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Genome-wide scan of reading ability in affected sibling pairs with attention-deficit/hyperactivity disorder: unique and shared genetic effects

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Attention-deficit/hyperactivity disorder (ADHD) and reading disability (RD) are common highly heritable disorders of childhood, which frequently co-occur. Data from twin and family studies suggest that this overlap is, in part, due to shared genetic underpinnings. Here, we report the first genome-wide linkage analysis of measures of reading ability in children with ADHD, using a sample of 233 affected sibling pairs who previously participated in a genome-wide scan for susceptibility loci in ADHD. Quantitative trait locus (QTL) analysis of a composite reading factor defined from three highly correlated reading measures identified suggestive linkage (multipoint maximum lod score, MLS > 2.2) in four chromosomal regions. Two regions (16p, 17q) overlap those implicated by our previous genome-wide scan for ADHD in the same sample: one region (2p) provides replication for an RD susceptibility locus, and one region (10q) falls ~35 cM from a modestly highlighted region in an independent genome-wide scan of siblings with ADHD. Investigation of an individual reading measure of Reading Recognition supported linkage to putative RD susceptibility regions on chromosome 8p (MLS=2.4) and 15q (MLS=1.38). Thus, the data support the existence of genetic factors that have pleiotropic effects on ADHD and reading ability—as suggested by shared linkages on 16p, 17q and possibly 10q—but also those that appear to be unique to reading—as indicated by linkages on 2p, 8p and 15q that coincide with those previously found in studies of RD. Our study also suggests that reading measures may represent useful phenotypes in ADHD research. The eventual identification of genes underlying these unique and shared linkages may increase our understanding of ADHD, RD and the relationship between the two.
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Introduction

Attention-deficit/hyperactivity disorder (ADHD) and reading disability (RD) (also referred to as developmental dyslexia) are among the most prevalent childhood-onset neurobehavioral disorders, each affecting approximately 5–10% of the population. [1,2] They are highly comorbid, with estimates of co-occurrence ranging from 25 to 40%.[3] The association of ADHD with RD, or poor reading achievement in general, has been widely documented.[4–6] Studies that have attempted to identify the mechanism underlying this association support a role for common genetic factors.[7–9]

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ADHD and RD are known to have strong genetic components, although the specific genetic risk variants have yet to be identified. Heritability estimates of ADHD are generally in the range of 60–80%.[10] Similarly high estimates of heritability have been found for reading deficits in children with RD; for example, a large-scale twin study reported heritabilities ranging between 45 and 61% for different reading-related measures.[11] Furthermore, twin and adoption studies have indicated that individual variation in reading performance is substantially influenced by genetic factors in normal populations.[12] Twin studies of both ADHD and RD suggest that the comorbidity of these two disorders may be, in part, due to common genetic underpinnings, although findings are conflicting with respect to the degree of genetic overlap, with estimates ranging from nominal to 50%.[8,9,13,14] One reason for the discrepancy may be that reading ability appears to be more strongly associated with inattentive symptoms and most

studies focus on the discrete ADHD phenotype, rather than specific subtypes. Willcutt *et al*[15] examined this possibility and found higher bivariate heritability estimates for inattention and RD (45%) than those for hyperactivity/impulsivity and RD (5%). Furthermore, ~95% of the phenotypic overlap of inattentive symptoms and reading disability was attributable to common genetic influences, compared to only 21% for hyperactive/impulsive symptoms and RD.[14]

Molecular genetic studies of RD support risk loci on several chromosomes, including 2, 3, 6, 15 and 18 (for a review, see Fisher and DeFries[16]). The most promising of these loci spans the human leukocyte antigen (HLA) region of chromosome 6p21.3, and has been linked to RD in most [17–21] but not all[22,23] studies. To date, the majority of molecular studies of ADHD have investigated candidate genes suggested by the efficacy of drug treatment, but it is clear that the effect sizes of genes evaluated in those studies are likely to be very small. Recently, systematic genome-wide scanning efforts have suggested promising regions for potential risk loci of larger effect on chromosomes 5, 6, 7, 15, 16 and 17.[24,25]

Based on findings thus far, two chromosomal regions appear to be commonly highlighted by independent studies of RD and ADHD: 6p and 15q. Odell *et al*[26] first suggested a potential role for the HLA region of 6p in ADHD susceptibility. Subsequently, in a genome-wide scan of 270 ASPs with ADHD, Ogdie *et al*[25] identified a broad region of linkage on chromosome 6, with a 1-lod support interval spanning 6p21–6q14. This region overlaps with the 6p21.3 locus that has been implicated by multiple studies of RD, but also with a 6q12 linkage that was suggested by one investigation.[27] Willcutt *et al*[28] assessed the linkage of 6p to ADHD in a sibling-pair sample that was originally ascertained for reading difficulties. The sample, which had previously shown linkage to 6p21.3 with multiple reading-related phenotypes,[19,21] also showed linkage to this region with ADHD symptom count, which was weaker but still present after controlling for reading deficits. On the basis of bivariate linkage analyses of ADHD and RD in this sample, Willcutt *et al*[28] proposed that the putative 6p21.3 susceptibility locus was pleiotropic for the two disorders.

Suggestive linkage to 15q was recently identified in an ADHD genome-wide scan carried out in the Netherlands.[24] The region of interest overlaps with that implicated by some linkage studies of RD.[23,29] Moreover, Morris *et al*[30] reported the association of RD with three-marker haplotypes containing marker D15S994, and this was the site of the highest single-point lod score (3.37) in the Bakker *et al* ADHD genome-wide scan.

The purpose of the present study was to identify, in a genome-wide fashion, chromosomal loci underlying variation in reading ability in an ADHD sample. Based on the phenotypic overlap and strong sibling correlations for reading ability in the affected sibling pairs (ASP), we hypothesized that unique and shared genetic loci of RD and ADHD might be contributing in the sample. Given that RD is likely to represent the bottom tail of the distribution of reading ability,[31] we did not restrict the sample to require an RD proband, but instead performed the linkage analysis of reading performance in all ADHD ASPs. We used QTL mapping to investigate the linkage to reading measures in this sample, analyzing the data from ~400 microsatellite markers spanning the entire genome.

Materials and methods

The sample comprised 183 families (233 total sibling pairs) with children aged 5–18 (mean=10.5, SD=3), who were a subset of those included in our earlier ADHD genome-wide scanning efforts.[25,32] The total ADHD ASP sample, previously analyzed by Ogdie *et al*,[25] consisted of 204 families (270 total sibling pairs). However, reading scores were not available for every proband for the following reasons: cognitive data were not collected for 10 probands who had participated in an earlier family study and 18 probands who were older than age 18 years; so the reading battery was not administered. Families were ascertained through clinics, hospitals, schools and community organizations in the Greater Los Angeles area, and visited UCLA for evaluation. During their first visit, parents signed consent forms and children signed assent forms approved by the UCLA Institutional Review Board.

Diagnostic assessments including the measures and procedures are given in detail in Fisher *et al*[32] and Smalley *et al*.[33] Briefly, probands were assessed using a semistructured interview (KSADS-PL; Kaufman *et al*[34]) to determine ADHD diagnoses as well as other psychopathology. Parent and teacher versions of the SNAP-IV,[35] the Child Behavior Checklist and the Teacher's Report Form[36] were used to supplement the material collected in the direct interview, and used in a best estimate procedure to obtain the diagnoses. Families were excluded from the study if a child affected with ADHD also met the criteria for schizophrenia or autism. Full-scale IQ was determined using the WISC-III[37] and academic achievement was assessed using the Peabody Individual Achievement Test-Revised (PIAT-R; Markwardt [38]). Three measures of reading ability are available from the PIAT-R: reading recognition (RR), spelling (SP) and reading comprehension (RC). All probands were assessed for the cognitive battery while off stimulant medication. Children with full-scale IQs below 70 were excluded from the study and the mean full-scale IQ of 106 (SD 14) was above the population average. Due to the high correlations among the three reading measures, a principal component analysis was used to define a factor score, READ, which accounted for 83% of the variance in the three reading measures. The factor loadings on the defined READ factor are 0.94, 0.90 and 0.89 for reading recognition, reading comprehension and spelling, respectively. For a detailed description of other demographic variables, see Ogdie *et al*.[25]

QTL linkage analysis

Genotype data from the sample were obtained previously across the whole genome, as described.[25,32] Data were available for 404 highly polymorphic markers, spanning 22 autosomes and the X chromosome. A denser map of microsatellite and single-nucleotide polymorphism (SNP) markers (~2 cM density) was available for a ~25 cM region on chromosome 16p13, resulting from a previous fine-mapping linkage study of ADHD in this ASP sample.[33] In order to assess whether any genomic regions might contain loci that influence reading ability in our ADHD sample, we used the maximum likelihood estimation of variance components (VCs) of the READ phenotype and each reading-related measure. VC analysis was performed using Genehunter Version 2.1. A model of no dominance variance was assumed, since twin and family data support largely additive gene effects in both ADHD and RD,[10,39] and because it was difficult to obtain convergence under models that included dominance variance. VC analyses are known to be powerful tests of linkage because they exploit almost all phenotypic variability within a family. The approach is based on a decomposition of the phenotype as a linear function of the effects of the QTL, residual genetic effects and random environmental effects.[40] For X-chromosome markers, we used the Haseman Elston method in the Mapmaker/SIBS software package 2.0,[41,42] analyzing all possible sibling pairs with no weighting scheme. For all analyses, we employed a 1 cM increment for IBD (inheritance-by-descent) scanning.

Simulations

VC methods are sensitive to violations of the assumption of multivariate normality, which can lead to loss of power or an increased false-positive rate.[43] Prior to VC analysis, we initially tested the univariate normality of the READ factor, as well as the individual reading measures. None were found to differ in skewness or kurtosis from that expected under a normal distribution, indicating that assumptions of phenotypic normality would be valid for our linkage analyses (data not shown). However, the VC method also assumes the normality of underlying genetic effects, which cannot be assessed by investigation of phenotypic distributions. As such, we used a simulation-based approach to assess the empirical significance of our results. The Simulate software package[44] was used to generate 1000 replicates of the entire autosomal genome under the null hypothesis of no linkage, employing actual marker parameters (eg allele number and frequency, recombination fraction) and genotype recovery frequencies. Each replicate maintained the family structures and phenotypic values of the original data set. All replicate data sets were analyzed with the VC method in Genehunter 2.1, as described above. The resultant MLS values were analyzed at various thresholds, allowing us to derive empirical *P*-values which were adjusted both for deviations from assumptions of the VC method, and for testing of multiple markers across the entire genome.

Results

The rate of RD in the ADHD sample is 18–23%, based on standard RD diagnostic methods using low reading achievement or intelligence-achievement discrepancy.[45] This estimate is comparable to that found among other populations of ADHD subjects, suggesting that multiplex families show similar rates of RD to nonmultiplex ADHD subjects. The distributions of scores attained on the PIAT-R reading subtests in the total sample were similar to those found in the general population, as shown in Table 1.

The reading scores did not significantly differ by gender or ADHD subtype (Combined *vs* Inattentive), in contrast to research, suggesting a stronger relationship for RD and Inattention.[14] However, this may result in part from restricted variance, since the sample is largely composed of Combined and Inattentive subtypes (~90%) and there is a lack of 'pure' Hyperactive–Impulsive subtypes. Support for

Table 1 Mean PIAT standard scores by sample demographics

	N	*Spelling Mean (SD)*	*Reading recognition Mean (SD)*	*Reading comprehension Mean (SD)*
Total sample	407	98.57 (18.86)	101.13 (16.77)	105.54 (18.5)
Gender				
Boys	296	98.68 (18.52)	102 (17)	106.39 (18.87)
Girls	111	98.28 (19.82)	98.82 (15.98)	103.32 (17.37)
ADHD type				
Combined	191	97.47 (18.58)	100.96 (16.51)	105.19 (18.46)
Inattentive	168	98.95 (18.79)	101.38 (17.03)	106.62 (18.75)
Hyper/impulsive	29	105.1 (18.68)	103.31 (14.08)	103.69 (15.48)

PIAT=Peabody Individual Achievement Test. PIAT scores presented are standardized for age; normal populations have a mean of 100 and SD of 15. No significant differences by gender or ADHD type.

this hypothesis is evident from the low spelling means for the Combined and Inattentive subtypes relative to the Hyperactive–Impulsive group (Table 1), although the difference is not statistically significant (F (2,383)=1.78, P=0.17).

Reading ability shows significant familial clustering in our ADHD sample (Tables 2 and 3). As shown in Table 2, the sibling correlations for the READ factor, as well as individual reading measures, range from 0.38 to 0.47, supporting strong familial influences.

As shown in Table 3, familiality of reading performance is also evident from an analysis of parent–offspring data. Although a direct measure of parental reading was not available, parent RD status was defined from a family history interview and a reported history of 'requiring outside help for reading difficulties such as tutoring, special classes, etc'. Using this family history measure of parental RD, we examined whether parental ADHD, RD, comorbid ADHD and RD or neither diagnosis was associated with their child's reading scores. Parental history of RD was significantly associated with children's PIAT-R scores for spelling F(3,373)=8.94, $P<0.0001$, reading recognition F(3,373)=14.55, $P<0.001$, and reading comprehension F(3,373)=11.21, $P<0.0001$, as well as the READ factor score F(3,373)=13.43, $P<0.0001$. *Post hoc* analyses (Tukey LSD) indicated that reading scores were significantly lower when children's parents had a diagnosis of RD or RD + ADHD than when parents had no diagnosis, or an ADHD only diagnosis (all differences $P<0.01$).

Linkage analyses

Multipoint analysis of the READ phenotype yielded four regions which exceeded the recommended threshold for suggestive linkage (MLS > 2.2; Lander and Kruglyak[46]). Table 4 compares these results to those obtained in previous large-scale genome-wide scans of ADHD and RD. One region (on chromosome 2) overlaps that found in multiple genome-wide scans of RD and further replicated in an additional sample.[47] The remaining three regions (10q, 16p and 17q) overlap those suggested by recent genome-wide linkage studies of ADHD.[24,25,32]

Results of the genome-wide analysis of the three individual reading measures were compared with the READ factor to determine if any one task contributed to the observed linkage findings and/or if any unique genetic variance underlying a reading measure might show linkage to a different chromosomal region. As shown in Table 5, three regions (8p, 16p and 17q) exceeded recommended thresholds for suggestive linkage (MLS 2.2) for RR, RC and RR, respectively, while other regions showed more modest evidence for linkage (1.0 < MLS < 2.2). The results do not show any obvious relationship between specific measures and different regions of linkage, and there is no evidence to support measure-specific effects for regions exceeding suggestive linkage. No single chromosomal

Table 2 Sibling correlations READ factor and PIAT reading subtests

	READ factor	*Spelling*	*Reading recognition*	*Reading comprehension*
Between sibling correlation				
READ factor	0.47	0.45	0.48	0.39
Spelling	**	0.45	0.46	0.35
Reading recognition	**	**	0.41	0.29
Reading comprehension	**	**	**	0.38
Within sibling correlation				
READ factor	1	0.90	0.94	0.91
Spelling	**	1	0.78	0.68
Reading recognition	**	**	1	0.80
Reading comprehension	**	**	**	1

Table 3 Mean reading scores by parental phenotype, indicating familial aggregation

	N	*READ factor Mean (SD)*	*Spelling Mean (SD)*	*Reading recognition Mean (SD)*	*Reading comprehension Mean (SD)*
No parental ADHD or RD	95	287.75 (42.24)[a]	102.39 (17.03)[a]	105.11 (15.86)[a]	108.34 (18.04)[a]
Parental ADHD only	112	292.77 (37.12)[a]	103.30 (18.47)[a]	106.59 (13.35)[a]	111.65 (15.27)[a]
Parental ADHD + RD	107	264.37 (43.79)[b]	92.61 (17.25)[b]	96.18 (16.19)[b]	101.39 (18.41)[b]
Parental RD only	63	261.19 (46.58)[b]	94.60 (19.75)[b]	94.03 (17.99)[b]	98.14 (18.54)[b]

Values with different superscripts (a and b) are significantly different from each other $P<0.01$. RD=reading disability; ADHD=attention-deficit hyperactivity disorder.

Table 4 Comparison of multipoint maximum LOD scores (MLS) for READ factor score to previous ADHD and RD linkage findings

Chromosome		*Read factor 270 ASPs*	*Nearest marker*	*RD*	*ADHD*	*Putative genetic effects*
2	MLS	2.25	D2S367	2.52[a]	**	Reading
	pos (cM)[b]	56		86		
10	MLS	2.69	D10S196	**	1.26[c]	Reading and ADHD
	pos (cM)[b]	79			59	
16	MLS	2.24	D16S3046	**	3.73[d]	Reading and ADHD
	pos (cM)[b]	44			18	
17	MLS	2.23	D17S787	**	2.98[d]	Reading and ADHD
	pos (cM)[b]	94			46	

[a]Multipoint MLS obtained using VC analyses of phoneme awareness in a large-scale QTL scan of US families, performed by Fisher *et al* (2002a). This region of chromosome 2 has been implicated in several independent RD samples, using qualitative diagnoses[51] or multiple reading-related measures[52,53].
[b]Haldane centimorgans from the most p-terminal genome-scan marker of the chromosome.
[c]ASP analyses of ADHD susceptibility, performed by Bakker *et al*.[24]
[d]ASP analyses of ADHD susceptibility, performed by Ogdie *et al*.[25]

Table 5 Multipoint maximum lod scores (MLS) >1 for individual PIAT-R reading subtests

Chromosome		*Spell*	*Nearest marker*	*Reading recognition*	*Nearest marker*	*Reading comprehension*	*Nearest marker*
2	MLS			1.01	D2S165	2.13	D2S165
	Position (cM)[a]			47		47	
4	MLS	1.53	D4S426	1.17	D4S2964		
	Position (cM)	240		102			
5	MLS			1.78	D5S407		
	Position (cM)			78			
8	MLS	1.7	D8S272	2.4	D8S258	1.6	D8S258
	Position (cM)	165		40		40	
9	MLS	1.2	D9S1677				
	Position (cM)	124					
10	MLS			1.78	D10S196	1.25	D10S196
	Position (cM)			78		77	
15	MLS			1.38	D15S153		
	Position (cM)			55			
16	MLS	1.44	D16S764			2.4	D16S3046
	Position (cM)	42				49	
17	MLS			2.61	D17S787	2	
	Position (cM)			94		90	D17S787
20	MLS			1.37			
	Position (cM)			54	D20S195		

[a]Haldane centimorgans from the most p-terminal genome scan marker of the chromosome.

region gave MLS values exceeding 1.0 for all the three measures in the same position. However, each of the four regions highlighted by the linkage analysis of the READ factor yielded an MLS exceeding 1.0 for at least two individual measures. Furthermore, for these regions, the positions of multipoint peaks were highly concordant between the individual analyses and those of the READ factor. Of interest, the region on

chromosome 8p which showed suggestive linkage (MLS=2.4; near D8S258) with RR and weaker evidence in the same location for RC (MLS=1.6) maps ~20 cM from a region that showed modest evidence for linkage to phonological decoding in a previous QTL-based genome-wide scan of RD (P=0.001 at D8S550[47]).

Simulations

Lander and Kruglyak[46] previously proposed that a result that is expected to occur by chance only once per genome scan should be designated as 'suggestive'. Assuming complete information extracted from a dense marker map, they demonstrated that this would correspond to a threshold of lod=2.2.[46] VC analyses of the READ phenotype in 1000 replicates of the entire autosomal genome-wide scan indicated that, for our data set, an independent region of linkage (IRL) with an MLS of 2.2 or more is expected to occur by chance only ~0.35 times per genome scan. This shows that the lod > 2.2 threshold for designation of suggestive linkage is appropriate, and even somewhat conservative for interpretation of our results. This finding is very similar to results of simulations by Wiltshire *et al*,[48] who reported that an IRL with lod > 2.2 was expected to occur by chance only ~0.2 times per scan in their genome-scan data set; as the authors pointed out, these results show that dense-map criteria are overly conservative for a typical primary genome scan. We also found that an MLS exceeding 2.69 (corresponding to our most significant linkage with the READ factor) is expected to occur by chance only ~0.12 times per scan. Thus, this MLS approaches the threshold for significant linkage, which corresponds to a result occurring by chance ~0.05 times per scan.[46] Overall, our simulations indicate that deviations from assumptions of multivariate normality are not leading to an increase in false-positive rate in our VC analyses. Instead, the MLS values we have obtained are in fact overly conservative in their assessment of linkage.

Discussion

This study is the first systematic examination of reading ability within a sample of multiplex ADHD ASPs. Consistent with previous genetic studies of RD and reading ability,[49,50] we found significant sibling and parent–offspring correlations indicating strong familial clustering of reading scores within this ADHD sample. The results of our genome scan suggest that loci contributing uniquely to variation in reading ability may map on chromosomes 2p, 8p and 15q, while common loci influencing reading measures and ADHD may be located on 16p, 17q and possibly 10q. These data are consistent with evaluations at the phenotypic level from twin studies supporting common and unique genetic effects in ADHD and RD.

We find evidence of replication of linkage (ie P<0.01; Lander and Kruglyak[46]) for two potential QTLs influencing RD, on chromosomes 2p (with the READ factor) and 15q (with the RR measure). The involvement of a locus on 2p was first identified by study of a single multigenerational pedigree segregating RD,[51] and has since received independent support from linkage[47,52] and association[53] analyses in studies of large numbers of sibling pairs. Several independent RD studies have also pointed to a QTL on 15q, again supported by linkage[23,29,54] and association[30] analyses. For both these loci, the positions of our linkage peaks are remarkably concordant with those implicated by the previous studies of RD. We have also found suggestive evidence for linkage to reading recognition on chromosome 8, ~20 cM from a region that showed modest linkage to phonological decoding in a previous study of RD.[47] Since significant linkage was not found in the Fisher *et al*[47] study, the finding reported herein does not constitute a replication, but does give additional support that this region on chromosome 8 may play a role in reading abilities.

These findings support the idea that general reading ability and reading disability share common etiologic factors, which is consistent with prior phenotypic research indicating that they lie on the same continuum,[31] involve the same developmental pathways[55] and share the same predictors.[56] Our results also demonstrate the relatively robust nature of linkage signals with respect to reading and RD, since the specific tests used in the present study differ from those in previous investigations of phonological decoding, although they are highly correlated (eg the RR task and the Woodcock Johnson Word Attack have a correlation of 0.56).

Three chromosomal regions that are highlighted in the current scan with the READ phenotype have already been highlighted in previous scans of ADHD, specifically 10cen in a sample of Dutch ASPs[24] and 16p and 17q in the current data set.[25,32,33] However, it should be noted that while the 1-lod support intervals for the reading and ADHD linkages show overlap, the positions of peak MLS may differ by 20–40 cM. The strongest evidence for linkage in the current study of the READ phenotype falls on chromosome 10q. This region did not show evidence for linkage with ADHD in the current data set, only modest evidence for linkage with ADHD was observed in the Bakker *et al*[24] scan (MLS=1.26), and no evidence has been suggested from genetic investigations of RD. Thus, additional work and replication in independent data sets are required to evaluate the significance of this finding.

Common genes underlying reading and ADHD are suggested by the linkage findings on 16p and 17q in regions identified using the discrete classification of ADHD and the current findings using the READ phenotype. Phenotypic analysis of the relationship between reading ability and ADHD symptoms in the sample suggests that the variability in reading is not merely a reflection of number or type of ADHD symptom. However, lack of a strong relationship of inattentive behaviors and reading in the current

sample may be due to the restricted variance present in the inattentive domain. Nevertheless, the data suggest that reading may be a useful phenotype in ADHD research. Neither of the putative loci on chromosomes 16 and 17 has received any previous support in genetic studies of dyslexia, suggesting that these are likely to contribute uniquely to the variation in reading ability within ADHD.

These findings likely indicate shared biological or cognitive processes that underlie reading and ADHD, resulting in high rates of co-occurrence between ADHD and RD. Cognitive deficits such as inhibition, verbal working memory, color/number naming and response accuracy and speed have been observed in children with ADHD alone, RD alone and ADHD + RD, with the comorbid group exhibiting greater impairment than either group alone.[57,58] Alternatively, a common neural mechanism might be variation in cerebral lateralization, particularly related to language processing. Support for such a mechanism is evident from brain-imaging studies of dyslexic and ADHD individuals, in whom reversed asymmetry of hemisphere structures such as planum temporale, caudate nucleus and frontal lobes have been observed.[59,60] In the future, the relationship between potential risk loci and the various aspects of these traits may be explored using newly developed methods for fully multivariate linkage analyses of multiple related traits.[61]

As with all analyses of complex traits, the significance of the current linkage findings should be interpreted cautiously, and replication in independent data sets is needed. We have not adjusted for analysis of multiple measures, since a Bonferroni correction would be overly conservative due to the high correlation between different phenotypes. However, our simulation approach has allowed us to take into account any multiple testing resulting from analyses of several hundred markers across the genome, as well as any elevation in type I error that might have occurred as a consequence of using the VC method. Analyses of 1000 replicates indicate that the adopted threshold of MLS > 2.2 for declaring suggestive linkage is conservative when applied to our medium-density genome scan data set (comparable to earlier findings by other groups; Wiltshire *et al*[48]). Moreover, our simulation data show that the observed number (n=4) of IRLs with an MLS exceeding 2.2 is much greater than that expected by chance (n=0.3).

In conclusion, our study suggests the existence of unique and shared genetic influences on reading within an ADHD sample. The shared genetic influences may contribute to cognitive processes such as verbal working memory, inhibition or perhaps variation in cerebral asymmetry. This study highlights the potential power to detect risk loci in large samples of affected sibling pairs, not only for the trait on which they were ascertained, but also for comorbid psychiatric disorders and/or other commonly associated traits.

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Electronic-Database Information

The accession number and URLs for data presented herein are as follows:ASPEX Linkage Analysis Package, ftp://lahmed.stanford.edu/pub/aspex/index.htmlCenter for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/Cooperative Human Linkage Centre, http://lpg.nci.nih.gov/ABI/index.htmlGenehunter, http://www.fhcrc.org/labs/kruglyak/Downloads/Genethon, ftp://ftp.genethon.fr/pub/Gmap/Nature-1995/data/Mapmaker/SIBS, http://www-genome.wi.mit.edu/ftp/distribution/software/sibs/Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ADHD[25]) RECODE, http://watson.hgen.pitt.edu/registerResearch Genetics, ftp://ftp.resgen.com/pub/mappairs/human set/

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