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A Genomewide Scan for Loci Involved in Attention-Deficit/ Hyperactivity Disorder

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Attention deficit/hyperactivity disorder (ADHD) is a common heritable disorder with a childhood onset. Molecular genetic studies of ADHD have previously focused on examining the roles of specific candidate genes, primarily those involved in dopaminergic pathways. We have performed the first systematic genomewide linkage scan for loci influencing ADHD in 126 affected sib pairs, using a ~10-cM grid of microsatellite markers. Allele-sharing linkage methods enabled us to exclude any loci with a λ_s of $\geqslant$3 from 96% of the genome and those with a λ_s of $\geqslant$2.5 from 91%, indicating that there is unlikely to be a major gene involved in ADHD susceptibility in our sample. Under a strict diagnostic scheme we could exclude all screened regions of the X chromosome for a locus-specific λ_s of $\geqslant$2 in brother-brother pairs, demonstrating that the excess of affected males with ADHD is probably not attributable to a major X-linked effect. Qualitative trait maximum LOD score analyses pointed to a number of chromosomal sites that may contain genetic risk factors of moderate effect. None exceeded genomewide significance thresholds, but LOD scores were >1.5 for regions on 5p12, 10q26, 12q23, and 16p13. Quantitative-trait analysis of ADHD symptom counts implicated a region on 12p13 (maximum LOD 2.6) that also yielded a LOD >1 when qualitative methods were used. A survey of regions containing 36 genes that have been proposed as candidates for ADHD indicated that 29 of these genes, including DRD4 and DAT1, could be excluded for a λ_s of 2. Only three of the candidates—DRD5, 5HTT, and CALCYON—coincided with sites of positive linkage identified by our screen. Two of the regions highlighted in the present study, 2q24 and 16p13, coincided with the top linkage peaks reported by a recent genome-scan study of autistic sib pairs.

Introduction

Attention deficit/hyperactivity disorder (ADHD [MIM 143465]) is a common neurobehavioral disorder affecting ~5%–10% of children and adolescents and $\geqslant$3% of adults (Wolraich et al. 1996; Swanson et al. 1998; Scahill and Schwab-Stone 2000; Brown et al. 2001). It is a condition characterized by behavioral symptoms of inattention and/or hyperactivity-impulsivity, with onset in childhood and significant impairment in two or more settings (American Psychiatric Association 1994). Such symptoms include restlessness, difficulty with organizing tasks, distractibility, forgetfulness, difficulty awaiting turns, and frequent interrupting. Under the most recent diagnostic system, DSM-IV (American Psychiatric Association 1994), children may be classified with one of three subtypes—inattentive (I), hyperactive-impulsive (HI) or combined (C)—on the basis of whether they exceed symptom thresholds for I dimensions, HI dimensions, or both, respectively. The disorder is diagnosed more often in boys than in girls, with a ratio of 3–4:1 (Cantwell 1996; Swanson et al. 1998). Of ADHD cases, $\geqslant$60% occur with another major psychiatric disorder or learning disability (Cantwell 1996). On the basis of a review of the literature, Brown and colleagues (2001) found that the conditions most commonly comorbid with ADHD were oppositional defiant disorder (ODD) (33%), conduct disorder (CD) (25%), anxiety disorders (25%), depressive disorders (20%), and learning disabilities (22%).

Numerous investigations have supported a significant role for genetic influences in the etiology of ADHD (Smalley 1997). Family studies indicate a sibling relative risk (λ_s) of ~5 for this common disorder (Biederman et al. 1992). Over the past 6 years, >5,000 twin pairs from unselected population samples in the United States, United Kingdom, Norway, and Australia have been as-

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sessed for behavioral symptoms of inattention and hyperactivity-impulsivity, as well as for clinical diagnoses of ADHD (Edelbrock et al. 1995; Thapar et al. 1995; Gjone et al. 1996; Levy et al. 1997; Sherman et al. 1997; Hudziak et al. 1998; Eaves et al. 2000, Thapar et al. 2000). Heritability estimates from these studies have been consistently high, generally falling in the 60%–80% range, whether the evaluation is of qualitatively diagnosed ADHD or quantitative measures of behavioral dimensions correlated with ADHD.

Data from two epidemiologically based twin studies have suggested that a significant proportion of the genetic influences underlying ADHD may be contributing independently to the HI and I symptom dimensions, implying that there are unique (as well as shared) genetic effects for different subtypes (Sherman et al. 1997; Hudziak et al. 1998). In contrast, it has been found that, in families containing multiple individuals affected with ADHD, the I, HI, and C subtypes do not tend to "breed true," with a general lack of sibling similarity for each of the two separate symptom dimensions (Smalley et al. 2000). Therefore, the family-based studies appear to imply that—although there may be unique genetic effects—the majority of genetic liability is shared between subtypes. It may be that differences in ascertainment or diagnostic procedure are partly responsible for the distinct conclusions of the twin- and family-based studies. Alternatively, it is possible that unique genetic variance is smaller in extreme selected samples. The Smalley et al. (2000) sample was identified through volunteer responses to advertisements and may reflect a clinically severe population of ADHD families, compared with population-based twin samples. In the present report, we present molecular genetic investigations of a subset of affected sib pairs (ASPs) taken from the Smalley et al. (2000) sample of multiplex families.

To date, all previous molecular genetic studies of ADHD have targeted specific candidate genes for investigation, mainly through case-control and/or family-based association strategies. In general, candidate genes have been chosen on the basis of models of effective psychopharmacological intervention for treating the disorder. There is a 60%–80% response rate of children and adolescents with ADHD when given stimulants that target dopamine transport, release and reuptake (Spencer et al. 1996). In addition, knockout mice that completely lack the dopamine transporter gene (DAT1) demonstrate extreme hyperactivity (Giros et al. 1996). Most molecular genetic studies of ADHD have therefore focused on genes encoding proteins that are involved in the dopaminergic system, including DAT1, the dopamine receptors DRD2-5, dopa decarboxylase (DDC), dopamine beta-hydroxylase (DBH), and monoamine oxidase A (MAOA) (e.g., Cook et al. 1995; LaHoste et al. 1996; Gill et al. 1997; Smalley et al. 1998; Daly et al. 1999; McCracken et al. 2000; Barr et al. 2001; Faraone et al. 2001; Payton et al. 2001). Genes implicated in other systems, such as the serotonin processing pathway, have also been suggested as candidates for ADHD (Manor et al. 2001). Of all the candidate genes investigated thus far, the strongest evidence for association with ADHD has been found for polymorphisms in the DRD4 (LaHoste et al. 1996; Smalley et al. 1998; Faraone et al. 2001; Mill et al. 2001) and DAT1 (Cook et al. 1995; Gill et al. 1997; Daly et al. 1999) genes. Nevertheless, in each case there have been several studies that have not supported association (e.g., Palmer et al. 1999; Holmes et al. 2000), and the effect sizes of the putative risk alleles are estimated to be rather small (e.g., genotype relative risks 1.1–1.9 [Daly et al. 1999; Curran et al. 2001; Faraone et al. 2001]).

A complementary strategy for pinpointing genetic risk factors involved in ADHD susceptibility is to perform a systematic genomewide scan of affected subjects, using high-throughput genotyping technology. Although association-based methods are likely to be able to identify genes of very small effect, it is not yet practical to undertake this kind of analysis on a genomewide scale in outbred populations. First, to ensure a reasonable chance of detecting risk loci, such approaches require a prohibitively high density of markers (on the order of 1–20 markers/cM). Second, association-based methods are complicated by variation in the extent of linkage disequilibrium in different chromosomal regions and in different populations. Linkage-based methods offer a feasible alternative, needing only a relatively low density of evenly spaced markers (~1 every 10–20 cM). Linkage has proved to be a successful way to map both Mendelian and genetically complex traits, with the caveat that loci of minor effect are unlikely to be detected unless extremely large samples are investigated.

A segregation analysis of extended pedigrees by Faraone and colleagues (1992) previously suggested that a major gene may contribute to genetic liability for ADHD. As discussed above, although several candidate genes have been proposed to influence ADHD, their estimated effect sizes are very small. Furthermore, prior to the current investigation, no genomewide molecular studies have been used to explore the possibility of a major gene effect in this disorder. Thus, if a major risk gene does indeed exist for ADHD, it has yet to be identified. We have performed the first linkage-based genomewide scan for loci involved in ADHD in a sample of 126 ASPs, using microsatellite markers with an average spacing of ~10 cM. The ASP design allowed us to apply nonparametric allele-sharing methods, which do not rely on assumptions about the underlying genetic model for detection of linkage. Using such methods, a sample of one hundred affected sib pairs provides >90% power to detect a major gene effect ($\lambda_s > 3.5$), if a LOD-

score threshold of 3.0 is employed (Risch 1990). When a less stringent LOD-score threshold of 1.0 is adopted, the same sample size yields >90% power to detect susceptibility loci with smaller effects ($\lambda_s = 2.0$), although the reduced threshold is accompanied by an increase in type I–error rate (Weeks and Lathrop 1995). In addition, although all sibs in the present study had a positive diagnosis of ADHD, the severity of disorder was variable, and this was partly accounted for by familial factors. We therefore used a measure of total ADHD symptom count for quantitative trait locus (QTL) analysis, to search for genetic loci that might modify the severity of disorder within the ASP sample. Our study indicates that there is unlikely to be a major gene effect contributing to ADHD susceptibility but points to a number of chromosomal regions that may harbor genes of more moderate effect. These loci require further investigation in additional samples.

Subjects and Methods

Initial Ascertainment of Sample

Families were identified through clinics, hospitals, schools, and community organizations in the greater Los Angeles area, as part of an ongoing molecular genetic study of ADHD. The majority of families were initially ascertained through advertisements requesting the participation of families with at least two children ⩾5 years of age showing symptoms of ADHD. An additional 18 families were selected from a previous family study of ADHD because they were each known to contain an ASP. Families visited UCLA for evaluation, and, during their first visit, parents signed consent forms and children signed assent forms approved by the UCLA Institutional Review Board.

Diagnostic Instruments and Procedures

Assessment of psychiatric disorders, including ADHD, was performed using a semistructured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS-PL) (Kaufman et al. 1997). This was administered to the mother and was followed by a direct interview with the child if he or she was ⩾8 years of age. All interviews were conducted by clinical psychologists or highly trained interviewers, with extensive experience and reliability training in psychiatric assessment. Additional measures employed included the parent and teacher versions of the SNAP-IV (Swanson 1995), the Child Behavior Checklist, and the Teacher's Report Form (Achenbach 1993). Teacher's Report Forms were used to supplement information obtained in the direct interview. A best estimate procedure, using all available information, was employed to determine diagnoses, with senior psychiatrists (J.J.M. and J.T.M.) reviewing positive diagnoses in a weekly case-review meeting. The mean weighted kappa for psychiatric diagnoses was .84 (SD .14), with values of 1.0, .93, and 1.0 for ADHD, ODD, and CD, respectively. ADHD was diagnosed by DSM-IV criteria. A diagnosis was defined as "definite" when all criteria were met (i.e., at least six of nine symptoms on HI and/or I dimensions, accompanied by significant impairment in two or more settings) and as "probable" when subjects fell one symptom short but met the criterion for impairment. Other psychiatric disorders were based on lifetime diagnoses made by use of DSM-IV criteria (or DSM-IIIR, in the case of the 18 families drawn from the earlier family study). Families were excluded from the study if a child affected with ADHD also met criteria for schizophrenia or autism. However, other psychiatric diagnoses (such as ODD or CD) and/or evidence of specific learning disabilities were not grounds for exclusion. Full scale IQ was determined by use of the WISC-III (Weschler 1991), and academic achievement was assessed using the Peabody Individual Achievement Test-Revised (Markwardt 1989). Children with full-scale IQs <70 were excluded from the study. A more detailed description of the sample and measures is given by Smalley et al. (2000)

Demographic and Clinical Characteristics

The genome-scan sample comprised 104 families ascertained as described above. Several families included more than two affected siblings (table 1), yielding a total of 126 possible ASPs for analysis. Table 2 summarizes the demographic and clinical characteristics of the affected siblings in the sample. The distribution of males to females (3:1) was similar to that observed in epidemiological studies of ADHD (Cantwell 1996; Swanson et al. 1998). The sample was largely white (84%), with the greatest representation of families in socioeconomic classes II and III (67%). The mean age of affected siblings was 11 years (SD 4), and the mean full scale IQ of 105 (SD 14) was above the population average. Five subjects

Table 1

ASP Families Included in the Genomewide Scan

Subjects	*n*
Families:	
Two affected sibs	96
Three affected sibs	6
Four affected sibs	2
Total	104
Sib pairs:	
Completely independent[a]	114
All[b]	126

[a] A family with *n* sibs contributes $n - 1$ independent pairs.

[b] A family with *n* sibs contributes $n(n - 1)/2$ possible pairs.

Table 2

Demographics and Clinical Characteristics of 218 Affected Siblings

Characteristic	No. of Affected Siblings	% of Sample
Sex:		
Male	158	72
Female	60	28
Ethnicity:		
White	183	84
Latino	14	7
Asian	5	2
Other[a]	16	7
SES[b]:		
I	39	18
II	78	36
III	69	31
IV	28	13
V	4	2
ADHD diagnosis:		
Definite	205	94
Probable	13	6
ADHD subtype:		
C[c]	117	54
I[d]	87	40
HI[e]	14	6
Comorbidity:		
ODD	95	44
CD	45	21
Mood[f]	44	20
Anxiety[g]	28	13

[a] Includes parents of different ethnicity.
[b] According to Hollingshead (1957).
[c] C cases exceed symptom thresholds in both I and HI domains.
[d] I cases exceed symptom thresholds in the I domain, but not in the HI domain.
[e] HI cases exceed symptom thresholds in the HI domain, but not in the I domain.
[f] A mood disorder includes major depression, dysthymia, and/or bipolar disorder. Three cases of ADHD were also affected with bipolar disorder, but none were in the same ASP.
[g] An anxiety disorder includes two or more of the following: panic disorder, social or simple phobia, obsessive-compulsive disorder, and/or agoraphobia.

scored in the 70–80 range, but none of these were from the same ASP family. The majority (94%) of the ASP members met "definite" criteria for ADHD, and each family included at least one child with a "definite" diagnosis. The distribution of subtypes among the affected siblings was similar to that observed in epidemiological studies of ADHD, as were the frequencies of comorbid psychiatric disorders (Brown et al. 2001). The 126 ASPs included 66 brother-brother, 54 brother-sister, and 6 sister-sister pairs.

Genotyping

In children and parents from each family, 404 highly polymorphic markers, spanning all 22 autosomes and the X chromosome, were genotyped. Seven families included only one parent; the remaining 97 families included both. The majority of autosomal markers were taken from the ABI PRISM LMS2-MD10 panels (Applied Biosystems), whereas the X-chromosome markers came from the CHLC (Cooperative Human Linkage Center)/Weber Human Screening Set Version 6 (Research Genetics). Sex-averaged marker maps were derived primarily from the CHLC, were supplemented with data from Généthon (Dib et al. 1996), and were verified by comparison to maps estimated from the family sample. For autosomal markers, semiautomated fluorescent genotyping was performed by use of standard techniques, as described by Fisher et al. (1999). For X-linked genotyping, pooled PCR products were electrophoresed on a LICOR apparatus GeneReadIR 4200, and gel images were analyzed with Saga Genotyping Software version 1.0 (University of Washington). Raw allele-size data were checked for Mendelian inheritance and were converted to LINKAGE format by use of the GAS software package (version 2.0) (A. Young, Oxford University). The Discovery Manager (Genomica) database system was used for storage of genotypic and phenotypic data and for exporting files in the appropriate format for statistical analysis. As a final check on genotyping quality, marker haplotypes were generated from the data by use of Genehunter version 2.0 (Kruglyak et al. 1996), to identify any chromosomes showing an excessive number of recombination events. Allele frequencies were estimated from all founders in the sample.

Qualitative ASP Linkage Analysis

Singlepoint and multipoint sib-pair based linkage analyses of genotype data were performed under two qualitative classification schemes. We defined "broad" ADHD as when all sibs have a probable or definite DSM-IV diagnosis of ADHD (see above), which yielded a total of 126 pairs. A "narrow" definition reflected ASPs where all sibs met a definite diagnosis, yielding a subset of 110 pairs. Autosomal markers were analyzed by use of the Mapmaker/SIBS options (Kruglyak and Lander 1995) available in version 2.0 of the Genehunter software package (Kruglyak et al. 1996). Linkage was assessed by the maximum LOD score (MLS) method (Risch 1990), as implemented by the "estimate" command of Genehunter2.0. This involved comparison of maximum-likelihood estimates of allele-sharing proportions, derived under the restrictions of the "possible triangle" (Holmans 1993), to those under the null hypothesis of no linkage. Exclusion mapping was performed under a series of locus-specific values of λ_s, under the assumption of no dominance variance, using the "exclude" command of Genehunter 2.0. For X-chromosome markers, MLS and exclusion-mapping methods were run using the X-linked "estimate" and "exclude" options of the

Mapmaker/SIBS software package (Cordell et al. 1995; Kruglyak and Lander 1995). The X-linked MLS approach employed independent estimation of allele-sharing proportions in brother-brother, brother-sister, and sister-sister pairs, given the genetic restrictions described by Cordell et al. (1995), and the overall LOD score was taken as the sum of the separate LOD scores from each type of pair. For X-linked exclusion under a series of locus-specific values of λ_s, brother-brother, brother-sister, and sister-sister pairs were again considered separately, assuming no dominance variance, and LOD scores were summed for the three groups, yielding an overall estimate for evidence of exclusion. Details of the relationships between allele sharing proportions and values of λ_s for each type of pairing in the X-linked situation are given by Cordell et al. (1995). All analyses utilized all possible sibling pairs with no weighting schemes. Multipoint methods employed a 1-cM increment for IBD scanning.

Quantitative Trait Linkage Analysis

A quantitative measure of severity was defined from the total DSM-IV symptom count (D4-TOT) on the 18 ADHD symptoms (9 HI and 9 I) generated from the clinical interview. These symptom counts were derived from lifetime behaviors (in the worst time period, generally that between 7 and 12 years of age). We did not use data from the parent questionnaires (e.g., SNAP-IV) for direct QTL analyses in these initial investigations, since these were based on current behaviors and may be influenced by factors such as medication use, as well as by maternal report bias (Smalley et al. 2000). Although all siblings had a "broad" diagnosis of ADHD, there was still variability in symptom severity as indexed by D4-TOT (mean 13.3; SD 2.9). There was evidence to indicate that familial factors contribute to this variability; the proportion of variance attributable to such factors was estimated to be ~24% in this sample. As a consequence of subtype distribution, much of the variability in D4-TOT was a function of variability in the occurrence of HI symptoms. Specifically, although 94% of the sample were positive for at least five of nine I symptoms, only 60% were positive for five or more HI symptoms. (see table 2).

QTL analysis was performed via traditional Haseman-Elston (HE) regression of sib-pair squared trait differences against estimated IBD sharing (Haseman and Elston 1972), using the Genehunter 2.0 package. The HE approach has been validated in numerous studies and is generally robust to variation in ascertainment schemes. Variance components–based strategies were not employed in the present study; these rely on multivariate normality assumptions that are likely to be violated by our ASP sample and may lead to reduced power and/or elevated type I error (Allison et al. 1999). X-linked HE analyses were performed by use of Mapmaker/SIBS (Kruglyak and Lander 1995). As for qualitative analyses, the quantitative approach employed all possible sibling pairs with no weighting schemes and a 1-cM increment was used for IBD scanning.

In the present study, we have followed the recommendation of Elston (1997) by reporting precise *P* values without adjustment for multiple comparisons, so that they can be properly interpreted by the reader. The three different phenotypes investigated here (two overlapping classification schemes for qualitative analyses and a related measure for quantitative analyses) are correlated, so that a Bonferroni correction (which assumes independence of tests) would be too conservative.

Results

MLS Analyses

In single-point MLS analysis, one marker, D5S418 on 5p12, yielded a LOD score of >2, whereas additional markers on 2q, 4p, 7p, 9q, 10q, 12p, 12q, 13q, and Xp gave LODs >1 (table 3). Multipoint data implicated the same regions of 5p, 9q, 10q, 12q, 13q, and Xp as those highlighted by single-point analyses (fig. 1*a*). Multipoint LOD scores also exceeded 1 on chromosomes 11q and 16p (table 4). Three of the regions suggested by multipoint analyses—10q26, 12q23, and 16p13—yielded peak LOD scores of >1.5 under at least one diagnostic scheme (table 4). For X-linked MLS analyses the overall LOD score is taken as the sum of those separately calculated for brother-brother, brother-sister, and sister-sister pairings, since the allele-sharing restrictions differ for each type of pair (Cordell et al. 1995; see "Subjects and Methods" section). The Xp22 linkage identified in the ADHD ASP sample (tables 3 and 4) arose exclusively from the brother-sister pairings.

QTL Analyses

Investigation of the D4-TOT quantitative measure yielded LOD scores >1 for markers on 3q, 8p, 12p, 13q, 16q, and 21q in single-point analysis (table 3). The 8p, 12p, and 13q regions also yielded LODs >1 when multipoint data were used, with a peak LOD score of 2.6 in 12p13 (table 4; fig. 1*b*).

Exclusion Mapping

Sib-pair exclusion mapping involves calculation of the expected allele sharing proportions of a particular locus, under the assumption of a given locus-specific λ_s. The likelihood of the genotype data assuming this λ_s is compared to the likelihood under the null hypothesis of no linkage. If the resulting LOD score is <-2, this is traditionally taken as evidence for exclusion of the region

Table 3

Genome-Scan Markers Yielding Single-Point LOD Scores ≥1 in MLS or QTL Analyses of ADHD ASPs

					Value in MLS Analysis under Diagnostic Scheme					
					Narrow		Broad		QTL D4-TOT	
Chromosome	Position (cM)[a]	Most Likely Cytogenetic Location[b]	Marker	Heterozygosity (%)[c]	LOD	P[d]	LOD	P[d]	LOD	P[d]
2	139	2q14	D2S347	74	1.01	.0153	.85	.0238		
	184	2q24	D2S2330	86	.96	.0178	1.00	.0159		
3	169	3q24	D3S1569	83					1.37	.0060
4	25	4p15	D4S403	81	1.22	.0089				
5	68	5p12	D5S418	85	1.88	.0016	2.10	.0009		
7	41	7p15	D7S516	76	1.24	.0085	1.23	.0087		
8	0	8p23	D8S504	76					1.10	.0120
9	85	9q21	D9S167	85	1.22	.0089	.99	.0162		
	97	9q22	D9S283	80	1.45	.0048	1.16	.0104		
10	193	10q26	D10S212	60	.98	.0167	1.11	.0120		
12	10	12p13	D12S1725	81					1.59	.0034
	22	12p13	D12S336	67	1.07	.0132	.77	.0300	.83	.0253
	138	12q24	D12S79	87	1.11	.0119	.95	.0184		
	165	12q24	D12S324	67	.93	.0190	1.01	.0154		
13	0	13q12	D13S175	75	1.33	.0067	1.02	.0151		
	63	13q31	D13S170	88			1.04	.0143		
	103	13q33	D13S1265	86					1.49	.0044
16	77	16q21	D16S503	80					1.03	.0147
21	21	21q21	D21S263	75					1.02	.0151
X	0	Xp22	DXS9895	75	1.12	.0116	1.27	.0079		

Note.—The table lists only those markers that gave a LOD ≥1 in at least one of the three analyses (narrow, broad, or D4-TOT). For these markers, LOD scores and P values are shown for all analyses yielding $P < .05$.

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

[b] Most likely cytogenetic location of marker, according to draft genome sequence data.

[c] Heterozygosity of each marker, as estimated from the entire study sample.

[d] LODs were converted into nominal P values by multiplying by $2\log_e 10$ and then determining significance from χ^2 tables, taking into account the one-sided nature of the linkage test, as described elsewhere (Lander and Kruglyak 1995).

being investigated. Using multipoint data from all 126 ASPs, we were able to exclude 96% of all regions scanned from containing a locus with a λ_s of ≥3, and 91% from containing a locus with a λ_s of ≥2.5 (table 5). The investigated regions of chromosomes 18, 19, 21, and 22 could be entirely excluded from containing a locus with a λ_s of ≥2 under each of the diagnostic schemes (fig. 2). The X chromosome could be completely excluded for a λ_s of ≥2 under the narrow diagnostic scheme. This includes the Xp22 region implicated by MLS analyses of brother-sister pairs, but the evidence for exclusion of this region came exclusively from the brother-brother pairings.

Discussion

We have performed the first genomewide scan for loci influencing susceptibility to ADHD. Although some researchers have suggested the presence of a major gene effect predisposing to this disorder (Faraone et al. 1992), our data indicate that this is highly unlikely. Using allele-sharing methods, we were able to exclude the vast majority of the genome from containing a locus with a λ_s of ≥2.5 in our sample, which was specifically ascertained for familial ADHD. Therefore, the high heritability of ADHD is probably accounted for by multiple loci with small-to-moderate effect sizes. Note that we do not discount the possibility of rare instances in which extended families segregate apparently monogenic forms of ADHD, as is observed in other childhood learning disorders (see Fisher and Smith 2001; Lai et al. 2001). Nevertheless, we do conclude that there is unlikely to be a single major gene effect of relevance to the general population of ADHD cases. MLS mapping in our sample implicated several regions that may contain loci of more moderate effect involved in ADHD susceptibility—in particular, 5p12, 10q26, 12q23, and 16p13. However, none of these exceeded conventional thresholds for genomewide significance. Therefore, we caution against interpreting the present findings as more than early indications of potential regions of gene locations; additional studies in larger samples will be necessary to explore further the possible roles of these chromosomal regions in ADHD.

Prior to the present study, investigations of the mo-

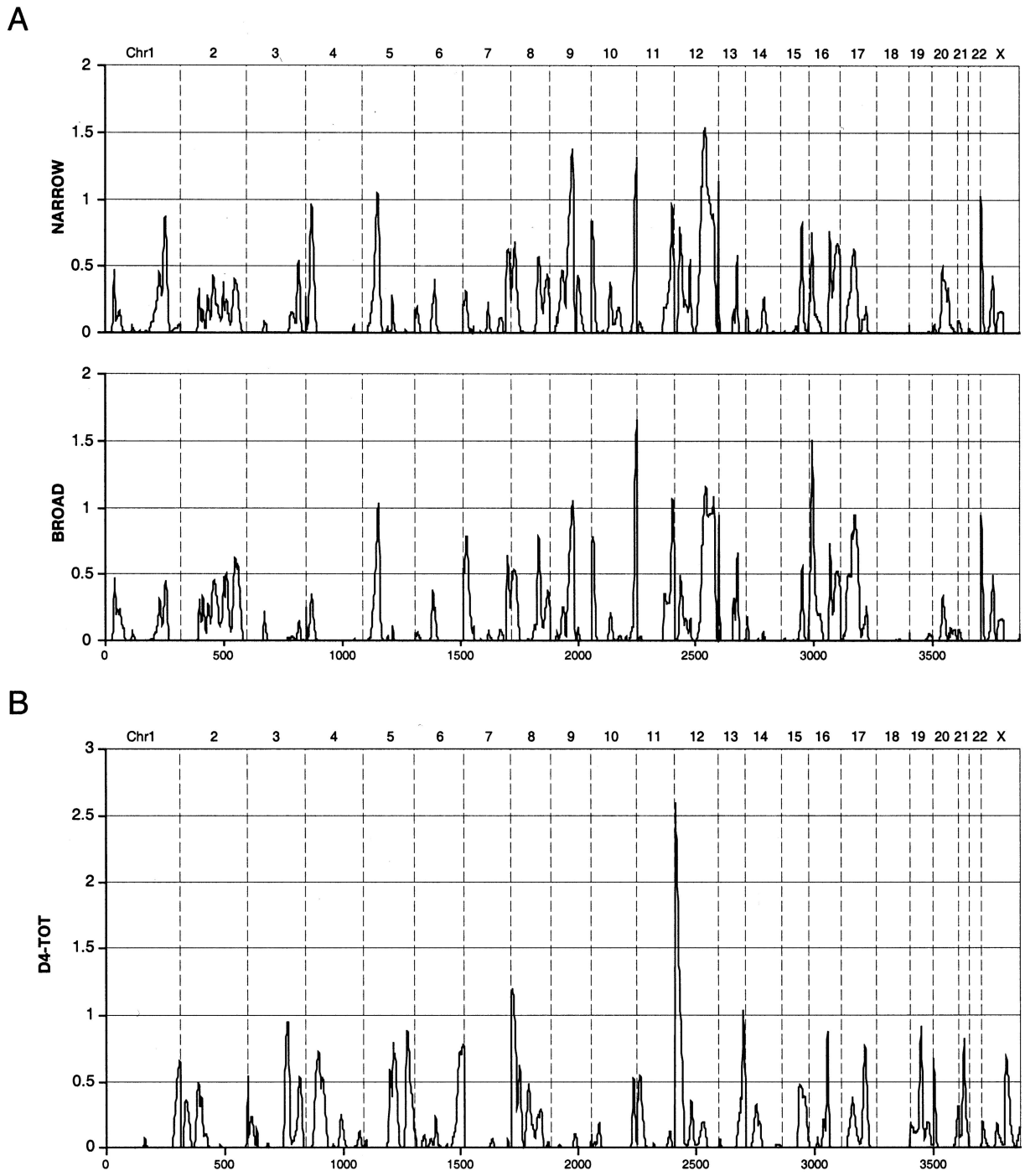

Figure 1 LOD score plots from multipoint analyses of the whole genome in ASPs with ADHD. *A*, MLS analyses for "narrow" and "broad" diagnostic schemes. *B*, QTL analyses for total symptom count derived from clinical interview. Cumulative distance in Haldane centimorgans is displayed along the bottom, with chromosome numbers at the top. Peak LOD scores >1 are summarized in table 4.

lecular genetic basis of ADHD have focused only on candidate genes, mostly those involved in the dopaminergic and serotoninergic systems. Having undertaken a complete genomewide analysis, we have been able to assess the likely contributions of each of the suggested candidate genes in our sample (table 6). Of 36 possible candidates, 29 could be excluded from having a λ_s of ≥ 2 with the "narrow" and/or "broad" classification of

Table 4

Regions Yielding Peak Multipoint LOD Scores ⩾1 in MLS or QTL Analyses of ADHD ASPs

				Value in MLS Analysis under Diagnostic Scheme					
				Narrow		Broad		QTL D4-TOT	
Chromosome	Position (cM)[a]	Most Likely Cytogenetic Location[b]	Nearest Marker[c]	LOD	P[d]	LOD	P[d]	LOD	P[d]
5	65–68	5p12	D5S418	1.05	.0141	1.04	.0145		
8	5–19	8p23	D8S504–D8S550	.69	.0373			1.20	.0094
9	94–97	9q22	D9S283	1.38	.0059	1.05	.0140		
10	193	10q26	D10S212	1.32	.0069	1.66	.0028		
11	151	11q25	D11S1320	.95	.0181	1.07	.0132		
12	0–22	12p13	D12S352–D12S336	.79	.0282			2.60	.0003
12	130–131	12q23	D12S78–D12S79	1.54	.0039	1.16	.0104		
12	165	12q24	D12S324	.89	.0212	1.09	.0126		
13	0	13q12	D13S175	1.13	.0111	.95	.0184		
13	103	13q33	D13S1265					1.04	.0143
16	14	16p13	D16S3075	.75	.0311	1.51	.0042		
X	0	Xp22	DXS9895	1.03	.0147	.95	.0182		

Note.—The table lists only those regions that gave a LOD ⩾1 in at least one of the three analyses (narrow, broad, or D4-TOT). For these regions, LOD scores and P values of linkage peaks are shown for all analyses yielding $P < .05$.

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

[b] Most likely cytogenetic location of highest peak, according to draft genome-sequence data.

[c] Genome-screen marker(s) nearest to the peak of linkage.

[d] Nominal P values were calculated from LODs as in table 3.

affection status. It is worth noting that both DRD4 and DAT1, the most well-studied of these candidates (e.g., Curran et al. 2001; Faraone et al. 2001), could be strongly excluded for such an effect size, regardless of diagnostic scheme. This is consistent with our earlier investigations of these genes in this ASP sample and with the genotype relative risks reported in the literature (Smalley et al. 1998; Palmer et al. 1999). Thus, our findings support the view that, although one or both of these two genes may be involved in ADHD, they make only a minor contribution to the overall genetic susceptibility. Seven candidate genes could not be excluded for a λ_s of 2, under either diagnostic scheme: DRD5, HTR1A, HTR1B, HTR1E, CALCYON, 5HTT, and SNAP25. The regions containing the DRD5, CALCYON, and 5HTT genes, in fact, yielded positive LOD scores in exclusion mapping, given this λ_s. The DRD5 gene maps in the vicinity of D4S403, which was one of the markers yielding a single-point LOD score >1 in MLS analyses (table 3), although the multipoint LOD score was just below this threshold (fig. 1). Similarly, the 5HTT gene, which encodes a sodium-dependent serotonin transporter, maps in a region of 17q11.2 that gave a multipoint MLS peak of 0.95 in our screen (fig. 1). Finally, the CALCYON gene, which encodes a DRD1 interacting protein, coincides with the strongest MLS result of the screen, in 10q26 (table 4). These results may be helpful in guiding further targeted studies of this set of known candidate genes.

The genome-scan ASPs contained an excess of affected males, consistent with epidemiological studies of ADHD prevalence rates (Cantwell 1996; Swanson et al. 1998). Previous investigations of familial clustering in this sample suggested that the observed sex differences are probably not attributable to a major X-linked gene but are more consistent with a model in which females require a greater loading of familial factors before they develop ADHD (Smalley et al. 2000). This hypothesis was supported by the molecular genetic analyses, which allowed us to exclude the X chromosome from containing a gene of major effect in brother-brother pairs. Although we did find some evidence for a possible X-linked locus at Xp22, this came exclusively from brother-sister pairs. Note that our sample lacked power for detection of sister-sister effects, because of the very small number of sister-sister pairs. It is unclear what biological mechanism could account for a genetic effect that is present in brother-sister pairs but absent in brother-brother pairs.

Diagnosis of ADHD is based on exceeding symptom thresholds for HI and/or I dimensions. As such, the disorder is sometimes viewed as one extreme of a quantitatively distributed trait, leading to the hypothesis that genetic risk factors for ADHD might be equivalent to the QTLs underlying symptom variability in the normal population. However, since the DSM classification system is specifically formulated with reference to disorder, DSM-IV–derived symptom counts can be of limited use for describing variability in unaffected individuals, the majority of whom show no ADHD symptoms and

Table 5

Nonparametric Exclusion Mapping in ADHD ASPs

	Proportion Excluded[a] (%)					
	Narrow Diagnostic Scheme			Broad Diagnostic Scheme		
Chromosome	$\lambda_s = 2$	$\lambda_s = 2.5$	$\lambda_s = 3$	$\lambda_s = 2$	$\lambda_s = 2.5$	$\lambda_s = 3$
1	58	83	91	81	95	100
2	63	80	93	53	80	90
3	79	89	96	93	100	100
4	75	85	88	83	93	100
5	68	84	90	78	90	93
6	86	95	100	94	100	100
7	60	94	100	80	92	97
8	52	70	83	53	76	92
9	38	58	77	69	100	100
10	65	83	92	75	94	95
11	64	84	88	77	87	89
12	25	66	74	67	77	85
13	83	95	97	81	97	100
14	54	89	100	85	100	100
15	72	100	100	91	100	100
16	33	47	76	32	59	86
17	58	78	87	54	70	83
18	100	100	100	100	100	100
19	100	100	100	100	100	100
20	39	71	92	71	93	100
21	100	100	100	100	100	100
22	100	100	100	100	100	100
X	100	100	100	96	100	100
Genome[b]	66	84	92	77	91	96

[a] Regions could be excluded if they yielded a LOD score of <-2.00.
[b] Proportion of entire genomewide scan.

would consequently score 0 out of 18. Furthermore, a definite or probable ADHD diagnosis requires the presence of at least five of nine symptoms in *either* the HI or the I domain, so there may still be significant variability in DSM-IV symptom count, even within a severely affected population. This was indeed the case within the ASP sample of the present study, and it was apparent that familial factors made at least a modest contribution to this observed variability in severity. We therefore investigated the total symptom count with a QTL approach in our ASP sample, in analyses that were complementary to the qualitative MLS analyses. Note that these investigations did not rely on assuming any specific genetic model for ADHD susceptibility. Such QTL analyses might identify some loci that only act to modify severity within an affected population (i.e., their action is conditional on the presence of ADHD). Alternatively, these analyses may point to loci that would also influence appropriate indices of HI or I behavior in the normal population and could be viewed as overall risk factors for ADHD.

As shown in tables 3 and 4, in general, the qualitative and quantitative analyses did not tend to highlight the same regions of the genome, which might suggest (as discussed above) the presence of some QTLs whose effects are only relevant within an ADHD population. An alternative interpretation could be that the quantitative phenotype is more closely related to the HI dimension, since most of the variability in D4-TOT reflects variability in HI symptoms (see the "Subjects and Methods" section), whereas the qualitative classifications represent overall risk. However, phenotypic studies of these ASP families suggest that familial variance unique to the HI domain is likely to be small (Smalley et al. 2000). Given associated problems of multiple testing and sample size constraints, we did not divide our data set into subtypes or analyze independent dimensions for linkage, so these issues await clarification in a larger set of families. It is also probable that a number of chromosomal regions implicated by either qualitative or quantitative analyses may be false positives. Notably, the strongest linkage with the DSM-IV total symptom count measure, on 12p13, did show reasonable concordance with the qualitative analyses. Specifically, this region of 12p13 was also implicated by MLS methods, with a single-point LOD score >1 (table 3) and a multipoint peak of 0.79 (fig. 1 and table 4) for the narrow diagnostic scheme. Again, additional experiments in larger samples may

Table 6

Exclusion Mapping of Regions Containing Candidate Genes in ADHD ASPs

Chromosome	Gene		Most Likely Cytogenetic Location	Markers[a]	Exclusion LOD under Scheme[b]						Excluded under Scheme[c]	
					Narrow			Broad				
	Symbol	Name			$\lambda_s = 2$	$\lambda_s = 2.5$	$\lambda_s = 3$	$\lambda_s = 2$	$\lambda_s = 2.5$	$\lambda_s = 3$	Narrow	Broad
1	HTR6	Serotonin receptor 6	1p36.13	D1S199–D1S234	−2.42	−3.77	−5.02	−1.99	−3.33	−4.51	X	
	HTR1D	Serotonin receptor 1D	1p36.12	D1S199–D1S234	−2.42	−3.77	−5.02	−1.99	−3.33	−4.51	X	
2	HTR2B	Serotonin receptor 2B	2q37.1	D2S396–D2S206	−2.03	−3.29	−4.38	−1.50	−2.70	−3.78	X	
3	HTR1F	Serotonin receptor 1F	3p11.1	D3S3681–D3S1271	−3.76	−5.45	−6.86	−3.94	−5.74	−7.25	X	X
	DRD3	Dopamine receptor D3	3q13.31	D3S1271–D3S1278	−2.90	−4.21	−5.32	−2.94	−4.36	−5.56	X	X
4	DRD5	Dopamine receptor D5	4p16.1	D4S2935–D4S403	.63	.08	−.50	−.78	−1.59	−2.30		
	TDO2	Tryptophan 2,3-dioxygenase	4q32.1	D4S424–D4S413	−4.65	−6.45	−7.92	−4.89	−6.87	−8.49	X	X
5	SLC6A3 (DAT1)	Sodium-dependent dopamine transporter	5p15.33	5pter–D5S1981	−4.42	−6.04	−7.34	−5.53	−7.52	−9.13	X	X
	HTR1A	Serotonin receptor 1A	5q12.3	D5S407–D5S647	−1.49	−2.72	−3.79	−1.82	−3.17	−4.35		
	HTR4	Serotonin receptor 4	5q33.1	D5S436–D5S410	−4.88	−6.76	−8.30	−5.32	−7.40	−9.11	X	X
	DRD1	Dopamine receptor D1	5q35.2	D5S400–D5S408	−2.37	−3.25	−3.94	−2.73	−3.76	−4.58	X	X
6	HTR1B	Serotonin receptor 1B	6q14.1	D6S257–D6S460	−.57	−1.48	−2.32	−1.34	−2.53	−3.62		
	HTR1E	Serotonin receptor 1E	6q15	D6S460–D6S462	−.56	−1.41	−2.17	−1.36	−2.51	−3.55		
	STX7	Syntaxin (vesicle receptor) 7	6q23.1−2	D6S262–D6S292	−3.46	−5.01	−6.34	−3.08	−4.68	−6.07	X	X
	STX11	Syntaxin 11	6q24.3	D6S308–D6S441	−3.57	−5.06	−6.29	−3.53	−5.12	−6.42	X	X
7	DDC	Dopa decarboxylase	7p12.2−3	D7S519–D7S502	−3.63	−5.15	−6.41	−3.99	−5.68	−7.09	X	X
	HTR5A	Serotonin receptor 5A	7q36.3	D7S798–D7S550	−1.29	−2.37	−3.32	−2.40	−3.85	−5.11		X
8	SLC18A1	Vesicular monoamine transporter	8p21.3	D8S261–D8S258	−3.03	−4.62	−6.01	−3.51	−5.28	−6.82	X	X
9	DBH	Dopamine beta-hydroxylase	9q34.2	D9S164–D9S1826	−3.37	−4.77	−5.90	−4.62	−6.35	−7.73	X	X
10	HTR7	Serotonin receptor 7	10q23.32	D10S1686–D10S185	−1.10	−2.00	−2.78	−2.12	−3.35	−4.42		X
	CALCYON	DRD1 interacting protein	10q26.3	D10S212−10qter	1.01	.47	−.11	1.23	.61	−.07		
11	DRD4	Dopamine receptor D4	11p15.5	11pter–D11S4046	−3.20	−4.81	−6.22	−3.27	−4.98	−6.47	X	X
	TPH	Tryptophan hydroxylase	11p15.1	D11S902–D11S904	−1.32	−2.09	−2.74	−2.18	−3.29	−4.21		X
	DRD2	Dopamine receptor D2	11q23.1	D11S898–D11S908	−2.88	−4.35	−5.61	−3.16	−4.91	−6.38	X	X
	HTR3A and HTR3B	Serotonin receptors 3A and 3B	11q23.2	D11S898–D11S908	−2.88	−4.35	−5.61	−3.16	−4.91	−6.38	X	X
13	HTR2A	Serotonin receptor 2A	13q14.2	D13S263–D13S153	−3.47	−4.97	−6.23	−3.21	−4.70	−5.98	X	X
15	SNAP23	23-kD synaptosomal-associated protein	15q15.2	D15S994–D15S978	−2.42	−3.65	−4.71	−2.53	−3.88	−5.05	X	X
17	SLC6A4 (5HTT)	Sodium-dependent serotonin transporter	17q11.2	D17S1857–D17S798	.13	−.47	−1.05	.58	.01	−.56		
20	SNAP25	25-kD synaptosomal-associated protein	20p12.3	D20S115–D20S186	−1.59	−2.57	−3.40	−1.92	−3.01	−3.94		
	STX16	Syntaxin 16	20q13.31	D20S100–D20S171	−2.97	−4.26	−5.33	−3.26	−4.76	−6.01	X	X
22	COMT	Catechol-o-methyltransferase	22q11.21	D22S420–D22S539	−2.05	−3.12	−4.03	−3.07	−4.44	−5.59	X	X
	SNAP29	29-kD synaptosomal-associated protein	22q11.21	D22S420–D22S539	−2.05	−3.12	−4.03	−3.07	−4.44	−5.59	X	X
X	MAOA and MAOB	Monoamine oxidases A and B	Xp11.3	DXS6810–GATA149D04	−6.90	−10.07	−12.76	−7.65	−11.23	−14.29	X	X
	HTR2C	Serotonin receptor 2C	Xq23-24	GATA172D05–GATA165B12	−4.87	−7.15	−9.04	−5.37	−7.99	−10.18	X	X

[a] Genome-scan markers flanking the gene, as determined from draft genome sequence data.
[b] Highest exclusion LOD scores are given for the interval containing each gene.
[c] X indicates that the interval can be fully excluded from containing a locus of $\lambda_s \geq 2$.

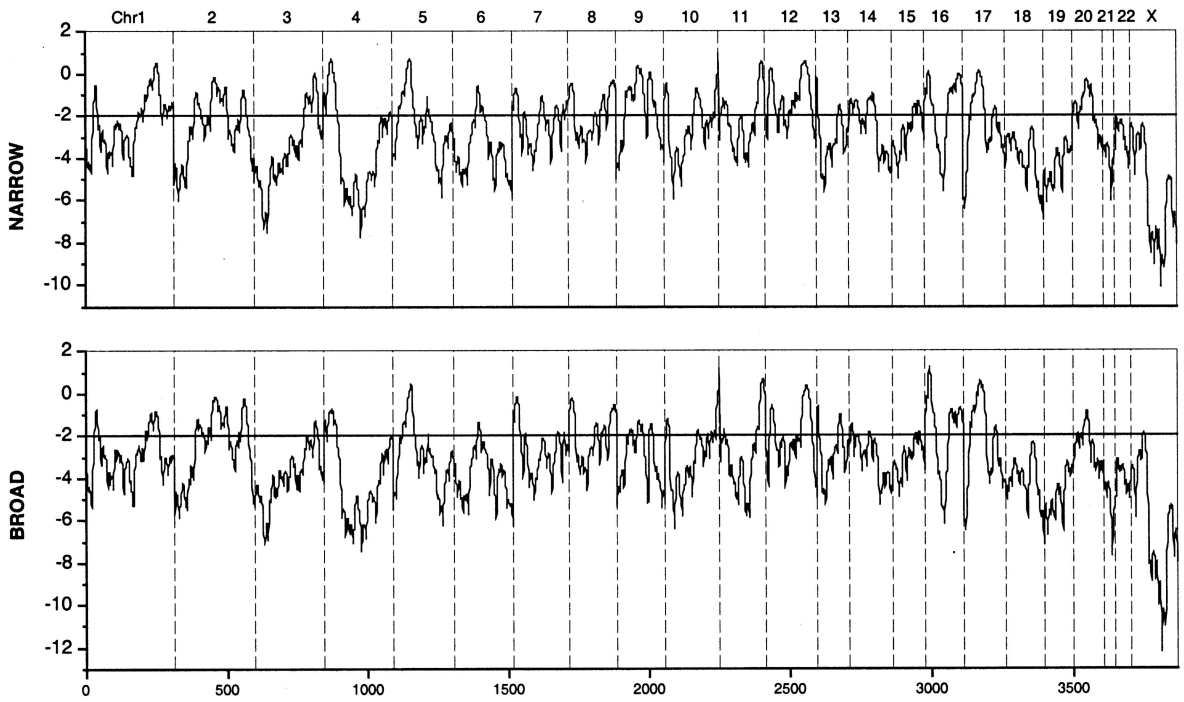

Figure 2 Exclusion mapping of the whole genome in ADHD ASPs for a λ_s of 2. LOD score plots are shown under narrow and broad diagnostic schemes. Regions are excluded if they produce a LOD of <-2. See tables 5 and 6 for more details. Cumulative distance in Haldane centimorgans is displayed along the bottom, with chromosome numbers at the top.

address whether this 12p13 QTL does indeed represent a general risk factor for ADHD.

Given that a significant proportion of ADHD cases also manifest some form of learning disability (Cantwell 1996; Brown et al. 2001), it is worth assessing the overlap between loci implicated here and linkages suggested by studies of other childhood disorders, such as dyslexia, speech and language impairments, and autistic disorder. It has been suggested that the observed comorbidity may reflect common genetic influences (Willcutt et al. 2000). In our sample of 126 ASPs, we did not find evidence for linkage of ADHD to the principle loci that have been implicated in dyslexia (2p12-16, 6p21, 15q21, or 18p11) (Fisher and Smith 2001; Fisher et al. 2002) or speech and language disorders (7q31, 16q24, or 19q13) (Fisher et al. 1998; Lai et al. 2001; SLI Consortium 2002). However, although autism was a criterion for exclusion from the present ASP sample, we found that two of the regions identified in our ADHD genome screen were concordant with two of the strongest linkage peaks from genomewide analyses of autistic sib pairs (IMGSAC 2001). The 2q24 locus that yielded a LOD of 1.00 in single-point MLS analysis is within 10 cM of the most significant linkage from the IMGSAC screen, which gave an MLS of 4.8 in strictly diagnosed autistic pairs (IMGSAC 2001). The 16p13 locus that gave a multipoint MLS of >1.5 in our ADHD sample is within ~1 cM of the third-highest linkage from the IMGSAC study (IMGSAC 2001). Finally, it is perhaps of interest to note that one linkage peak at 11q25 is within ~20 cM of a region in 11q23-24 that has been implicated in Gilles de la Tourette syndrome (Merette et al. 2000; Simonic et al. 2001).

In conclusion, the present study has provided, for the first time, a systematic overview of the entire genome with respect to susceptibility to ADHD. There is unlikely to be a single major-gene effect in this disorder, but it is hoped that future analyses in larger samples, building on the initial data reported here, may eventually lead to the identification of allelic variants at a number of risk loci. An increased understanding of the genetic basis of ADHD will ultimately lead to improvements in diagnoses and treatment.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Cooperative Human Linkage Centre, http://lpg.nci.nih.gov/ABI/index.html
Genehunter, http://www.fhcrc.org/labs/kruglyak/Downloads/
Généthon, 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 [MIM 143465])
Research Genetics, ftp://ftp.resgen.com/pub/mappairs/humanset/

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