached genome-wide significance ($p < 5 \times 1^{-8}$; Figures A2 and A3, Tables A1 and A2). We combined the results of individual analyses to obtain meta-analyses for combined ADHD symptoms, inattention, and hyperactivity–impulsivity, and present the SNP effects in Figure 2 and Table 3.

No SNPs reached genome-wide significance — the strongest effect was for rs2110267 on chromosome 7, which was positively associated with symptoms of hyperactivity–impulsivity (4.6×10^{-7}). The results of the gene-based test (Table 4) for combined symptoms, inattention, and hyperactivity–impulsivity, respectively, showed no genome-wide significance; GPR139 showed the strongest association with ADHD (6.4×10^{-5}), specifically for symptoms of inattention.

To examine whether our results replicate previous findings from case control analyses, we combined the SNP effects that we found with the 50 best SNPs in a meta-analysis by Neale and colleagues (2010) using Metal. We found stronger effects for rs12375086 and rs12673393 than found separately in either of the studies. The Metal results approached genome-wide significance for the effect of rs12375086 on combined symptoms of ADHD (9.9×10^{-8}) and hyperactivity–impulsivity (7.4×10^{-8}), and we present these in Table 5. This provides evidence for replication of an association between these SNPs and ADHD — this genetic region is illustrated in Appendix B (Figure B1). However, we found no genome-wide significant effects in any of our analyses due to insufficient power, given the relatively small size of our replication sample.

Discussion

In this study we used a novel quantitative measure of ADHD to describe the full spectrum of behavior relating to DSM-IV-defined ADHD symptoms. There was evidence for replication of two SNP effects previously found in a meta-analysis of ADHD case-control GWAS. However, no novel results reached significance. Our qq-plots for data from the NU study appear to be underpowered, indicating fewer *p*-values at the higher end of the distribution than would be expected by chance. This may be due to reduction in power associated with (1) a reduced sample size, and (2) a reduced effect — the scale used for NU study was 5-point in comparison to the 7-point scale used in the MN study. ADHD symptoms appear to be influenced by many genes of small effect, and as previously found with GWAS, pooling

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TABLE 4

Gene-Based Test Results of SNP Effects From Meta-Analysis of MN and NU Combined, Inattentive, and Hyperactive–Impulsive Symptoms

Chr	Gene	No. SNPS	Start	Stop	χ^2 test	*p*-value	Best SNP	SNP *p*-value	Genes within this region $p < 1e\text{-}04$
Combined									
14	RNASE3	69	20429401	20430347	371.38	4.03e-04	rs11623919	5.72e-05	
16	GPR139	136	19950543	19992601	654.79	4.47e-04	rs12596252	9.60e-06	
10	DCLRE1A	71	115584473	115603597	315.92	7.54e-04	rs12767773	3.07e-04	C10orf81 8.95e-04
15	GABPB2	137	48356680	48434687	623.63	7.61e-04	rs1797311	1.91e-04	
2	REG1B	120	79165656	79168658	463.20	8.45e-04	rs11678047	1.82e-04	
9	SHB	219	37905894	38059210	1193.09	9.26e-04	rs10973642	2.44e-04	
2	LIMS2	82	128112470	128138583	352.71	1.11e-03	rs4662750	9.66e-04	
Inattention									
16	GPR139	136	19950543	19992601	784.61	6.40e-05	rs12919130	1.60e-06	
6	TBC1D7	236	13413162	13436593	1255.47	2.31e-04	rs449727	1.09e-04	
9	SHB	219	37905894	38059210	1353.41	3.79e-04	rs10758467	1.12e-04	
12	KRT71	221	51223959	51233170	816.67	5.66e-04	rs3847846	1.33e-03	
10	CSGALNACT2	109	42953939	43000755	580.76	8.99e-04	rs10899779	6.32e-04	
3	DCUN1D1	81	184143252	184181020	408.02	1.04e-03	rs13099939	1.04e-03	
11	DDX6	81	118123682	118167182	407.70	1.27e-03	rs10892272	4.34e-04	ARCN1 1.27e-03
Hyperactive–Impulsive									
11	FAM55D	130	113946522	113971694	802.11	2.54e-04	rs991513	6.42e-04	FAM55A 4.09e-04
2	REG1B	120	79165656	79168658	508.94	4.07e-04	rs7608639	1.04e-04	REG1A 4.21e-04; REG1A 4.47e-04
10	GPR123	95	134751398	134795169	386.29	4.20e-04	rs4838786	1.52e-04	
10	DCLRE1A	71	115584473	115603597	334.55	4.36e-04	rs12767773	4.57e-04	C10orf81 5.52e-04
14	RNASE3	69	20429401	20430347	364.48	4.60e-04	rs1889771	3.97e-05	
15	GABPB2	137	48356680	48434687	622.79	7.92e-04	rs1797311	3.02e-04	

TABLE 5

Top SNPs Identified by Neale et al. (2010) and SNP Effects Within This Study Combined Using Metal

Markers	Effect this study	*p*-value this study	Effect Neale et al. (2010)	*p*-value Neale et al. (2010)	Combined samples *p*-value	Tested allele AL1	Non-tested allele AL2
Combined							
rs12375086	+	1.16e-02	+	2.56e-06	9.94e-08	t	c
rs12673393	+	1.40e-02	+	3.09e-06	1.41e-07	a	g
rs12673272	+	1.43e-02	+	8.14e-06	3.85e-07	t	c
rs17611827	–	1.55e-02	–	1.45e-05	7.40e-07	a	g
rs1449591	+	3.60e-02	+	2.39e-05	2.43e-06	t	c
rs1464807	+	5.23e-01	+	1.10e-06	2.65e-06	t	g
rs1004561	+	8.26e-02	+	2.26e-05	4.76e-06	a	t
rs17499178	+	1.75e-01	+	1.41e-05	6.42e-06	t	g
rs7176964	–	3.31e-01	–	1.17e-05	1.59e-05	a	t
rs17167761	+	3.66e-01	+	1.51e-05	1.63e-05	a	c
Inattention							
rs12375086	+	2.91e-02	+	2.56e-06	2.16e-07	t	c
rs12673393	+	3.37e-02	+	3.09e-06	2.97e-07	a	g
rs17611827	–	7.49e-03	–	1.45e-05	4.28e-07	a	g
rs12673272	+	3.42e-02	+	8.14e-06	7.88e-07	t	c
rs1464807	+	4.58e-01	+	1.10e-06	2.15e-06	t	g
rs1004561	+	5.55e-02	+	2.26e-05	3.32e-06	a	t
rs17499178	+	1.54e-01	+	1.41e-05	5.59e-06	t	g
rs1449591	+	1.27e-01	+	2.39e-05	7.61e-06	t	c
rs17167761	+	3.22e-01	+	1.51e-05	1.39e-05	a	c
rs16938747	–	2.16e-01	–	2.30e-05	1.62e-05	c	g
Hyp-Imp							
rs12375086	+	8.05e-03	+	2.56e-06	7.46e-08	t	c
rs12673393	+	9.86e-03	+	3.09e-06	1.06e-07	a	g
rs12673272	+	1.01e-02	+	8.14e-06	2.93e-07	t	c
rs1449591	+	8.50e-03	+	2.39e-05	7.92e-07	t	c
rs17611827	–	6.56e-02	–	1.45e-05	2.49e-06	a	g
rs1464807	+	5.57e-01	+	1.10e-06	2.95e-06	t	g
rs17499178	+	2.40e-01	+	1.41e-05	9.10e-06	t	g
rs1004561	+	1.66e-01	+	2.26e-05	9.43e-06	a	t
rs4747989	+	8.72e-02	+	2.74e-05	1.22e-05	t	c
rs4866023	+	2.83e-01	+	2.03e-05	1.55e-05	a	g

Note: The marker effect for Neale et al.'s meta-analysis (2010) represents the direction of the *z*-score associated with each SNP. The combined samples *p*-value represents the combined SNP effects.

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samples to increase sample size and the size of the effects achieved would be the most appropriate way forward. This is supported by the suggested replication of previous results. We could not adequately compare our results with those of Lasky-Su and colleagues (2008) as neither direction of effects nor reference alleles were presented in their article, but as described below there was suggested replication.

The methodology we used differs somewhat from that of the previous GWAS of quantitative ADHD symptoms. Lasky-Su and associates (2008) used a family-based association test (FBAT), which employs parental genotype and/or the trait distribution in offspring as controls when calculating association between markers and traits. This essentially controls for population stratification and skewness; however, it is unlikely that the variation in our results is due to skewness (see Table 2) or population stratification due to the quality control prior to conducting the GWAS. The second quantitative measure in the study of Lasky-Su et al. represented the sum of positive responses to each ADHD symptom. In contrast, our scale addressed the full spectrum of ADHD-related behaviors, providing more power to detect genetic association and at the same time greater phenotypic variation. This variation in scales might partially account for variation in results.

We were unable to adequately compare our effect sizes with the best SNPs of Lasky-Su and colleagues (2008) due to the absence of alleles and directional effects in their article, but there were three SNPs with suggested replication in our study: rs17651978 in association with inattention and ADHD total score ($p_{\text{Lasky-Su}} = 6.1 \times 10^{-6}$, $p_{\text{Ebejer}} = 4.4 \times 10^{-3}$), rs7992643 in association with ADHD total score ($p_{\text{Lasky-Su}} = 5.5 \times 10^{-6}$, $p_{\text{Ebejer}} = 9.4 \times 10^{-3}$), and rs10767942 in association with hyperactivity–impulsivity ($p_{\text{Lasky-Su}} = 7.9 \times 10^{-6}$, $p_{\text{Ebejer}} = 8.4 \times 10^{-3}$). Of interest, rs7992643 was uniquely associated with combined symptoms of ADHD. Within our sample, the top 25 SNPs for the combined symptoms phenotype were associated with either symptoms of inattention or hyperactive–impulsivity and not unique to the combined subtype, but overall approximately two-fifths of the strongest 100 SNP effects were unique to combined symptoms. There has been evidence to suggest there may be a genetically distinct form of combined ADHD (Christiansen et al., 2008) but this has not been conclusively proven, and given the heterogeneous results we see across GWAS of ADHD, it remains speculation. Teasing apart the genes contributing to the subtypes and latent classes of ADHD will provide important information about the etiology of symptoms and the distinction of phenotypes.

The primary limitation of this study was the small size of our replication sample. In addition, we were unable to exclude possible cases of autism or phenotypes that could mimic ADHD and this could have influenced our findings. There are arguments for and against the exclusion of specific disorders when measuring ADHD. Doing so may exclude natural variation in symptoms and important etiological information, both genetic and phenotypic; a more restrictive analysis of symptoms allows a more specific focus on one dimension of behavior. An additional limitation was the use of retrospective parental report, possibly leading to a reinterpretation of behaviors that can occur with time.

In conclusion, there was suggested overlap in the genetic effects found for diagnosed cases of ADHD and ADHD measured as a quantitative trait. Questions remain regarding the genetic overlap between combined symptoms of ADHD, inattention, and hyperactivity–impulsivity. Within a population sample such as ours, genetic effects are likely to be more heterogeneous than a clinical sample due to the specificity of diagnosis in a clinical study. Paradoxically, it may be a community-based sample that provides the greatest insight into the true variation and comorbidity associated with ADHD symptoms, given the impairment reported by adults with subthreshold symptoms. Increasing the sample size of GWAS for quantitative measures of ADHD symptoms and examining the overlap between ADHD subtypes and comorbid disorders in conjunction with molecular genetics will provide information necessary for development of appropriate treatments.

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Appendix A

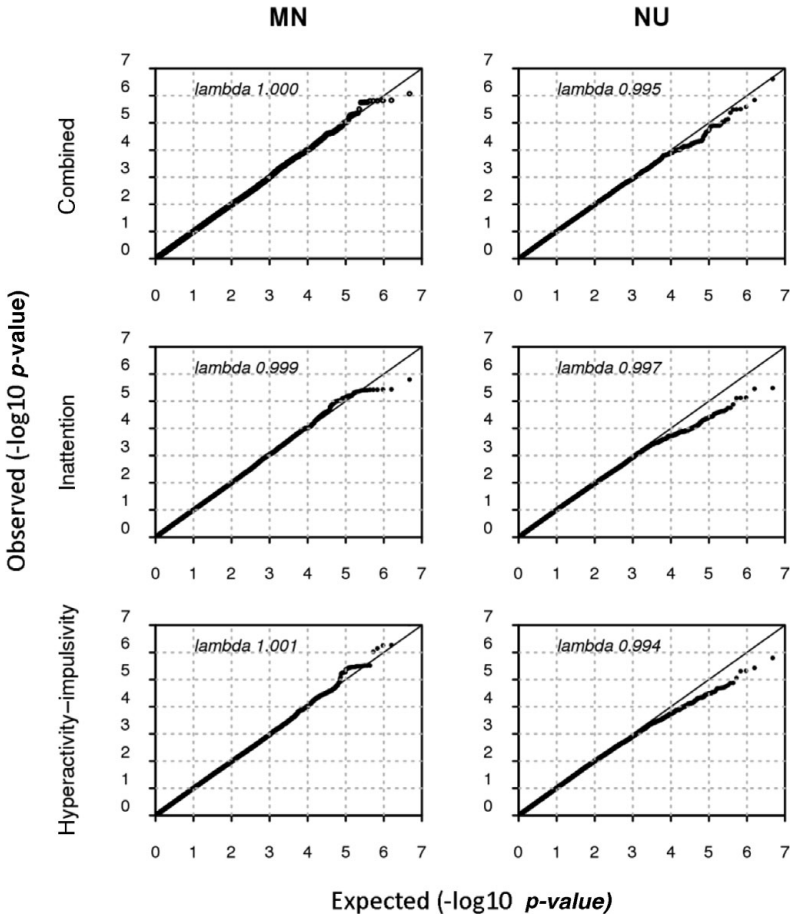

FIGURE A1

qq-plots for combined symptoms, inattention, and hyperactive–impulsive ADHD symptoms generated separately for data collected within the Melanocytic Naevi (MN) and Nineteen-Up (NU) studies.

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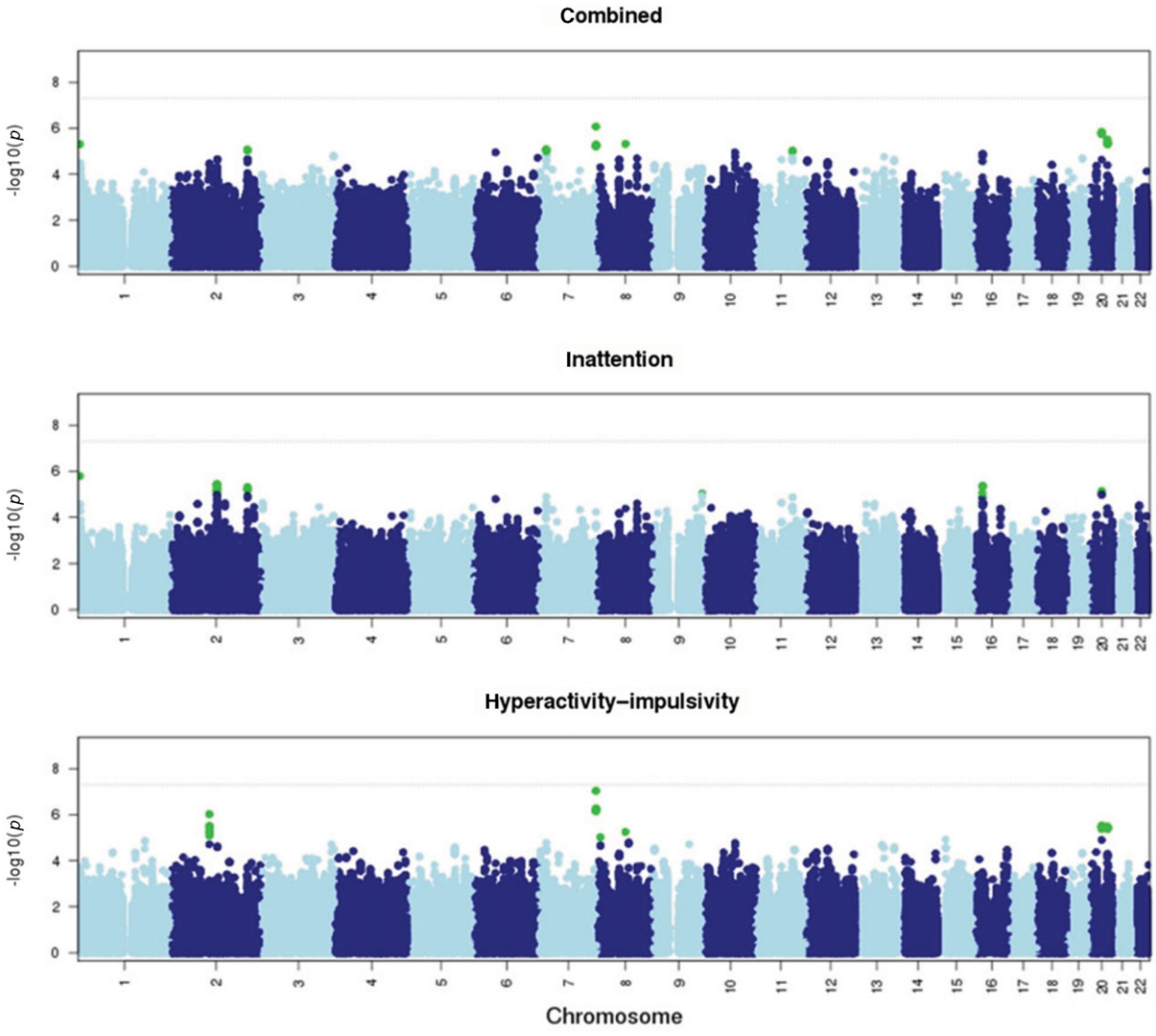

FIGURE A2

(Colour online) Manhattan plot of GWAS results indicating the strength of genetic associations with SWAN data collected within the Melanocytic Naevi study.

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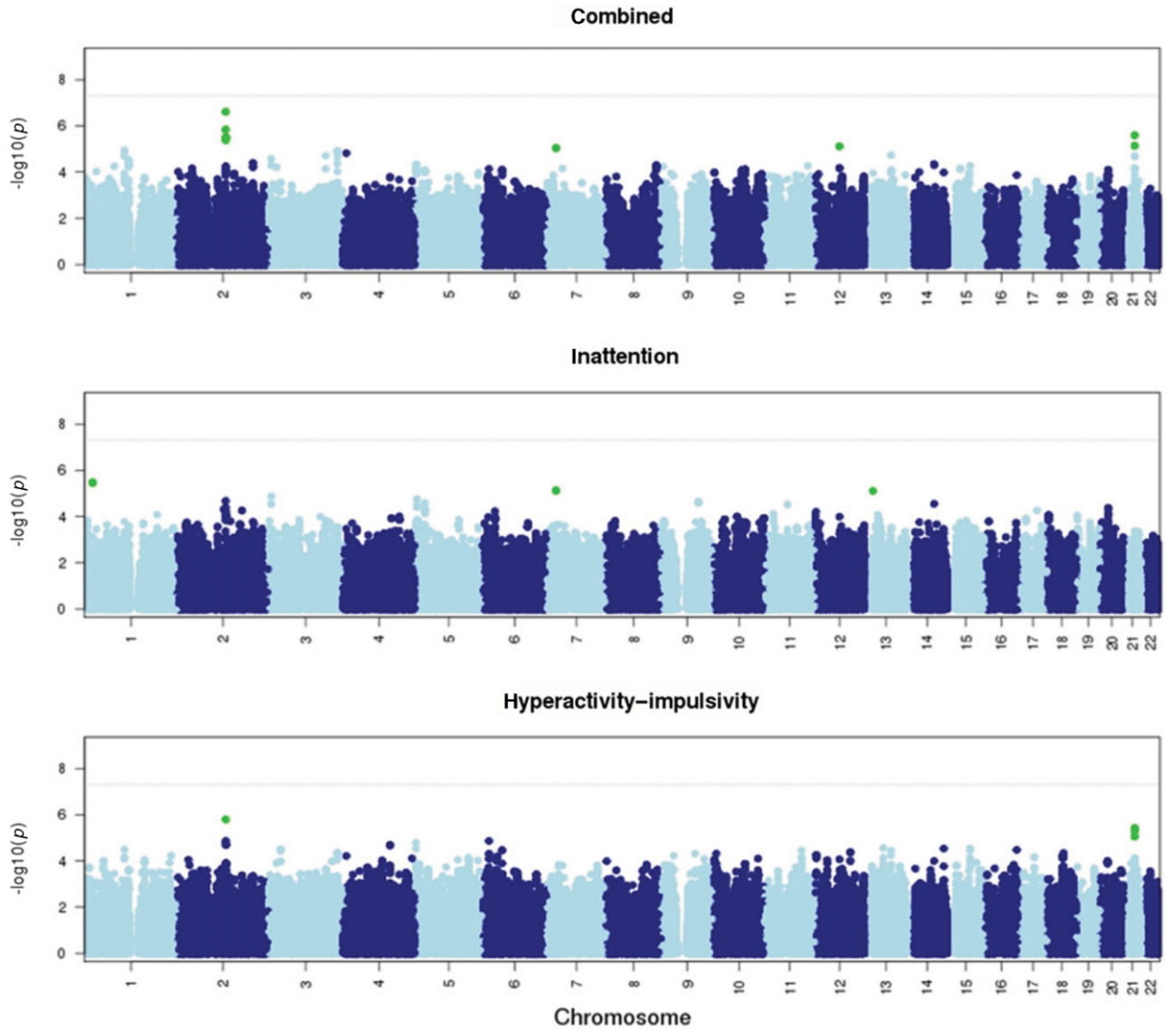

FIGURE A3

(Colour online) Manhattan plot of GWAS results indicating the strength of genetic associations with SWAN data collected within the Nineteen-Up study.

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TABLE A1

Descriptive Statistics of GWAS Indicating the Strongest 25 SNP Associations with SWAN-Measured ADHD Subtypes in Study of Melanocytic Naevi

Ch	Marker	Freq	effect	SE	h^2	*p*-value	Ch	Marker	Freq	effect	SE	h^2	*p*-value	Ch	Marker	Freq	effect	SE	h^2	*p*-value
	Combined							*Inattention*							*Hyp-imp*					
7	rs2110267	0.75	0.29	0.06	2.40	8.48e-07	1	rs11579593	0.94	-0.62	0.13	2.96	1.61e-06	7	rs2192271	0.78	0.27	0.05	1.90	5.39e-07
20	rs6057648	0.02	-0.80	0.17	2.07	1.48e-06	2	rs2419987	0.31	-0.22	0.05	1.40	3.66e-06	7	rs6947495	0.78	0.27	0.05	1.88	5.57e-07
20	rs6119285	0.98	0.80	0.17	2.08	1.51e-06	2	rs4848873	0.31	-0.22	0.05	1.41	3.70e-06	7	rs12671878	0.22	-0.27	0.05	1.77	7.14e-07
20	rs6057652	0.98	0.79	0.17	2.00	1.55e-06	2	rs6742416	0.31	-0.22	0.05	1.39	3.78e-06	2	rs6758152	0.10	-0.34	0.07	1.60	9.49e-07
20	rs6057651	0.02	-0.79	0.17	2.01	1.55e-06	2	rs4848871	0.69	0.22	0.05	1.39	3.79e-06	20	rs6057652	0.98	0.80	0.17	1.92	3.04e-06
20	rs7270085	0.02	-0.79	0.17	2.00	1.56e-06	2	rs4848872	0.69	0.22	0.05	1.39	3.81e-06	20	rs7270085	0.02	-0.80	0.17	1.92	3.05e-06
20	rs6119286	0.02	-0.79	0.17	2.03	1.75e-06	2	rs2670610	0.31	-0.22	0.05	1.39	3.94e-06	20	rs6057651	0.02	-0.80	0.17	1.92	3.06e-06
20	rs6057659	0.02	-0.80	0.17	2.01	1.76e-06	2	rs2256248	0.31	-0.22	0.05	1.39	3.96e-06	2	rs11903187	0.16	-0.28	0.06	1.57	3.16e-06
20	rs8123073	0.98	0.80	0.17	2.01	1.77e-06	2	rs2670605	0.69	0.22	0.05	1.40	3.97e-06	2	rs10193430	0.16	-0.28	0.06	1.56	3.23e-06
20	rs17123726	0.98	0.80	0.17	2.01	1.78e-06	2	rs2419979	0.69	0.22	0.05	1.38	4.08e-06	20	rs910191	0.70	0.22	0.05	1.55	3.23e-06
20	rs910191	0.70	0.22	0.05	1.56	3.13e-06	16	rs12596252	0.24	-0.28	0.06	1.90	4.32e-06	2	rs12613775	0.84	0.28	0.06	1.54	3.24e-06
20	rs4458264	0.71	0.21	0.05	1.44	4.46e-06	16	rs1902813	0.24	-0.28	0.06	1.88	4.43e-06	2	rs1036736	0.16	-0.28	0.06	1.54	3.24e-06
20	rs4402823	0.29	-0.21	0.05	1.44	4.49e-06	16	rs12926725	0.76	0.28	0.06	1.87	4.51e-06	20	rs6057659	0.02	-0.81	0.17	1.93	3.46e-06
20	rs4810796	0.29	-0.21	0.05	1.43	4.74e-06	2	rs2707549	0.32	-0.22	0.05	1.36	4.74e-06	20	rs8123073	0.98	0.81	0.17	1.92	3.49e-06
8	rs11994034	0.99	-1.01	0.22	2.14	4.82e-06	2	rs11681930	0.21	-0.25	0.06	1.38	4.86e-06	2	rs2119507	0.87	0.29	0.06	1.48	3.49e-06
1	rs11579593	0.94	-0.54	0.12	2.66	4.91e-06	2	rs10153620	0.21	-0.25	0.06	1.36	5.64e-06	20	rs17123726	0.98	0.81	0.17	1.92	3.51e-06
20	rs13043694	0.29	-0.21	0.05	1.43	4.99e-06	2	rs11891025	0.16	-0.27	0.06	1.30	6.25e-06	20	rs6119285	0.98	0.79	0.17	1.96	3.58e-06
7	rs2192271	0.78	0.24	0.05	1.57	5.20e-06	2	rs11892551	0.16	-0.27	0.06	1.30	6.26e-06	20	rs6057648	0.02	-0.79	0.17	1.94	3.59e-06
7	rs6947495	0.78	0.24	0.05	1.56	5.32e-06	2	rs11901919	0.84	0.27	0.06	1.30	6.27e-06	20	rs4458264	0.71	0.22	0.05	1.46	3.74e-06
7	rs12671878	0.22	-0.24	0.05	1.47	6.27e-06	2	rs12612808	0.67	0.21	0.05	1.34	6.35e-06	20	rs4402823	0.29	-0.22	0.05	1.46	3.76e-06
7	rs10257873	0.83	0.24	0.05	1.26	8.04e-06	2	rs10496613	0.65	0.22	0.05	1.39	6.38e-06	20	rs4810796	0.29	-0.22	0.05	1.45	3.95e-06
2	rs11681930	0.21	-0.23	0.05	1.30	8.39e-06	2	rs7561456	0.67	0.21	0.05	1.33	6.55e-06	20	rs13043694	0.29	-0.22	0.05	1.45	4.16e-06
2	rs10153620	0.21	-0.22	0.05	1.29	9.55e-06	2	rs6541914	0.67	0.21	0.05	1.33	6.65e-06	20	rs6119286	0.02	-0.79	0.17	1.91	4.16e-06
11	rs10750131	0.12	0.39	0.09	2.46	9.70e-06	2	rs6756857	0.69	0.22	0.05	1.37	6.93e-06	2	rs12622900	0.86	0.28	0.06	1.41	5.39e-06
7	rs3807950	0.80	0.23	0.05	1.31	9.83e-06	20	rs6057648	0.02	-0.82	0.18	1.84	7.36e-06	2	rs17029462	0.14	-0.28	0.06	1.42	5.44e-06

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TABLE A2

Descriptive Statistics of GWAS Indicating the Strongest 25 SNP Associations with SWAN-Measured ADHD Subtypes in Nineteen-Up Study

Ch	Marker	Freq	eff	SE	h^2	*p*-value	Ch	Marker	Freq	Eff	SE	h^2	*p*-value	Ch	Marker	Freq	Effe	SE	h^2	*p*-value
	Combined							*Inattention*							*Hyp-imp*					
2	rs13001970	0.82	-0.50	0.10	22.99	2.45e-07	1	rs10917006	0.93	-0.79	0.17	18.46	3.28e-06	2	rs13001970	0.82	-0.55	0.11	19.84	1.60e-06
2	rs11678590	0.82	-0.44	0.09	17.23	1.44e-e6	1	rs9662008	0.94	-0.79	0.17	17.32	3.51e-06	21	rs363518	0.21	-0.45	0.10	14.57	3.72e-06
21	rs363518	0.21	-0.39	0.08	15.06	2.58e-e6	7	rs1978122	0.14	0.55	0.12	16.87	7.38e-06	21	rs363517	0.77	0.41	0.09	12.88	4.74e-06
2	rs4641887	0.19	0.44	0.09	17.81	3.09e-06	7	rs17211952	0.14	0.54	0.12	16.84	7.56e-06	21	rs2226333	0.23	-0.41	0.09	12.82	4.91e-06
2	rs7573598	0.20	0.44	0.09	18.53	3.18e-06	13	rs7319068	0.28	-0.41	0.09	16.69	7.74e-06	21	rs363514	0.83	0.44	0.10	11.79	8.72e-06
2	rs1113307	0.19	0.44	0.09	17.70	3.22e-06	3	rs9814302	0.85	-0.52	0.12	17.31	1.32e-05	2	rs11678590	0.82	-0.46	0.11	14.04	1.34e-05
2	rs13027475	0.81	-0.43	0.09	17.39	4.22e-06	5	rs440485	0.13	0.46	0.11	11.58	1.77e-05	6	rs6913355	0.85	0.46	0.11	11.89	1.36e-05
21	rs363514	0.83	0.37	0.08	12.00	7.28e-06	5	rs585394	0.13	0.46	0.11	11.54	1.78e-05	5	rs1632064	0.13	0.55	0.13	15.57	1.61e-05
12	rs1252268	0.31	0.37	0.08	17.87	7.72e-06	2	rs13001970	0.82	-0.46	0.11	15.42	2.08e-05	2	rs7573598	0.20	0.47	0.11	15.69	1.79e-05
7	rs1978122	0.14	0.48	0.11	16.75	9.12e-06	9	rs10817736	0.72	-0.38	0.09	13.84	2.32e-05	2	rs4641887	0.19	0.47	0.11	14.92	1.94e-05
7	rs17211952	0.14	0.48	0.11	16.73	9.25e-06	9	rs17425177	0.72	-0.38	0.09	13.81	2.33e-05	2	rs1113307	0.19	0.47	0.11	14.83	2.01e-05
1	rs11184888	0.13	-0.48	0.11	16.22	1.13e-05	9	rs10982644	0.72	-0.38	0.09	13.94	2.39e-05	2	rs13027475	0.81	-0.47	0.11	14.90	2.04e-05
1	rs2991371	0.18	-0.39	0.09	13.72	1.26e-05	9	rs10982647	0.28	0.38	0.09	14.07	2.49e-05	4	rs17492080	0.89	-0.67	0.16	18.65	2.07e-05
3	rs9814216	0.23	0.41	0.10	18.29	1.27e-05	9	rs10817739	0.72	-0.38	0.09	14.18	2.59e-05	4	rs1368509	0.89	-0.67	0.16	18.55	2.10e-05
3	rs7641401	0.23	0.41	0.10	18.29	1.27e-05	5	rs3846559	0.44	-0.32	0.08	12.50	2.63e-05	4	rs17007553	0.11	0.67	0.16	18.54	2.10e-05
3	rs7641467	0.23	0.41	0.10	18.29	1.27e-05	14	rs2238247	0.79	-0.39	0.09	11.97	2.80e-05	8	rs2084803	0.22	-0.66	0.16	32.93	2.46e-05
3	rs4859146	0.23	0.41	0.10	18.29	1.27e-05	3	rs9843022	0.14	0.51	0.12	15.00	2.87e-05	13	rs11618779	0.26	0.39	0.09	12.99	2.75e-05
3	rs6443838	0.23	0.41	0.10	18.29	1.27e-05	11	rs7925016	0.21	-0.39	0.09	11.95	2.99e-05	15	rs7177131	0.90	0.65	0.16	16.81	2.88e-05
3	rs4859260	0.77	-0.41	0.10	18.28	1.27e-05	5	rs424336	0.89	-0.60	0.14	16.61	3.42e-05	14	rs857060	0.74	-0.40	0.10	13.86	2.88e-05
3	rs2055762	0.23	0.41	0.10	18.43	1.30e-05	5	rs372208	0.90	-0.59	0.14	14.99	3.70e-05	5	rs369488	0.14	0.50	0.12	13.43	2.93e-05
3	rs1509229	0.77	-0.41	0.10	18.24	1.34e-05	5	rs436704	0.10	0.59	0.14	14.95	3.74e-05	3	rs6762182	0.17	-0.52	0.12	16.26	3.18e-05
3	rs9878775	0.77	-0.41	0.10	18.25	1.34e-05	5	rs26426	0.90	-0.59	0.14	14.95	3.99e-02	1	rs2991371	0.18	-0.44	0.11	12.45	3.19e-05
4	rs4077958	0.25	-0.41	0.09	19.29	1.53e-05	5	rs26424	0.10	0.59	0.14	14.92	8.22e-02	3	rs7650219	0.17	-0.52	0.12	16.26	3.21e-05
13	rs1326684	0.13	0.46	0.11	14.38	1.86e-05	5	rs153267	0.90	-0.59	0.14	14.88	3.86e-05	3	rs9864339	0.83	0.52	0.12	16.25	3.21e-05
3	rs7622233	0.84	-0.45	0.11	16.24	1.96e-05	2	rs11678590	0.82	-0.42	0.10	12.32	4.08e-05	16	rs4843469	0.37	-0.39	0.09	15.22	3.29e-05

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Appendix B

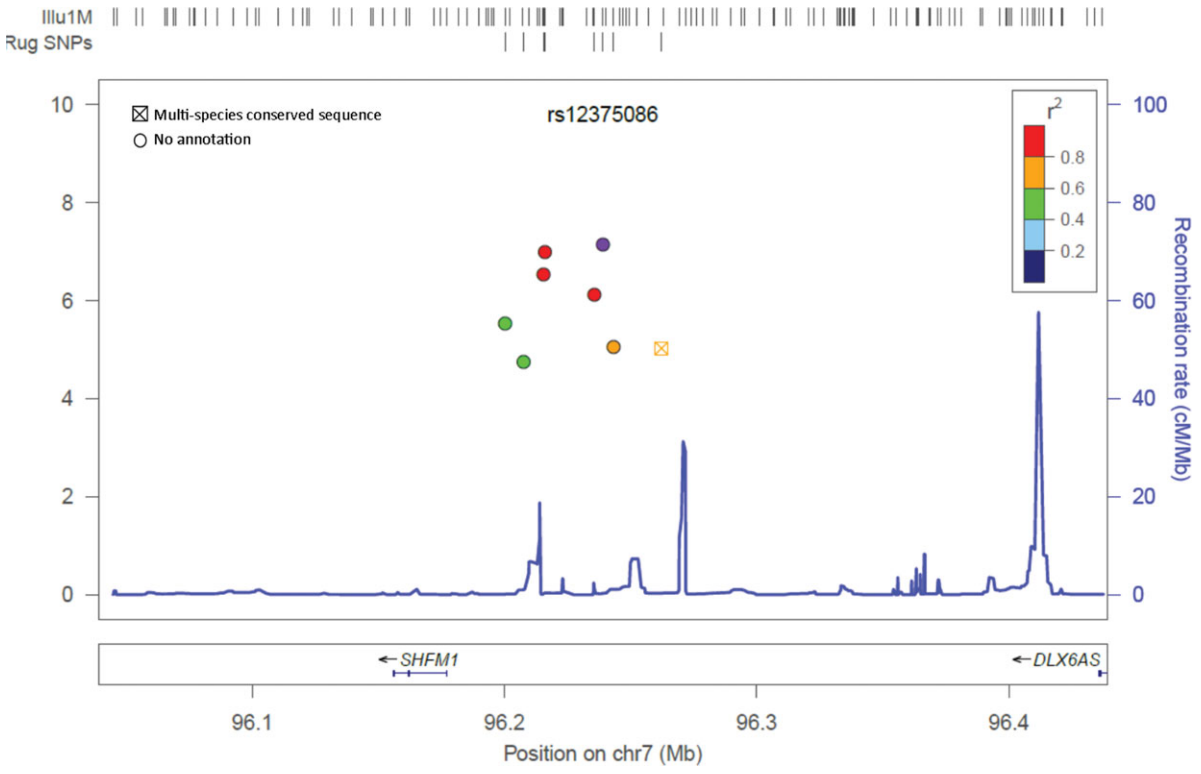

FIGURE B1

(Colour online) Combined results of this study with the meta-analysis of Neale et al. (2010) indicated the association between the SNP located in genomic position 96038981–96438981 on chromosome 7 of build 18 and SWAN-measured ADHD near genome wide significance (9.9×10^{-8}) with combined symptoms and (7.4×10^{-8}) with hyperactivity-impulsivity

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