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ORIGINAL ARTICLE

A high-density SNP linkage scan with 142 combined subtype ADHD sib pairs identifies linkage regions on chromosomes 9 and 16

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As part of the International Multi-centre ADHD Genetics project we completed an affected sibling pair study of 142 narrowly defined *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition combined type attention deficit hyperactivity disorder (ADHD) proband–sibling pairs. No linkage was observed on the most established ADHD-linked genomic regions of 5p and 17p. We found suggestive linkage signals on chromosomes 9 and 16, respectively, with the highest multipoint nonparametric linkage signal on chromosome 16q23 at 99 cM (log of the odds, LOD = 3.1) overlapping data published from the previous UCLA (University of California, Los Angeles) (LOD > 1, ~95 cM) and Dutch (LOD > 1, ~100 cM) studies. The second highest peak in this study was on chromosome 9q22 at 90 cM (LOD = 2.13); both the previous UCLA and German studies also found some evidence of linkage at almost the same location (UCLA LOD = 1.45 at 93 cM; German LOD = 0.68 at 100 cM). The overlap of these two main peaks with previous findings suggests that loci linked to ADHD may lie within these regions. Meta-analysis or reanalysis of the raw data of all the available ADHD linkage scan data may help to clarify whether these represent true linked loci.
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Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders of childhood, characterized by the early onset of age inappropriate hyperactivity, impulsivity and inattentiveness. Family studies indicate a sibling relative risk (λ_s) around 4–6.[1–3] A recent review of 20 population twin studies from around the world found an average heritability of 76%, suggesting that genetic

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influences play a major role in the etiology of ADHD.[4] Candidate gene studies have so far confirmed associations to genetic variants within or close to the dopamine D4 and D5 receptor genes[5] and identified variants in several other genes that appear to increase the risk of ADHD.[4] The genetic variants identified so far contribute only a small amount to the phenotypic variance explained by genetic factors and the expectation is that further genes will be found that are associated with the disorder.[6]

A major strategy in the search for novel genes that increase the risk for ADHD and other complex disorders is the use of genome-wide linkage scans to identify chromosomal regions containing susceptibility loci. To date five independent ADHD genome-wide linkage studies have been completed. Four of them adopted the affected sib pair strategy with samples from University of California, Los Angeles (UCLA),[7,8] MGH,[9] the Netherlands[10] and Germany.[11] The fifth used extended pedigrees ascertained from a population isolate in Columbia.[12] With the exception of the MGH scan, each study identified novel genomic regions that might harbor ADHD-associated genes. The most significant findings reported on chromosomes 5p and 17p where linkage signals were found in multiple studies.[8,11,12] Although as yet no genes explaining any of the linkage findings have been reported in the published literature, one study suggested that genetic variation of the dopamine transporter gene (*DAT1*) might explain linkage on chromosome 5p.[13]

In the current study we contribute to linkage findings from affected sibling pair studies of ADHD, using a sample of 142 *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) combined subtype ADHD proband–sibling pairs, ascertained by the International Multi-centre ADHD Genetics (IMAGE) project.[1,6] Using a panel of highly informative single nucleotide polymorphisms (SNPs) our main aim was to identify genetic linkage regions using a sample ascertained with a relatively homogeneous phenotype. In light of the background genetic heterogeneity observed within our multi-country sample at 51 ADHD candidate genes,[14] we also performed simulations to investigate the potential impact of locus-specific genetic heterogeneity on the linkage signals observed in this study.

Materials and methods

Sample ascertainment and diagnosis

Families were identified by the IMAGE consortium through clinically diagnosed combined subtype ADHD cases at specialist clinics in eight European countries: Belgium, England, Germany, Ireland, Israel, the Netherlands, Spain and Switzerland. To ensure the genetic homogeneity of the sample only white Caucasians of European ancestry were included based on information on ethnicity going back to grandparents of the affected sibling pairs. Entry criteria for research assessments were (1) a proband with the ADHD combined subtype, (2) availability of one or more siblings of each affected proband and (3) both the probands and siblings aged between 5 and 17 at the time of assessment,[14] both the children and at least one of their biological parents were available for DNA collection. Eligible families were then invited to the research centers or assessed during home assessments by qualified child psychiatrists or trained interviewers using clinical research assessments. Blood or buccal samples were collected for DNA extraction. Exclusion criteria applied to both probands and siblings: (1) IQ < 70, (2) a diagnosis of schizophrenia or autism that might confound the diagnosis of ADHD and (3) neurological disorders such as epilepsy and brain injury, as well as any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD.

Clinical procedures

Parental account of childhood symptom. Parental account of childhood symptom (PACS) is a semi-structured, standardized, investigator-based interview developed as an instrument to provide an objective measure of child behavior.[15–17] A trained interviewer administers PACS with parents, who are asked for detailed descriptions of the child's typical behavior in a range of specified situations. Such situations either by external events (for example, watching television, reading a book or comic, playing alone, playing with friends, going to bed, traveling) or by behaviors are shown (for example, crying, worried talk, tempers, fighting with siblings). Interviewers then make their own ratings on the basis of a formal training and written definitions of the behaviors to be rated, on a four-point scale of severity and frequency in the previous week and previous year. The Hyperactivity subscale is made up of attention span (time spent on a single activity, rated separately for four different kinds of activity), restlessness (moving about during the same activities), fidgetiness (movements of parts of the body during the same activities) and activity level (rated for structured situations such as mealtimes and car journeys), with other subscales covering defiant, emotional and other comorbid disorders including autistic spectrum disorders.

Inter-rater reliability is high with previous estimates of product–moment correlations for pairs of interviewers ranging from 0.92 to 0.95 for 'hyperactivity', 0.89 to 0.95 for 'defiance' and 0.79 to 0.90 for 'emotional problems'.[17] The internal consistency of the scales for behavior was acceptably good: Cronbach's α was 0.89 for 'hyperactivity' and 0.87 for 'defiance'.[15] For this study, all interviewers from each site attended a 5-day PACS training course in the United Kingdom. Each site further nominated a chief investigator who attended annual inter-rater reliability exercises. For sites with more than one interviewer, the chief investigator undertook further inter-rater reliability checks regularly. A mean

κ coefficient across all the sites of 0.88 (range 0.71–1.00) and an average agreement percentage of 96.6% (range 78.6–100) were obtained, indicating a high level of inter-rater agreement. Concurrent validity of PACS diagnosis is confirmed by the bi-serial correlation between PACS diagnosis of combined type ADHD with Conners' teacher N-scale scores (the 18 DSM items for ADHD) of 0.68 and Conners' parent N-scale scores at 0.78.

Rating scales. Rating scales used to quantify ADHD symptoms included the Long Version of Conners' Parent Rating Scale, the Long Version of Conners' Teacher Rating Scale (CTRS-R:L) and parent and teacher versions of the Strengths and Difficulties Questionnaires (SDQ).[18,19] In the analyses presented here only ADHD symptoms derived from the CTRS-R:L were included as part of the diagnostic algorithm for ADHD with parent data derived from the PACS interview (see below). To exclude autism spectrum disorders that might confound the analysis of ADHD, both probands and siblings were screened using the Social Communication Questionnaire (SCQ) in conjunction with the prosocial scale from the SDQ. Individuals falling above thresholds for the SCQ ($\geqslant$15) and SDQ ($\leqslant$4) were further evaluated using the autism spectrum disorder section of the PACS interview. A diagnosis of possible autism or autism spectrum disorder led to exclusion from the study.

DSM-IV diagnoses. All raw data were centralized and stored on a secure database at the MRC Social Genetic Developmental Psychiatry research center in London. A standardized algorithm was applied to PACS to derive each of the 18 DSM-IV ADHD items, providing operational definitions for each behavioral symptom. These were combined with items that scored 2 or 3 from the teacher rated Conners' ADHD subscale, to generate the total number of items from the DSM-IV symptom checklist. Situational pervasiveness was defined as some symptoms occurring within two or more different situations from the PACS interview plus the presence of one or more symptoms scoring 2 or more from the ADHD subscale of the Conners' teacher ratings. In a few cases where teacher Conners data were unavailable, pervasiveness was defined on the basis of PACS data alone.

Sample selection. After pedigree correction using the linkage markers to check for expected family relationships, the final sample in this study consisted of 577 subjects, including 276 ADHD combined subtype cases from 134 nuclear families. With eight families having three affected children, a total of 142 independent sibling pairs with combined subtype ADHD were formed. Table 1 summarizes the clinical characteristics of the sample according to the ascertainment procedure, alongside those from previously published affected sibling pair studies of ADHD. Genotypes were available to maximize identity-by-descent information from both parents in 111 families and from one parent plus an additional unaffected sibling in the remaining 23 families. All the families gave informed consents for interview, DNA and cell line storage at Rutgers University Cell and DNA repository (Piscataway, NJ, USA) and sharing of anonymous clinical and genotype data at the National Institute of Mental Health central depository. Ethical approval for the study was obtained from National Institute of Health registered ethical review boards from each center.

Genotyping and data cleaning

The genotyping service was provided by the Center for Inherited Disease Research (http://www.cidr.jhmi.edu/) using the Illumina BeadArray technology on a BeadLab system. A total of 5873 SNPs from the Illumina Linkage IVB SNP panel were successfully assayed with a reproduction rate of 99.994%. The markers were ordered and placed on the physical map according to Genome Build 35. Interpolated genetic distances from the deCODE genetic map were used to estimate genetic map distances.[20]

Pedigree errors were identified and corrected by testing pairwise subject relationships with the program Relpair.[21] Genotypes causing Mendelian inconsistencies were identified by Pedcheck and removed by a custom script.[22] Hardy–Weinberg equilibrium (HWE) for each marker was calculated using Pedstats and 138 SNP markers with significant departure from HWE ($P \leqslant 0.01$) were dropped from the analysis.[23] Unlikely genotype combinations leading to double recombinations over short genetic distance in a few cases were removed by Merlin.[24]

Linkage analysis

Nonparametric linkage was examined by Merlin using Whittemore and Halpern's S_{all} statistics and Kong and Cox's log of the odds (LOD) score transformation.[24–26] Linkage disequilibrium has been shown between tightly linked markers on the Illumina Linkage IV SNP panels[14] and treating them as independent markers can inflate LOD scores.[27] Merlin overcomes this problem by clustering markers that are in LD and estimating the haplotype frequencies to perform multipoint linkage analysis with the composite markers.[28] We implemented the 'rsq 0.05' constraint which requires a pairwise LD measure of $r^2 < 0.05$ between adjacent markers to create marker clusters; as suggested by a comprehensive simulation study.[29]

Results

Figure 1 illustrates the nonparametric linkage multipoint LOD scores on the autosomes and the X chromosome. Table 2 lists the genomic regions showing at least nominal linkage signals (multipoint LOD > 1.0) and the markers associated with the peak scores. Nominal linkage signals were found on chromosome 2, 11, 14, 21 and the X chromosome. There are two suggestive linkage signals with

Table 1 Clinical features of the IMAGE sample and comparison with other ADHD-affected sibling pair linkage scans

Study	*IMAGE*		*UCLA*		*Germany*		*Netherlands*	
Number of affected siblings	276		438		229		199	
Male (%)	78.6		71.9		72.1		83.9	
White Caucasian (%)	100		80		100		100	
ADHD Subtype	N	*(%)*	N	*(%)*	N	*(%)*	N	*(%)*
Combined	276	100	211	48	158	69	170	85
inattentive	0	0	196	45	61	27	25	13
Hyperactive-impulsive	0	0	31	7	10	4	4	2
Comorbid disorder								
Oppositional defiant disorder	156	57	239	55	55	24	82	41
Conduct disorder	72	26	64	15	8	3	14	7
Mood disorder	41	15	97	22	4	2	15	8
Anxiety disorder	96	35	45	10	18	8	27	14
Age and IQ	*Mean*	*S.d.*	*Mean*	*S.d.*	*Mean*	*S.d.*	*Mean*	*S.d.*
Age	10.6	3.1	11.1	3.6	11.1	—	10	3
IQ	98.3	14.5	105.9	14.2	102.4	—	>80	—

Abbreviations: ADHD, attention deficit hyperactivity disorder; IMAGE, International Multi-centre ADHD Genetics; IQ, intelligence quotient; UCLA, University of California, Los Angeles.

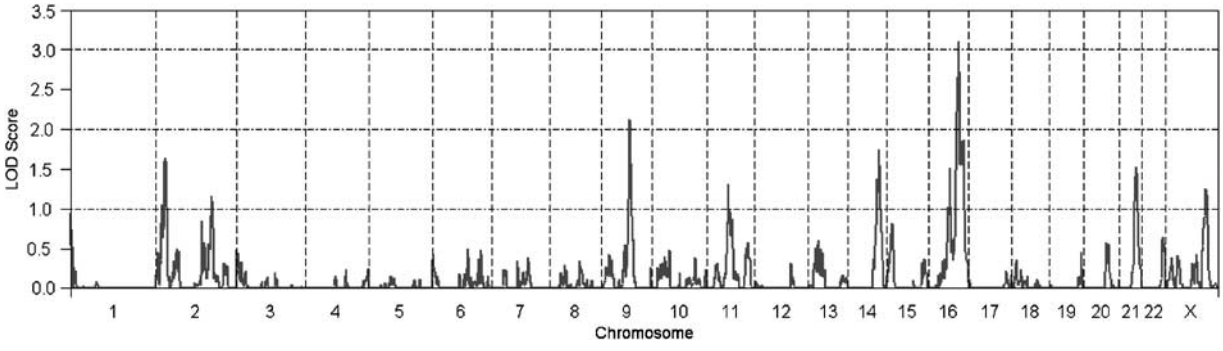

Figure 1 Genome-wide multipoint nonparametric log of the odds (LOD) scores for combined subtype attention deficit hyperactivity disorder (ADHD).

multipoint LOD scores exceeding 2.0 on chromosome 9 (LOD = 2.13; $P = 0.0009$) and chromosome 16 (LOD = 3.1; $P = 0.00008$). Detailed linkage signal profiles at these two regions are shown in Figure 2.

Since the IMAGE project is a multi-country cooperative project, the presence of genetic heterogeneity is a potential concern for molecular genetic studies. If there is locus-specific genetic heterogeneity where the allele frequencies of the linked locus are significantly different between countries, it might be advantageous to test for linkage with a stratified sample based on *a priori* knowledge.[30] Given that we found a certain level of background genetic heterogeneity in the IMAGE sample which was reflected by significant allele frequency differences between the Israeli samples and the rest of the IMAGE samples in our previous investigation of 51 ADHD candidate genes,[13] we repeated the same nonparametric linkage analysis without the 18 Israeli families. As shown in Table 2, the suggestive linkage peak on chromosome 16 increased above the provisional criteria of significant linkage while the peak on chromosome 9 decreased. To examine whether the newly derived LOD scores were statistically different from the original findings, we repeated the nonparametric linkage analysis 10 000 times by randomly dropping 18 families each time. For the chromosome 9 finding, a LOD score less than 1.43 occurred 1561 times, suggesting that the contribution of the Israeli families to this linkage peak was not significantly different from the others. For chromosome 16, a LOD score above 3.82 occurred on

Table 2 Chromosome regions with nonparametric multipoint LOD > 1.0

Chromosome	*Marker*	*Physical position*	*Genetic distance*[a]	*LOD*	*No. of markers*[b]	*S-LOD*[c]
2	rs1510834	13694789	34.5	1.64	8 (7.9)	—
2	rs2033866	174914536	181.5	1.16	3 (0.7)	—
9	rs7043803	88533215	90	2.13	9 (10.2)	1.43
11	rs630759	62933285	69	1.31	6 (2.1)	—
14	rs1361525	94339381	100	1.75	15 (8)	—
16	rs837529	54043795	70.7	1.51	5 (3.2)	—
16	rs424074	77792088	99	3.10	34 (29.6)	3.82
21	rs875060	42817300	61.4	1.53	11 (7.8)	—
X	rs728186	137867027	141.9	1.25	4 (2.6)	—

Abbreviation: LOD, log of the odds.
[a]deCODE genetic map positions.
[b]Number of consecutive SNP markers at the peak with multipoint LOD > 1.0 and (in brackets) the genetic distance they spanned in cM.
[c]Multipoint LOD scores calculated in a stratified sample without the 18 Israeli families. Analysis was restricted to the two suggestive linkage peaks.

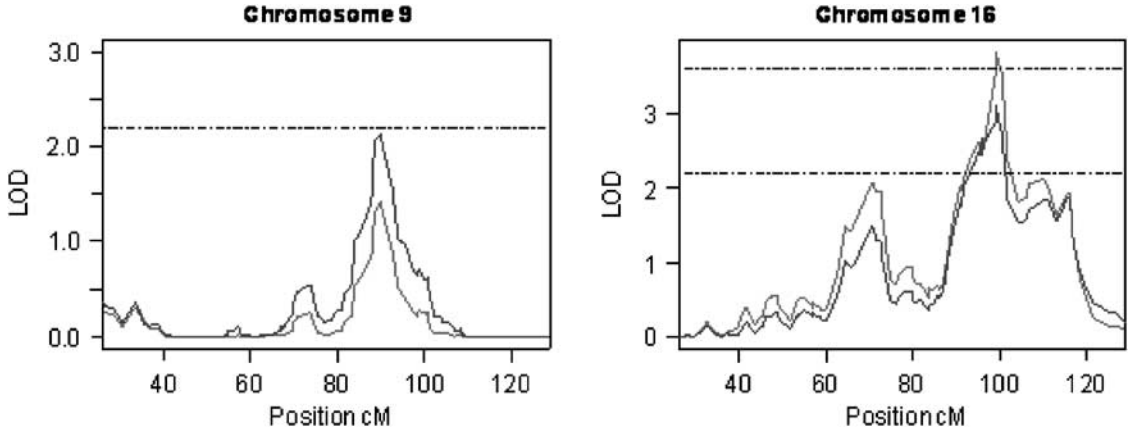

Figure 2 Nonparametric multipoint log of the odds (LOD) scores on chromosomes 9 and 16. Nonparametric multipoint LOD scores on chromosomes 9 and 16 in full sample (blue lines) and stratified sample without 18 Israeli families (red lines). The dash lines are provisional criteria for suggestive (LOD = 2.2) and significant linkage (LOD = 3.6) suggested by Lander and Kruglyak.

348 occasions, suggesting that the contribution of the Israeli families to this linkage peak was significantly lower than the others.

Discussion

In this study we performed a whole-genome linkage scan with 142 combined subtype ADHD sib pairs. By using a state-of-the-art SNP linkage panel, we were able to extract more than 95% of the information content for linkage throughout the genome. Suggestive linkage was found on chromosomes 9 and 16 along with the other nominal linkage signals. Table 3 lists all the linkage evidence observed in the current study and a detailed comparison with the other ADHD linkage scans. To make more accurate comparisons, all the genetic map positions reported in previous studies were transformed into deCODE map position.[20]

Our highest linkage signal of LOD = 3.1 was found on chromosome 16q23. The multipoint nonparametric LOD peaks at 99 cM on the deCODE genetic map in the vicinity of SNP rs424074. It appears to be an entirely different peak from that reported by the UCLA study on chromosome 16p13 at position 34.5 cM on the deCODE map with a LOD score of 3.73.[8] However, both the UCLA sample and the narrow phenotype analysis of the Dutch sample[10] gave nominal linkage signals on 16q ($1.0 < MLS < 1.5$, no details reported) at positions around 95 and 100 cM, respectively. Both of them fall within the LOD-1 interval of the main peak observed in the current study. Furthermore, when the raw data from the UCLA and Dutch samples were pooled in a combined analysis, a slightly higher maximum LOD score (MLS) was obtained in the same genomic region ($1.5 < MLS < 2.0$).[31]

Alongside our main peak there is another weaker linkage peak on chromosome 16q12 with multipoint

Table 3 Comparison of the main findings emerged in this study with previous studies

Chromosome	IMAGE *Location*	*LOD*	*UCLA Location*	*MLS*	*Netherlands Location*	*MLS*	*Germany Location*	*LOD*
2	34.5	1.64	—	—	—	—	—	—
2	181.5	1.16	171	1.00[a]	—	—	—	—
9	90	2.13	93	1.45	132.9	2.05	99.7	0.68
11	69	1.31	72.1	1.17[a]	—	—	—	—
14	100	1.75	—	—	—	—	—	—
16	70.7	1.51	—	—	—	—	—	—
16	99	3.1	≈90 cM	>1.0	≈100 cM	>1.0	—	—
21	61.4	1.53	—	—	—	—	—	—
X	141.9	1.25	—	—	—	—	—	—

Abbreviations: IMAGE, International Multi-centre ADHD Genetics; MLS, maximum LOD score; UCLA, University of California, Los Angeles.
[a]Single-point LOD score.

LOD = 1.51 at 70.7 cM. Although the linkage signal in this region is only nominal, it is worth noting that the noradrenergic neurotransmitter transporter gene (*SLC6A2/NET1*) located at position 75.5 cM. *SLC6A2* has been reported to show association with ADHD in several studies and warrants further investigation.[1,32,33]

We found the second suggestive linkage peak of LOD = 2.13 on chromosome 9q22 at position 90 cM. Both the UCLA and the German studies found some linkage evidence at almost the same location with LOD scores of 1.45 and 0.68, respectively. Although the Dutch study also found suggestive linkage (MLS = 2.05) at the adjacent 9q33 region, the peak position was at 132.9 cM with no overlap of confidence intervals with the linkage signal found in this study.

It is encouraging that both loci identified in our study showed overlap with linkage signals from previous studies. This indicates an increased possibility that one or more genes located in these two regions make a real contribution to the risk for ADHD. Assuming that the two main peaks on chromosomes 16 and 9 are true linked loci, we estimate that they each contribute a genotypic sibling risk (λ_s) of 1.65 and 1.89, respectively to the overall familial risk of ADHD ($\lambda_s = 1/4z_0$, where z_0 is the estimation of sharing 0 allele at the locus).[34]

As shown in Table 3, we were unable to identify any other significant overlap of linkage peaks with the three published affected sibling pair studies and none with the study of Columbian multiplex families. The MGH scan found no significant evidence for linkage across the genome in an affected sibling pair analysis on 217 families (Faraone *et al.*, submitted). Furthermore, no linkage was observed in our study at the most established ADHD-linked genomic regions of 5p and 17p; indeed neither of these two loci was consistently found in previous scans and most other observations were single hits. Overall, there is a general lack of consistency across all the ADHD linkage scans as found in many other psychiatric and common complex disorders. Furthermore, these data suggest that there are unlikely to be genes of moderate to large effect shared across the various populations studied.

One obvious reason for the observed pattern of findings is the complex genetic etiology of ADHD, which likely involves the combination of multiple small additive and interaction effects.[6] The presence of significant clinical and demographical diversity in the studied samples is another potential reason. Factors that might increase heterogeneity between the studies include differences in the populations sampled, although the German and Dutch samples are from closely related northern European populations and the UCLA and MGH samples largely consist of families of European ancestry (~80%). The clinical sample studied here, consisting of 100% combined type cases, is more closely comparable to the Dutch (85%) and the German (69%) than the UCLA (48%) samples; yet both of the top two loci overlap with data from UCLA. It is feasible that our more homogeneous sample of combined type probands might have led to the relatively high LOD scores for these two loci. However, the polygenic nature of ADHD genetics and the stochastic fluctuations originating from modest sample size can be expected to show a certain level of fluctuation of true linkage signals.[35]

A major design feature of the current study is that the analysis was restricted to the DSM-IV combined subtype ADHD diagnosis to reduce the potential genetic heterogeneity caused by clinical heterogeneity. It has been suggested that there may be some difference in the genetic influences acting on the DSM-IV subtypes of ADHD.[36–38] The DSM-IV combined subtype of ADHD has been shown to fall entirely within an empirically derived latent class with a high level of subtype concordance within twin pairs.[39,40] The combined subtype is also the most common presentation of ADHD within child and adolescent psychiatric clinics and is associated with high levels of hyperactive-impulsive, inattentive and comorbid problems.[36] Furthermore, since the whole IMAGE sample were ascertained through DSM-IV combined subtype ADHD probands, there were not as many inattentive or hyperactive subtype children in

the IMAGE sample as in the other nonselected ADHD samples. Therefore, we opted to apply the more stringent diagnosis to achieve more genetic homogeneity in our main report rather than a bigger sample with more confounding possibilities.

To avoid the loss of power associated with multiple testing of different phenotypic definitions, we decided *a priori* to restrict the main test of linkage to the analysis of combined subtype samples alone. To allow for comparison with the previous linkage scans that combined all three of the ADHD subtypes, we repeated the nonparametric linkage analysis with a relaxed criteria to include all ADHD cases, regardless of subtype. In this extended analysis there were 227 families containing the equivalent of 246 affected sibling pairs. As shown in the online Supplementary Figure 1, there is no suggestive linkage signal across the genome and both suggestive linkage signals at chromosomes 9 and 16 are diminished compared to the main report. While it is feasible that our more homogeneous sample might have led to the relatively high LOD scores at these two loci, stochastic fluctuations could also lead to the pattern of observations accrued so far.

One potential concern is that locus-specific genetic heterogeneity within the IMAGE multi-site dataset could hinder the linkage test results. For example, the low frequency of a genetic risk factor in one of the subpopulations studied would reduce the overall effect size across the combined dataset, resulting in a loss of power. Based on our previous investigation, we decided to specifically reanalyze the two suggestive linkage loci in a stratified sample without the 18 Israeli families.[13] Interestingly, the linkage signal on chromosome 16 increased and passed the provisional significance criteria for linkage, with a LOD score of 3.82. Our further simulations demonstrated that this increase was statistically significant ($P = 0.035$). This result showed that the linkage evidence could be enhanced when sample stratification was taken into account based on prior knowledge. However, because our full sample size is small and the numbers of families from individual countries are even smaller, random sampling bias could also account for the level of observed genetic heterogeneity.

To explore this possibility, we went on to check more systematically for the effect of dropping families from other recruiting sites, and did indeed find additional evidence of heterogeneity from other sites (Supplementary Table 1). However, since we performed several such tests we completed a further simulation of 10 000 datasets in which we dropped samples representing the proportions of each of the six-country groups, to generate an empirical distribution of 60 000 ($6 \times 10\,000$) simulated LOD scores. The overall levels of significance adjusted for each of the heterogeneity tests were no longer significant, indicating no overall significant evidence of heterogeneity. The results suggested that stratification of samples is unlikely to improve the chance to detect a real linkage signal due to the problem of multiple testing. Nevertheless, testing for heterogeneity might be a useful approach where there is prior evidence of genetic heterogeneity. In this study we cannot clearly establish whether the population mixture in this sample has compromised the power of the analysis until we have identified specific alleles that account for the linkage signals identified.

In summary, we have identified two suggestive ADHD linkage regions on chromosomes 9 and 16, respectively. It is encouraging that both loci overlapped with some evidence of linkage in previous ADHD linkage scans, however the current study and the previous scans all used relatively small sample sizes that do not provide sufficient statistical power to consistently detect linkage to loci conferring relatively small genetic risks. As shown in a recent combined study of two previous linkage scans of ADHD, meta-analysis and reanalysis of the combined raw data provided not only enhanced linkage signals, but also evidence of genetic heterogeneity at chromosome 5p.[31] Thus, a meta-analysis of all available linkage data is now warranted. Although whole-genome association is theoretically a more powerful method to detect common ADHD genes, an important obstacle toward interpretation of such data is the multiple test correction.[41,42] Applying the prior knowledge of genomic linkage may help to prioritize specific regions with lower multiple test correction penalties. Linkage approaches can also be useful for gene mapping if the 'common disease multiple rare allele' scenario, where multiple causal alleles exist within genes, holds true.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)