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# Report

# Attention Deficit Hyperactivity Disorder: Fine Mapping Supports Linkage to 5p13, 6q12, 16p13, and 17p11

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We completed fine mapping of nine positional candidate regions for attention-deficit/hyperactivity disorder (ADHD) in an extended population sample of 308 affected sibling pairs (ASPs), constituting the largest linkage sample of families with ADHD published to date. The candidate chromosomal regions were selected from all three published genomewide scans for ADHD, and fine mapping was done to comprehensively validate these positional candidate regions in our sample. Multipoint maximum LOD score (MLS) analysis yielded significant evidence of linkage on 6q12 (MLS 3.30; empiric $P = .024$) and 17p11 (MLS 3.63; empiric $P = .015$), as well as suggestive evidence on 5p13 (MLS 2.55; empiric $P = .091$). In conjunction with the previously reported significant linkage on the basis of fine mapping 16p13 in the same sample as this report, the analyses presented here indicate that four chromosomal regions—5p13, 6q12, 16p13, and 17p11—are likely to harbor susceptibility genes for ADHD. The refinement of linkage within each of these regions lays the foundation for subsequent investigations using association methods to detect risk genes of moderate effect size.

Attention-deficit/hyperactivity disorder (ADHD [MIM 143465]) is one of the most commonly diagnosed neurobehavioral disorders of childhood, affecting ~5%–7% of children and ~3% of adults (Wolraich et al. 1996; McCracken 1998; Swanson et al. 1998). ADHD is defined as the childhood onset of multiple symptoms of inattention and/or hyperactivity-impulsivity leading to significant impairment in at least two settings (American Psychiatric Association 1994). Heritability estimates in the range of 60%–90% (Levy et al. 1997; Faraone and Doyle 2001), sibling relative risk estimates ($\lambda_s$) in the range of 4–8 (Smalley 1997; Faraone et al. 2000), and consistent prevalence rates across diverse regions of the world (Anderson et al. 1987; Gomez et al. 1999; Tahir et al. 2000; Wilens et al. 2002) suggest a strong genetic

etiology.

The vast majority of molecular genetic studies of ADHD have been predicated on the detection of association between ADHD and the allelic variants of functional candidates. The selection of functional candidates has relied on assumptions about the molecular mechanisms underlying ADHD and has been generally constrained to the most obvious genes integral to the dopaminergic, serotonergic, and adrenergic pathways. This approach is fundamentally limited by our current understanding of the pathways involved in this disorder, as well as the molecular components of a given pathway. Although positive associations with polymorphisms near or within the dopamine transporter gene (*DAT-1*), dopamine receptor D4 gene (*DRD4*), and dopamine receptor D5 gene (*DRD5*) have been reproduced in independent studies, failures to replicate these results in adequately sized populations are also evident (Palmer et al. 1999; Holmes et al. 2000), and the purported effect sizes are small (Cook et al. 1995; LaHoste et al. 1996; Gill et al. 1997; Smalley et al. 1998; Daly et al. 1999; McCracken et al. 2000; Faraone et al. 2001; Mill et al. 2001; Lowe et al. 2004). Other candidate genes have

been the subject of fewer investigations, and both positive and negative findings are reported (Barr et al. 2000; Brophy et al. 2002; Kustanovich et al. 2003).

Although the pooling of resources within the ADHD-genetics community may improve the power to detect subtle associations, the effect of such alleles is proving to be small (Lowe et al. 2004). Genomewide linkage methods provide a complementary and powerful approach to candidate-gene studies, because they do not rely on prior knowledge of the molecular etiology, and novel genes may be identified through positional cloning. Three genomewide linkage scans of ADHD have been published to date with the use of affected sibling pair (ASP) sampling (Fisher et al. 2002; Bakker et al. 2003; Ogdie et al. 2003). The first genomewide scan was conducted on 126 ASPs (Fisher et al. 2002) and identified four nominal regions (5p12, 10q26, 12q23, and 16p13) with multipoint maximum LOD scores (MLSs) >1.5, but none exceeded recommended thresholds for suggestive or significant linkage. A second genomewide scan in an independent set of 101 families was pooled with this initial group of 126 ASPs (270 ASPs total), and six chromosomal regions were identified with MLS values >1 (5p13, 6q14, 11q25, 16p13, 17p11, and 20q13), with one region exceeding suggestive evidence of linkage (17p11; MLS 2.98) (Ogdie et al. 2003). An independent team of investigators (Bakker et al. 2003) completed a genomewide scan of 164 Dutch ASPs with ADHD and presented evidence for four strong-candidate chromosomal locations (7p13, 9q33, 13q33, and 15q15), with overlap of only one nominally significant region (5p13) across the scans.

Fine mapping of the 16p13 region highlighted in our genomewide scans was completed and described elsewhere in an extended sample, and results of that analysis demonstrated genomewide significance under both theoretical and empirical criteria (MLS 3.73; empiric $P = .01$) (Ogdie et al. 2003; Smalley et al. 2002). In this report, we describe fine mapping of nine additional regions in an extended sample of 308 ASPs. The nine regions included five selected on the basis of our genomewide linkage analyses (5p13, 6q12/6q14, 11q25, 17p11, and 20q13) and the four strongest regions identified in the Dutch sample (7p13, 9q33, 13q33, and 15q15) (Bakker et al. 2003).

The sample of 308 ASPs with ADHD is derived from 226 multiplex families (194 two-sib families, 26 three-sib families, and 6 four-sib families), containing a total of 490 affected children and 308 ASPs (all possible pairs). The current sample contains 269 of the 270 ASPs reported in the previous genomewide scans (Fisher et al. 2002; Ogdie et al. 2003) and an independent set of 39 ASPs. Parents of all ASPs were genotyped, with both parents available for 289 (94%) ASPs and one parent available for 19 (6%) ASPs. The affected individuals in the sample are 73% male, 78% white, and fairly representative of the subtype proportions evident in epidemiological studies of ADHD (49% combined, 44% inattentive, and 7% hyperactive-impulsive) (Wolraich et al. 1996). ADHD was diagnosed in accordance with DSM-IV criteria, by use of a best-estimate procedure (American Psychiatric Association 1994). A definite ADHD diagnosis was made for 95% of the ASP members, whereas a probable ADHD diagnosis (i.e., the individual showed one less symptom than the diagnosis requirement but met criteria of impairment and age at onset) was made in 5% of the sample. All ASPs have at least one member with a definite diagnosis. Details of the sample characteristics are published elsewhere (Smalley et al. 2000). Expected psychiatric comorbidity is present in the sample and includes oppositional-defiant disorder (46%), conduct disorder (11%), mood disorders (major depression, dysthymia, and bipolar disorder) (17%), and anxiety disorders (8%). Although five of the ASP members had a comorbid diagnosis of bipolar disorder, none came from the same family. We tested the impact these cases might have had on the MLS results by removing them from the data set and rerunning the MLS analysis. There were no significant changes in the MLS values for any of the chromosomes of interest in the sample from which the five cases were excluded.

The nine chromosomal regions selected for fine mapping (table 1) were defined by the 1-LOD support intervals of the linkage peaks presented in the genomewide scans. For the five candidate regions identified in our sample (5p13, 6q14, 11q25, 17p11, and 20q13), we selected microsatellite markers to create an ∼2-cM grid across the 1-LOD support intervals (12–19 markers per region). For the four candidate regions identified in the Dutch cohort, we selected microsatellite markers to create an ∼3-cM grid across the 1-LOD support intervals (8–10 markers per region). The genetic positions of all markers were initially determined using the deCODE high-resolution map (Kong et al. 2002) and Marshfield (Center for Medical Genetics) genetic maps and were validated by mapping procedures within our own data set by use of ASPEX v. 2.3 sib_map (Hinds and Risch 1996). In addition, the physical-mapping positions and order of all markers were verified with both the University of California–Santa Cruz (UCSC) genome database build hg16 and the National Center for Biotechnology Information (NCBI) build 34. Genotyping was performed in accordance with standard procedures (Ogdie et al. 2003). Mendelian inheritance errors were identified and removed using GAS 2.0 (A. Young, Oxford University), and improbable genotypes, as determined by the presence of unlikely recombination events, were identified and removed using Simwalk2 (Sobel and Lange 1996).

Multipoint MLS analysis (Risch 1990) was conducted

**Table 1**

**Multipoint MLS Values in Chromosomal Regions of Fine Mapping**

| | | LOCATION | | | P | |
| | | | Genetic[c] | | | |
| CHROMOSOME | MARKER[a] | Cytogenetic[b] | (cM) | MLS | Nominal[d] | Empiric[e] |
|---|---|---|---|---|---|---|
| 5 | D5S418 | 5p13 | 59 | 2.55 | .00058 | .091 |
| 6 | D6S430 | 6q12 | 83 | 3.30 | .000098 | .024 |
| 7 | D7S1818 | 7p13 | 69 | .00 | .60 | 1.000 |
| 9 | D9S1825 | 9q33 | 136 | .00 | .60 | 1.000 |
| 11 | D11S4126 | 11q25 | 173 | 1.00 | .026 | .931 |
| 13 | D13S796 | 13q33 | 94 | .84 | .039 | .972 |
| 15 | D15S146 | 15q15 | 35 | .28 | .18 | 1.000 |
| 16[f] | D16S3114 | 16p13 | 23 | 3.73 | .000035 | .012 |
| 17 | D17S947 | 17p11 | 38 | 3.63 | .000045 | .015 |
| 20 | D20S1106 | 20q13 | 101 | 1.09 | .020 | .871 |

[a] Marker nearest to the center of the 1-LOD support interval.

[b] Approximate cytogenetic position, as determined by physical mapping of markers under a 1-LOD support interval.

[c] The approximate Marshfield genetic position of the center of the 1-LOD support interval. For the four Utrecht regions presenting MLSs <1 (7p, 9q, 13q, and 15q), the listed genetic position was determined by the center of the fine-mapping marker panel.

[d] LOD scores were converted into nominal pointwise P values: $P(LOD) = .5 \times (\chi_1^2 > 2 \ln 10 \times LOD) + .098 \times (\chi_2^2 > 2 \ln 10 \times LOD)$ (Nyholt 2000).

[e] Approximate empiric P values were determined from 1,000 replicates of the genomewide data set under the null hypothesis at an artificially high density of one marker every 2 cM across the genome. Calculated as $(x + 1)/(n + 1)$, where $x$ is the number of independent regions of linkage presenting an MLS greater than or equal to the threshold and $n$ is the number of replicates. For peaks yielding MLS values that occurred more frequently than once per replicate, the P value was calculated as $(r + 1)/(n + 1)$, where $r$ is the number of replicates yielding an MLS greater than or equal to the threshold (7p, 9q, 11q, 13q, 15q, and 20q).

[f] Data for 16p13 was published elsewhere by Ogdie et al. (2003) and is presented here for reference.

by ASPEX sib_ibd v. 2.3 (Hinds and Risch 1996), under the multiplicative model with parameters restricted to the possible triangle (Holmans 1993). MLSs were calculated at 1-cM increments, with all possible pairs treated as independent. Single-point MLS analysis was performed by Genehunter v. 2.1 with the use of Mapmaker/Sibs commands (Kruglyak and Lander 1995; see Kruglyak Laboratory and Mapmaker/Sibs Web sites). ASPEX sib_ibd uses only fully informative transmissions, whereas single-point MLS analysis in Genehunter uses all inheritance information for the reconstruction of missing parental genotypes and for the determination of identity-by-descent (IBD) and thus maximizes the number of ASPs contributing to a single-point MLS. MLS values were converted to pointwise P values by the derivation for MLS calculated under the possible triangle: $P(LOD) = .5 \times (\chi_1^2 > 2 \ln 10 \times LOD) + .098 \times (\chi_2^2 > 2 \ln 10 \times LOD)$ (Holmans 1993; Nyholt 2000). In accordance with convention, we have defined the nominal threshold as a pointwise P value <.05. To estimate empiric P values, simulations were performed using the unique parameters of the current data set, including marker parameters, pedigree structure, and missing genotypes. The purpose of the current simulations is to

estimate a threshold of significance that accounts for genomewide sampling (i.e., an MLS equivalent to P = .05 or an event likely to randomly occur once in 20 genomewide scans) and to estimate how often one would encounter an independent region of linkage with an MLS exceeding a particular level in a genomewide scan. Theoretically derived thresholds of significance do not account for missing data points, uninformative markers, or the variable density of markers employed in linkage studies. A total of 1,000 replicates of the genomewide data were generated under the null hypothesis of no linkage, by use of Simulate 2.4 (Terwilliger et al. 1993), and were analyzed by the same procedures as the actual data set. Simulate 2.4 distributes alleles among the founders of each pedigree on the basis of the allele frequencies present in the real data set, creates recombination events on the basis of the probabilities defined by the marker maps, and randomly transmits chromosomes to progeny. We generated replicates of the data set at an artificially high genomewide density of one marker every 2 cM, accounting for the assumption that fine mapping within this sample will continue in the future. The empiric P values presented in this study are intended to estimate the likelihood of observing a given MLS value in a 2-

cM genomewide scan performed in a sample of 308 ASPs without linkage to a disease.

Multipoint MLS analysis yielded significant evidence of linkage for the regions on 6q12-6q14 (MLS 3.30; empiric $P = .024$) and 17p11 (MLS 3.63; empiric $P = .015$) (table 1 and fig. 1). Region 5p13, the only region presenting evidence of linkage in both our sample and the Dutch sample, yielded suggestive evidence (MLS 2.55; empiric $P = .091$). Evidence of linkage to 11q25 (MLS 1.00; empiric $P = .931$) and 20q13 (MLS 1.09; empiric $P = .871$) remained below the suggestive threshold and did not increase above that of the 10-cM data set. Region 13q33 yielded evidence of linkage above the nominal threshold (MLS 0.84; pointwise $P = .039$; empiric $P = .972$), whereas analysis of the other three regions identified by Bakker et al. (2003) failed to yield even nominal evidence of linkage in our sample and did not vary appreciably from the evidence provided by our 10-cM data set, indicating that the 10-cM genomewide scan provided an accurate estimate of IBD sharing in these unlinked regions (table 1 and fig. 1). To assess the evidence of linkage present in the independent set of 39 ASPs—included in the current study and absent from the previously reported genomewide scans—we performed a separate multipoint MLS analysis of this independent set. Although the sample of 39 independent ASPs is not large enough to demonstrate statistical significance comparable to the samples described in the genomewide scans (Fisher et al. 2002; Ogdie et al. 2003), the trend of excess sharing continues, and evidence of linkage is present: 5p13 (sharing 63.55%, MLS 0.22), 6q12 (sharing 70.09%, MLS 1.27), and 17p11 (sharing 59.79%, MLS 0.18). Thus, the increased evidence of linkage is the result of both greater marker density and the expansion of the sample size. Results from single-point MLS analyses were highly consistent with multipoint findings (table 2). Of note, in fine-mapping regions on chromosomes 5, 6, and 17, several markers yielded MLSs >1 under each peak (three markers in 5p13, seven markers in 6q12, and nine markers in 17p11).

The MLS analysis presented here, in conjunction with previously published work (Smalley et al. 2002), strongly supports four chromosomal regions (5p13, 6q12, 16p13, and 17p11) as likely candidate locations of susceptibility loci for ADHD. The 5p13 region is highlighted, despite not reaching genomewide significance, because of the overlap of this region with that presented by the independent scan in the sample of Dutch ASPs (MLS 1.43) (Bakker et al. 2003). The estimated IBD sharing parameters for all four regions indicate loci of moderate effect size, with $\lambda_s$ in the range of 1.4–1.6, under a multiplicative model with a recombination fraction of zero ($\theta = 0$) (Risch 1990). The current analysis eliminates the possibility that our failure to detect linkage in the four major regions identified in the Dutch study is

the result of poor coverage. The present study does not address the lack of linkage detected in the Dutch sample for 6q12, 16p13, and 17p11. To assess the likelihood of observing three linkage peaks above the threshold of significance, we assumed a Poisson distribution (Lander and Kruglyak 1995; Wiltshire et al. 2002) and derived a posterior probability of this event under the null hypothesis. The cumulative Poisson distribution indicates that the probability of observing the three significant linkage peaks within this sample is $<2.3 \times 10^{-6}$, strongly suggesting that at least one susceptibility gene is located in one of these three regions (6p12, 16p13, and 17p12).

The region on 5p13 is centered at D5S418 (58 cM, Marshfield; 40 Mb, UCSC hg16), with a 1-LOD support interval spanning ~7 cM (15 Mb) from D5S2105 to D5S1968. Fine mapping of 5p13 resulted in an increase from an MLS of 1.77 to an MLS of 2.55 and significantly narrowed the 1-LOD support interval from ~20 cM to ~7 cM. The region on 6q12-6q14 is centered at D6S430 (81 cM, Marshfield; 67 Mb, UCSC hg16), with a 1-LOD support interval spanning ~18 cM (33 Mb) from D6S465 to D6S1609 and a maximum MLS value on 6q14 (~89 cM, D6S460). The fine-mapping data increased the MLS from 1.75 to 3.30 and reduced the 1-LOD support interval by 12 cM. Note that the gene encoding serotonin receptor 1B (*HTR1B*) is directly under the maximum MLS (89 cM), and the gene encoding serotonin receptor 1E (*HTR1E*) resides just outside of the 1-LOD q-boundary. Elsewhere, Quist et al. (2003) have reported a trend toward excess transmission of a polymorphism in HTR1B in a sample of 115 families with ADHD ($P = .09$). The region on 16p13 is centered at D16S3060 (28 cM, Marshfield; 12 Mb, UCSC hg16), with a 1-LOD support interval spanning ~12 cM (7 Mb) from D16S519 to D16S499, and overlaps a region highlighted in genomewide scans for autism (Smalley et al. 2002). The 1-LOD support interval on 17p11, centered at D17S839 (37 cM, Marshfield; 14 Mb, UCSC hg16) and spanning ~20 cM (25 Mb) across the centromere from D17S947 to D17S798, also overlaps with two genomewide scans in autism (International Molecular Genetic Study of Autism Consortium 2001; Yonan et al. 2003). Fine mapping of this region increased the evidence of linkage from an MLS of 2.98 to an MLS of 3.63 and refined the 1-LOD support interval by 5 cM. The gene encoding serotonin transporter (5-HTT), a commonly cited functional candidate for both ADHD and autism, is located on 17q11 within the q-boundary of the 1-LOD support interval. Manor et al. (2001) reported an association between ADHD and a promoter polymorphism in 5-HTT (5-HTTLPR) in 98 trios ($P = .008$). In addition, Seeger et al. (2001) have reported an association between hyperkinetic disorder and the 5-HTTLPR long variant ($P = .009$). These four regions do not contain the most commonly studied func-
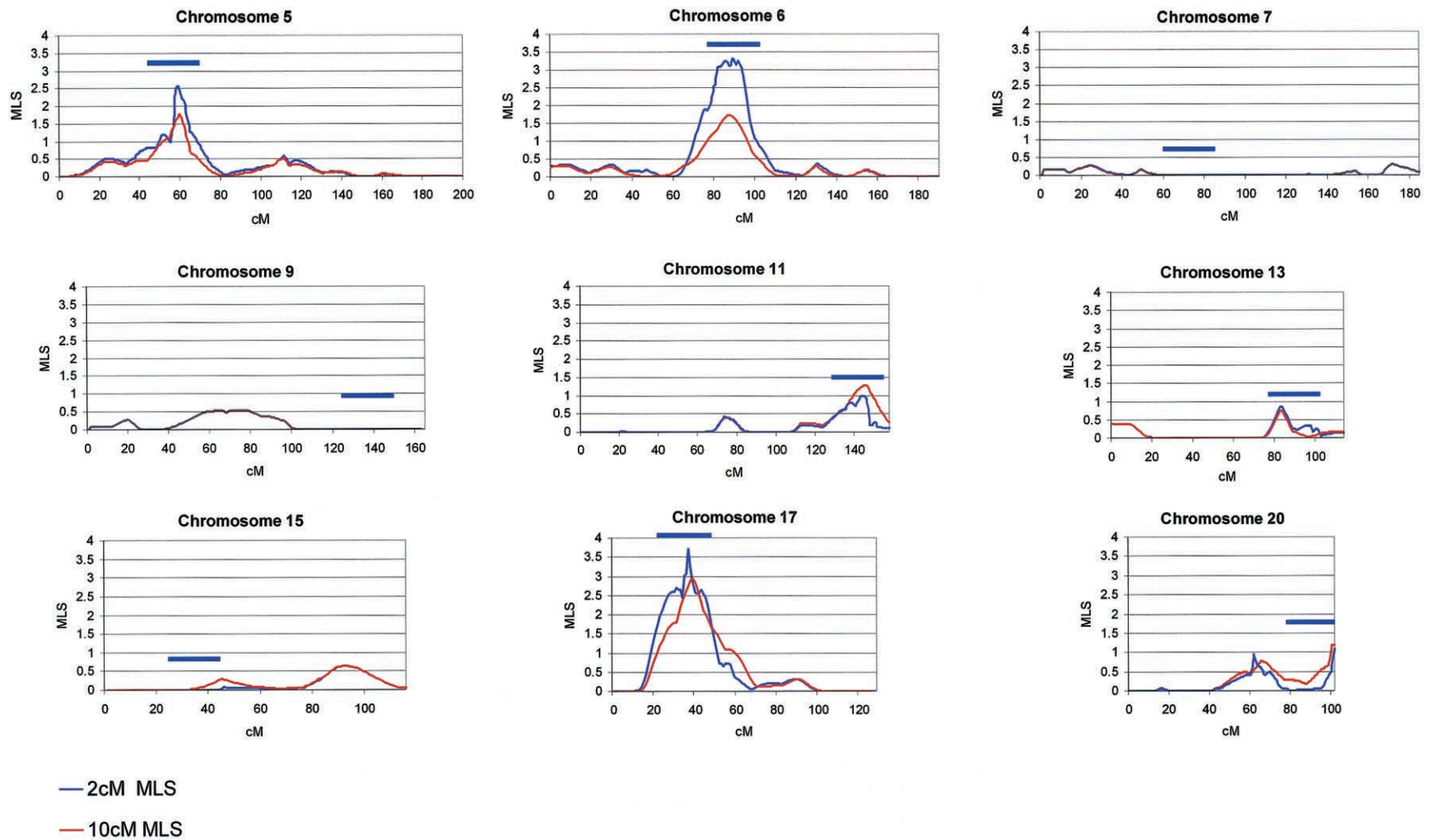
**Figure 1** Multipoint MLS values for nine candidate regions in 308 ASPs with ADHD. The X-axis values are distances from the p-telomere, in Kosambi cM. The MLS values for the 10-cM genomewide scan of 270 ASPs (Ogdie et al. 2003) are shown in red. The fine-mapping values, at ∼ 2-cM marker density in candidate regions, are shown in blue. The blue bar indicates the approximate fine-mapping interval. The identical MLS values for the 2-cM and 10-cM analyses for chromosomes 7 and 9 and a large portion of chromosome 15 give the appearance of a single line. MLS analysis was performed by ASPEX sib_ibd, under the possible triangle.

**Table 2**

**Markers Yielding Single-Point MLS >1 in Fine-Mapping Regions**

| CHROMOSOME AND MARKER | LOCATION | | HETEROZYGOSITY[a] (%) | MLS | NOMINAL $P$[b] |
| | Cytogenetic[c] | Genetic[d] (cM) | | | |
|---|---|---|---|---|---|
| 5: | | | | | |
| D5S418 | 5p13 | 58.6 | 80 | 3.24 | .00011 |
| D5S1958 | 5p12 | 59.9 | 58 | 1.24 | .014 |
| D5S1968 | 5q11 | 60.9 | 77 | 1.26 | .013 |
| 6: | | | | | |
| D6S465 | 6p12 | 74.3 | 75 | 2.46 | .00072 |
| D6S1960 | 6p12 | 76.6 | 74 | 1.05 | .022 |
| D6S257 | 6p12 | 79.9 | 87 | 1.83 | .0033 |
| D6S430 | 6q12 | 81.5 | 83 | 1.72 | .0043 |
| D6S1557 | 6q13 | 82.6 | 76 | 1.97 | .0023 |
| D6S460 | 6q14 | 89.8 | 81 | 1.06 | .022 |
| D6S1609 | 6q14 | 92.3 | 80 | 1.50 | .0074 |
| 11: | | | | | |
| D11S4126 | 11q25 | 138.6 | 54 | 1.19 | .016 |
| 16[e]: | | | | | |
| D16S3114 | 16p13 | 23.3 | 79 | 1.74 | .0041 |
| D16S3060 | 16p13 | 28.3 | 81 | 1.42 | .0090 |
| 17: | | | | | |
| D17S947 | 17p12 | 32.0 | 76 | 1.72 | .0043 |
| D17S799 | 17p12 | 32.1[f] | 90 | 1.54 | .0067 |
| D17S1856 | 17p12 | 35.6 | 81 | 2.51 | .00064 |
| D17S839 | 17p11 | 37.8 | 64 | 1.84 | .0032 |
| D17S953 | 17p11 | 43.0 | 68 | 1.23 | .014 |
| D17S1857 | 17p11 | 43.1[f] | 71 | 2.06 | .0019 |
| D17S2196 | 17p11 | 44.6 | 84 | 1.70 | .0045 |
| D17S1824 | 17q11 | 49.7 | 82 | 1.35 | .011 |
| D17S798 | 17q11 | 53.4 | 74 | 1.41 | .0092 |
| 20: | | | | | |
| D20S1106 | 20q13 | 101.2[f] | 71 | 2.11 | .0017 |

[a] Heterozygosity calculated from the entire study sample.

[b] LOD scores were converted into nominal pointwise $P$ values: $P(\text{LOD}) = .5 \times (\chi_1^2 > 2\ln 10 \times \text{LOD}) + .098 \times (\chi_2^2 > 2\ln 10 \times \text{LOD})$ (Nyholt 2000).

[c] Approximate cytogenetic position, as determined by physical mapping of markers under 1-LOD support interval.

[d] The approximate Marshfield genetic position of the marker.

[e] Data for 16p13 was published elsewhere by Ogdie et al. (2003), and we have presented two markers here for reference.

[f] The genetic position was estimated from physical-mapping position and/or deCODE.

tional candidate genes, highlighting the importance of genomewide linkage strategies for complex traits.

In conclusion, we have defined three genomic regions yielding empirically significant linkage to ADHD (6q12, 16p13, and 17p11) and a fourth region yielding suggestive evidence (5p13). Association studies (e.g., with the use of high-density–SNP data) constitute a viable and realistic strategy for the identification of causal polymorphisms in these regions. From the predicted $\lambda_s$ values (1.4–1.6) observed in our fine-mapping studies, the genotype relative risks are estimated to be >3 (Risch and Merikangas 1996), indicating that a sample of 170 trios would provide adequate power for the detection of common effect alleles. Replication of linkage in these regions in an independent sample would provide an important

validation. Thus, ongoing collection of ADHD samples is critical for the replication of both linkage and association, given the genetic heterogeneity demonstrated by the discordance of linkage studies and the small population–attributable risks found for previously associated polymorphisms. Finally, the refinement of phenotypes and trait measures more closely reflecting the true biological underpinnings may greatly facilitate efforts to identify susceptibility genes for ADHD.

## Acknowledgments

## Electronic-Database Information

The URLs for data presented herein are as follows:

ASPEX Linkage Analysis Package, http://hpcio.cit.nih.gov/lserver/ASPEX.html

GAS, http://hpcio.cit.nih.gov/lserver/GAS.html (for genotype linkage analysis)

Kruglyak Laboratory, http://www.fhcrc.org/labs/kruglyak/Downloads/ (for Genehunter)

Mapmaker/Sibs software, http://www-genome.wi.mit.edu/ftp/distribution/software/sibs/

Marshfield Clinic Research Foundation (Center for Medical Genetics) http://research.marshfieldclinic.org/genetics/

NCBI, http://www.ncbi.nlm.nih.gov/genome/guide/human/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ADHD)

UCSC Genome Bioinformatics, http://genome.cse.ucsc.edu/

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