Identifying Loci for the Overlap Between Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder Using a Genome-wide QTL Linkage Approach

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Objective: The genetic basis for autism spectrum disorder (ASD) symptoms in children with attention-deficit/hyperactivity disorder (ADHD) was addressed using a genome-wide linkage approach. **Method:** Participants of the International Multi-Center ADHD Genetics study comprising 1,143 probands with ADHD and 1,453 siblings were analyzed. The total and subscale scores of the Social Communication Questionnaire (SCQ) were used as quantitative traits for multipoint regression-based linkage analyses on 5,407 autosomal single-nucleotide polymorphisms applying MERLIN-regress software, both without and with inclusion of ADHD symptom scores as covariates. **Results:** The analyses without ADHD symptom scores as covariates resulted in three suggestive linkage signals, i.e., on chromosomes 15q24, 16p13, and 18p11. Inclusion of ADHD symptom scores as covariates resulted in additional suggestive loci on chromosomes 7q36 and 12q24, whereas the LOD score of the locus on chromosome 15q decreased below the threshold for suggestive linkage. The loci on 7q, 16p, and 18p were found for the SCQ restricted and repetitive subscale, that on 15q was found for the SCQ communication subscale, and that on 12q for the SCQ total score. **Conclusions:** Our findings suggest that QTLs identified in this study are ASD specific, although the 15q QTL potentially has pleiotropic effects for ADHD and ASD. This study confirms that genetic factors influence ASD traits along a continuum of severity, as loci potentially underlying ASD symptoms in children with ADHD were identified even though subjects with autism had been excluded from the IMAGE sample, and supports the hypothesis that differential genetic factors underlie the three ASD dimensions. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(7):675–685. **Key Words:** ADHD, autism spectrum disorder, linkage, comorbidity

C hildren with attention-deficit/hyperactivity disorder (ADHD) often show symptoms of autism spectrum disorders (ASD), with approximately one third of those children meeting criteria for a pervasive developmental disorder according to the *Diagnostic and Statistical Manual,* fourth edition (DSM-IV).[1,2] Studies on the common etiology of ADHD and ASD in community twin samples have shown that a substantial part of genetic influences are shared between ADHD and ASD.[3,4] Our own studies confirmed the familiality of ASD symptoms in children with ADHD and their siblings.[5,6] Moreover, genetic overlap is suggested by genetic

linkage studies for ADHD and ASD, in which overlapping sets of suggestive disease loci have been identified, [7-9] including 5p13 and 9q33.[10-16] Both of these loci are supported by at least two independent studies of autism (although not necessarily of genome-wide significance), and at least one study of ADHD.

Although several linkage studies have been performed for ADHD and ASD separately, genome-wide linkage analysis has thus far never been applied to the investigation of the co-occurrence of ASD symptoms and ADHD. Addressing ASD symptoms in children with ADHD may aid in the search for susceptibility loci for the overlapping disorders, as this may reduce heterogeneity.[5,6] A quantitative trait locus (QTL) approach is the most suitable method to find those loci, given that children diagnosed with ADHD according to DSM-IV criteria have ASD symptoms below diagnostic cut-offs. The QTL approach preserves all variation in ASD severity, which increases power of the analyses.[17] The QTL approach follows the assumption that ASD traits lie along a continuum of severity, which is supported by findings of elevated levels of ASD symptoms in parents and siblings of cases compared with controls,[18,19] and variation of ASD traits that has been found in the general population.[20,21]

In the present study, we aimed at identifying loci that underlie ASD symptoms in children with ADHD, all participating in the International Multicenter ADHD Genetics (IMAGE) project. We investigated both the total level of ASD symptoms as well as scores on the three ASD symptom domains, i.e., qualitative impairments in social interaction, in communication, and restricted repetitive and stereotyped patterns of behavior, thus taking into account the potential differential genetic origin of different ASD symptom domains (reviewed by Happé and Ronald [22]). QTL linkage analyses for the different ASD domains were carried out using 5,407 single nucleotide polymorphisms (SNPs) spanning the entire genome.

METHOD

Participants
The study was conducted in participants of the IMAGE project.[23] This is an international collaborative study in seven European countries (Belgium, Germany, Ireland, Spain, Switzerland, the Netherlands, and the United Kingdom) and Israel that aims to identify genes that increase the risk of ADHD using QTL linkage and association strategies.[24] Ethical approval was obtained from National Institutes of Health recognized local ethical review boards, and all families gave written informed consent before participation. To participate in IMAGE, probands had to have a clinical diagnosis of DSM-IV combined subtype of ADHD, as well as one or more full siblings and at least one biological parent available for ascertainment of clinical information and DNA collection. All children participating were 5 to 17 years of age and of white European descent. Exclusion criteria were an IQ <70, autism (assessed as described below), epilepsy, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD.

The children were recruited from families referred to participating (academic) child psychiatric and pediatric outpatient clinics. All probands were included after having completed clinical evaluations by a pediatrician or child psychiatrist prior to the study. The clinical diagnosis of the ADHD probands and siblings (if possible) was verified with the Parental Account of Childhood Symptoms (PACS)[25] by a trained interviewer. A standard algorithm for PACS was applied to all raw data to yield diagnoses based on operational DSM-IV criteria. More detailed information is available in a report by Brookes et al.[24]

Children were excluded from participation in IMAGE when classical or atypical autism was diagnosed. For this, both probands and siblings were screened using the Social Communication Questionnaire (SCQ)[26] in conjunction with the prosocial scale of the Strengths and Difficulties Questionnaire (SDQ).[27] Individuals falling above thresholds for the SCQ (i.e., ≥15) and SDQ (i.e., ≤4) were further evaluated using the autism spectrum disorder section of the PACS. Classical or atypical autism was regarded to be present in these children in case they showed ASD symptoms in at least two out of three DSM-IV autism domains, together with a developmental delay in at least one autism domain before the age of 3 years, according to DSM-IV definitions. Attention was given especially to symptoms that distinguish ASD from ADHD. Furthermore, a lack of relationships with peers alone was not sufficient for social impairment of the autistic type. The final sample investigated in this study included 1,143 ADHD probands and 1,453 siblings from 1,143 families.

Measures
To assess ASD symptoms, the lifetime version of the SCQ was used. The SCQ is a parent-rated questionnaire that consists of 40 items based on the Autism Diagnostic Interview–Revised.[28] Three subscales that relate directly to the three autism core domains as defined in the DSM-IV can be scored, i.e., the social (15 items), the communication (13 items), and the restricted and repetitive (eight items) scales. The SCQ appeared to have good discriminative validity for the discrimination of ASD from non-ASD in at-risk samples at the cut-off of ≥15 established by Berument et

TABLE 1 Phenotypic Characteristics of the International Multi-site ADHD Genetics (IMAGE) Project Sample

	Mean (SD)	
	Probands (n = 1,143)	Siblings (n = 1,453)
Age (years)	10.9 (2.8)	10.9 (3.4)
Intelligence Quotient	100.6 (15.8)	102.1 (14.1)
Gender (% female)	13.2	48.4
SCQ scores		
SCQ total	8.6 (6.2)	4.5 (4.2)
Social	2.8 (2.8)	1.3 (1.9)
Communication	3.4 (2.4)	2.3 (2.0)
Restricted and repetitive	1.8 (1.9)	0.7 (1.3)
Conners scores		
Inattentive	19.4 (5.1)	7.6 (7.4)
Hyperactive–impulsive	17.7 (5.6)	5.8 (6.4)

Note: SCQ = Social Communication Questionnaire.

al.[26] In the final sample, 233 children had SCQ scores of ≥15, 189 of whom were probands (additional information on SCQ scores in Table 1).

The DSM-IV inattentive and hyperactive–impulsive scales of the Conners' parent rating scale, long form, were used to assess ADHD symptom severity in both probands and siblings.[29] The correlation between the Conners' DSM-IV total score (calculated by adding up the Conners' DSM-IV inattentive and hyperactive-impulsive scale scores) and the SCQ total score was 0.44 (p < .01) in our sample.

Genotyping and Data Cleaning

An extensive description of DNA extraction and genotyping is provided elsewhere.[24,30] Briefly, DNA was extracted from blood samples or immortalized cell lines at Rutgers University Cell and DNA Repository (Piscataway, NJ). In a few cases, oral swabs were used to extract DNA at the Social Genetic and Developmental Psychiatry laboratories in London (UK). Illumina BeadArrayTM technology on a BeadLab system was used, which was provided by the Center for Inherited Disease Research (CIDR; http://www.cidr.jhmi.edu/). A total of 5,545 autosomal SNPs from the Illumina Linkage IVb SNP panel were successfully assayed with a call rate of 99.6% and 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 map distances.[31]

Pedigree errors were identified and corrected by testing pairwise subject relationships with the program Relpair.[32] Genotypes causing Mendelian inconsistencies were identified by PEDCHECK and removed by a custom script.[33] Unlikely genotype

combinations leading to double recombinations over short genetic distance in a few cases were removed by MERLIN.[34,35] Following data cleaning, 5,407 autosomal SNPs with an average resolution of 1.66 SNP/centimorgan (cM) were entered into the linkage analyses.

Data Analyses

Multivariate QTL linkage was examined for the SCQ total scale and each of the SCQ subscales. Age and gender were used as covariates. All analyses were repeated with scores on the ADHD/DSM-IV inattentive and hyperactive-impulsive scales of the Conners' parent rating scale, long form, simultaneously added as additional covariates. The latter analyses served to investigate whether QTLs found in the first analyses were independent from ADHD (which would be the case if signals persisted after inclusion of ADHD scores), and also whether new QTLs would appear. Signals that would disappear could be suggestive of pleiotropic effects, whereas remaining and new QTLs could harbor genes uniquely contributing to ASD symptoms.

The linkage analyses were carried out using Merlin-regress software, which implements a regression based procedure using trait-squared sums and differences to predict Identity by Descent (IBD) sharing between relative pairs.[34,36] With the population distribution parameters of mean, variance, and heritability specified, this method can be applied to selected samples with a statistical power similar to variance component linkage tests.[30] Because treating tightly linked markers as independent markers can inflate LOD scores, we applied the criteria of $r^2 < 0.05$ between SNPs to cluster SNPs into combined markers.[30,37] For this study, heritability estimates were based on values previously reported for the broader ASD spectrum in twins from the general population by Constantino and Todd [38] and Ronald et al.[39] Empirical p values were derived using Merlin software by running 1,000 simulations under the null hypothesis of no linkage, while preserving the original phenotypes, family structures, allele frequencies, LD structure, and missing data pattern.[30,34] In each simulated data set, linkage was defined as peak LOD scores equal to or higher than the experimental LOD.

RESULTS

Table 1 presents sample characteristics are presented. Figures 1 to 5 and Tables 2 and 3 show the results of the multivariate QTL linkage analyses.

No results surpassed the criteria for genome-wide significance, but we did find several suggestive linkage signals. In the primary analyses (i.e., Conners' scores not included as covariates),

FIGURE 1 Logarithm of the odds (LOD) score graphs of the Social Communication Questionnaire (SCQ) total scale on chromosome 12.
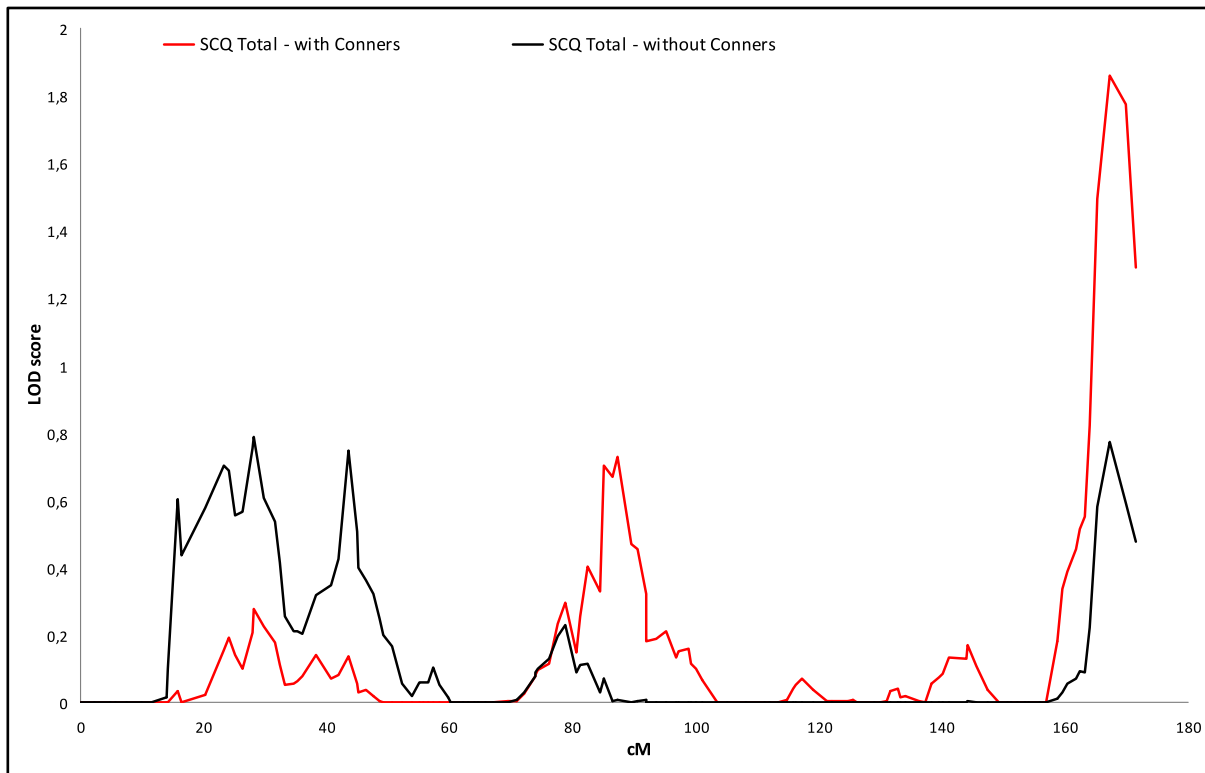
the highest LOD score (LOD 3.216) was found for rs1557299 on 18p11.32 for the SCQ restricted and repetitive subscale. Other regions that showed suggestive linkage were found on 15q24 and 16p13, for the communication and the restricted and repetitive subscale, respectively.

For the analyses corrected for Conners inattentive and hyperactive–impulsive scores, suggestive linkage was again found for 18p11.32 and 16p13 for the restricted and repetitive scale. The LOD for the region on 15q24 (LOD 1.692) just dropped below the empirically derived value for suggestive linkage. Additional regions that showed increased significance and surpassed thresholds for suggestive linkage in this analysis were found on 7q36.2 for the restricted and repetitive scale and on 12q24 for the total scale.

DISCUSSION
In the current study, multivariate QTL linkage analysis was performed on ASD symptom domains in 1,143 children with ADHD and 1,453 of their siblings from 1,143 families, using an autism screening questionnaire, i.e., the SCQ. We identified five suggestive quantitative trait loci, with the highest overall LOD scores identified for the SCQ restricted and repetitive subscale on 18p11 (LOD 3.216). Additional suggestive QTLs were 7q36, 16p13 (both for the restricted and repetitive scale), 15q24 (for the communication scale), and 12q24 (for the total scale). Our findings suggest that linkage studies regarding the occurrence of ASD symptoms in children with ADHD may assist in elucidating the genetics underlying ADHD and ASD. Furthermore, the findings support the assumption that ASD traits are influenced by genetic risk factors along a continuum of severity, as loci potentially underlying ASD symptoms in children with ADHD were identified that correspond with identified loci or genes for clinical PDD, even though autistic cases had been excluded from the IMAGE sample. In addition, our findings appear to confirm the hypothesis that the different ASD symptom domains have partially different genetic origins.[22]

Among the suggestive loci identified in the present study, the QTL on chromosome 15q

FIGURE 2 Logarithm of the odds (LOD) score graphs of the Social Communication Questionnaire (SCQ) communication scale on chromosome 15.
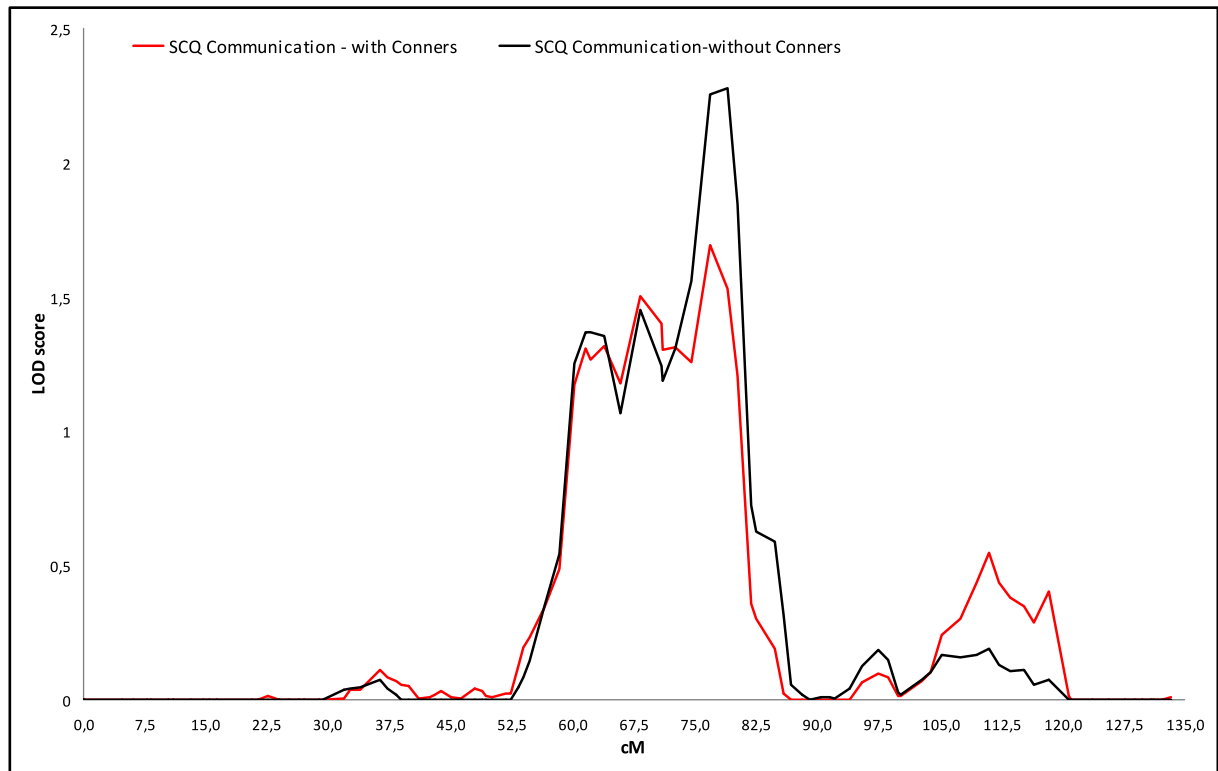
could potentially have pleiotropic effects on ADHD and ASD, given that its LOD score decreased below the threshold for suggestive linkage after including ADHD symptom scores in the analyses. The other suggestive QTLs (i.e., on chromosome 7q, 12q, 16p, and 18p) appear to be primarily associated with ASD symptoms, independent of ADHD symptom scores, as LOD scores did not change substantially, and in the case of chromosome 12q24 even appeared, after inclusion of Conners' scores as covariates. Supporting the ASD specificity of our results, there is no overlap between the suggestive QTLs that we found and those observed in the IMAGE sample for ADHD symptoms as quantitative traits, i.e., genome-wide significant linkage to 1p36, and suggestive linkage findings for 9p23 and 11q21.[30]

The most prominent result in terms of significance was the signal that we found on chromosome 18p11, which only just failed to reach genome-wide significance in the analyses uncorrected for ADHD symptoms. This region has never been reported in previous linkage studies for ADHD, but has been found to be a possible locus for ASD, in particular Asperger's syn-

drome, in one study.[40] Here, suggestive linkage for marker D18S59, at 0 cM (184 kb from our peak SNP) was reported. The SNPs that showed the highest LOD scores in our study lie within an intergenic region, but are flanked by an interesting gene approximately 19 kb upstream, called adenylate cyclase activating polypeptide 1 ADCYAP1). This gene encodes a neuropeptide, and in animal studies has been shown to be associated with hyperactivity, increased exploratory behavior, and abnormal social behavior.[41,42] Investigating the role of ADCYAP1 in ADHD, autism, and the overlap between the two may be an interesting target for future studies. The nearest gene downstream of the linked SNPs on 18p11 lies at a large distance from our peak (1.6 Mb), and is a gene of unknown function called methyltransferase-like 4 (METTL4), which may also prove to be associated with ADHD or ASD.

Another interesting result is the signal that we found for chromosome 7q36. This lies within the most replicated linkage region for autism, namely 7q21.2 to 36.2 (reviewed by Yang and Gill[9] and Abrahams and Geschwind[43]), and our results once more confirm the importance of this

FIGURE 3 Logarithm of the odds (LOD) score graphs of the Social Communication Questionnaire (SCQ) restricted and repetitive scale on chromosome 7.
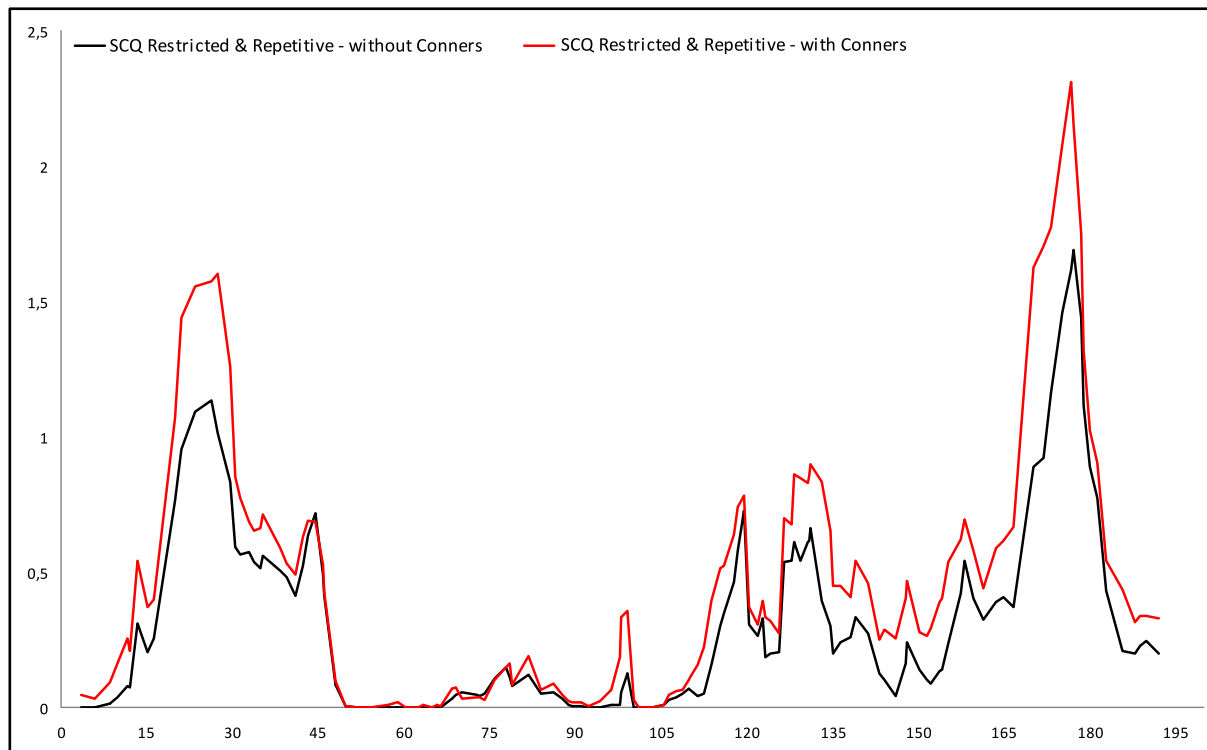
region for ASD symptoms. The peak SNP lies within the paired box interacting protein 1 (PAXIP1) gene, which encodes a nuclear protein important for genome stability, chromatin condensation, and progression through mitosis. Its role in psychiatric disease has never been investigated thus far, but it has been reported as a candidate gene for Alzheimer's disease.[44] An interesting and replicated autism gene in the vicinity of our 7q peak is Engrailed 2 (EN2), located at ~180 cM.[45,46] Our study is the first to suggest the relevance of the 7q36 region for ASD symptoms in a non-ASD sample, making this region and the genes herein, including PAXIP1 and EN2, even more interesting targets for further ASD research.

Two other peaks identified in the present study, i.e., those on chromosome 15q and 16p, are also in the vicinity of regions identified for ASD in other studies. Our peak SNP on chromosome 15q24 lies at a 2.6-Mb distance of a peak SNP (rs1372828) identified for autism by Szatmari et al.,[12] and is located within a locus known to harbor microdeletions in mental retardation.[47] Also, Marshall et al. identified structural variations in this region in

individuals with ASD.[48] The SNP with the highest LOD score we identified on chromosome 16p13 lies in a brain-expressed gene of provisional status called ankyrin repeat and sterile alpha motif domain containing 3 (ANKS3). Furthermore, at respectively 5Mb and 7 Mb from our peak SNP,[49-51] suggestive linkage peaks have been found for ASD. In addition, trisomy of 16p has been reported in individuals with autistic traits.[52]

Correspondence to previous linkage studies for ADHD was found for the chromosome 12q and the 16p QTL. In two independent samples, suggestive linkage at, respectively, 129 kb and 4 Mb from our peak SNP at 12q24 was found.[10,53-55] Smalley et al. found genome-wide significant linkage for a broad region on 16p13, with the most significant SNP (D16S3114) at 7 Mb from the SNP with the highest LOD score in the present study (rs859302).[56] No previous studies report linkage to 15q24 for ADHD, which would have supported the pleiotropic effects of this region that our findings suggest.

In summary, our results for 7q, 18p, 15q, and 16p show overlap with previous studies for ASD, which suggests that these findings may not be confined to ASD symptoms within the context of

FIGURE 4 Logarithm of the odds (LOD) score graphs of the Social Communication Questionnaire (SCQ) restricted and repetitive scale on chromosome 16.
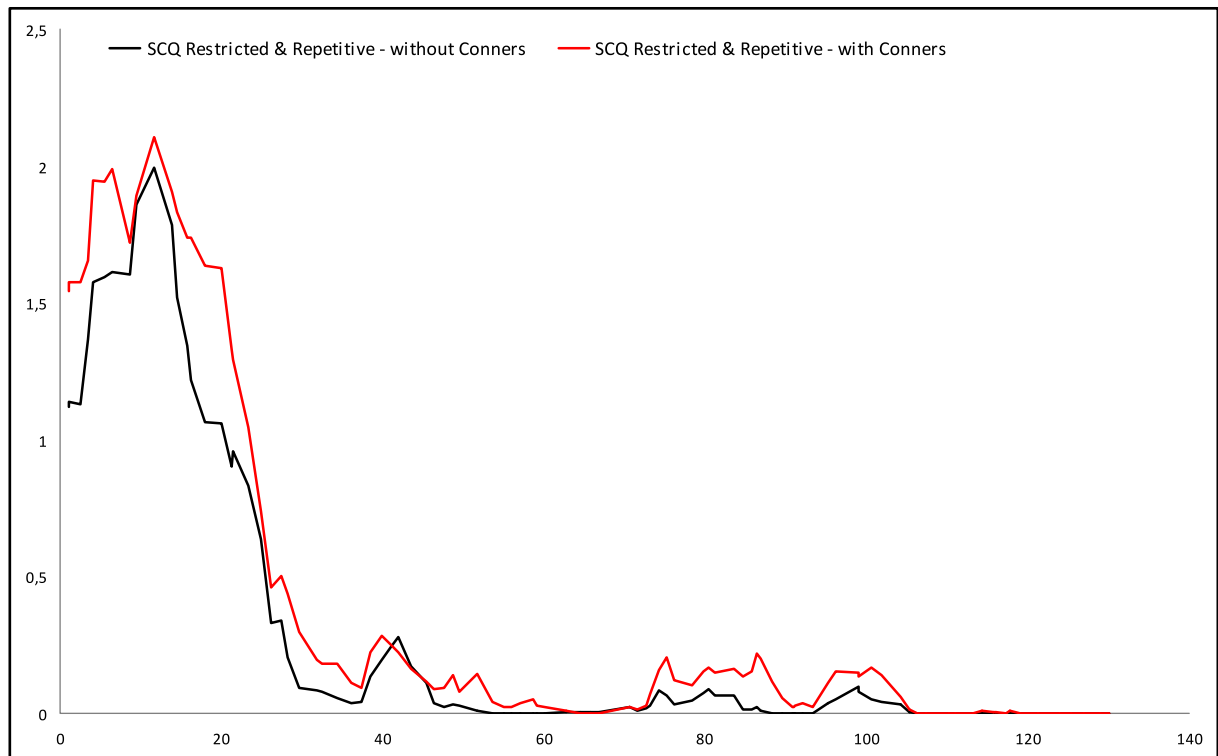

ADHD. One hypothesis worth testing is whether our 18p result may indicate the existence of a unique ADHD subtype associated with hyperactivity, increased exploratory behavior, and abnormal social behavior. Furthermore, our results for 12q and 16p correspond to previous ADHD findings. From the QTLs identified in this study, those on 12q, 16p, and 18p may be the most likely to explain the ASD comorbidity in ADHD, given their identification in previous ADHD (linkage) studies, and given their possible role in ASD symptoms as found in the current study and in previous autism linkage studies (16p and 18p). However, it cannot be precluded that these previous ADHD linkage results were driven by ASD symptoms, as subtle ASD symptoms may still have been present in the ADHD samples analyzed even when ASD cases were excluded. In line with recent discussions in neurocognitive ADHD and ASD research,[57] our results suggest that subsequent ADHD genetic studies may need to consider correcting for ASD symptoms.

Notably, three regions we found to coincide with previously reported linkage peaks for ASD were all identified for the SCQ restricted and repetitive scale, and one was found for the SCQ communication scale. This may indicate domain-specific effects for these loci, which appears to be in line with the apparent genetic independence of the three ASD symptom domains[22] and with findings suggesting that restricted and repetitive behavior may have a relatively high heritability compared to other ASD traits.[5,58] As far as we know, only one previous autism linkage study has specifically addressed restricted behaviors;[59] however the regions identified in that study do not overlap with our suggestive linkage peaks. Similarly, several ASD linkage studies have addressed the communication domain (e.g., Alarcon et al.[60]), but none has reported linkage to 15q. Notably, in two independent samples of individuals with autism, genome-wide significance was found for a quantitative trait for language acquisition at 7q36, whereas we found suggestive linkage to this region for restricted and repetitive behavior.[15,60] Clearly, our results need replication in independent samples.

A limitation of our study may have been that the most severe ASD cases were excluded from participation in the IMAGE project. However,

FIGURE 5   Logarithm of the odds (LOD) score graphs of the Social Communication Questionnaire (SCQ) restricted and repetitive scale on chromosome 18.
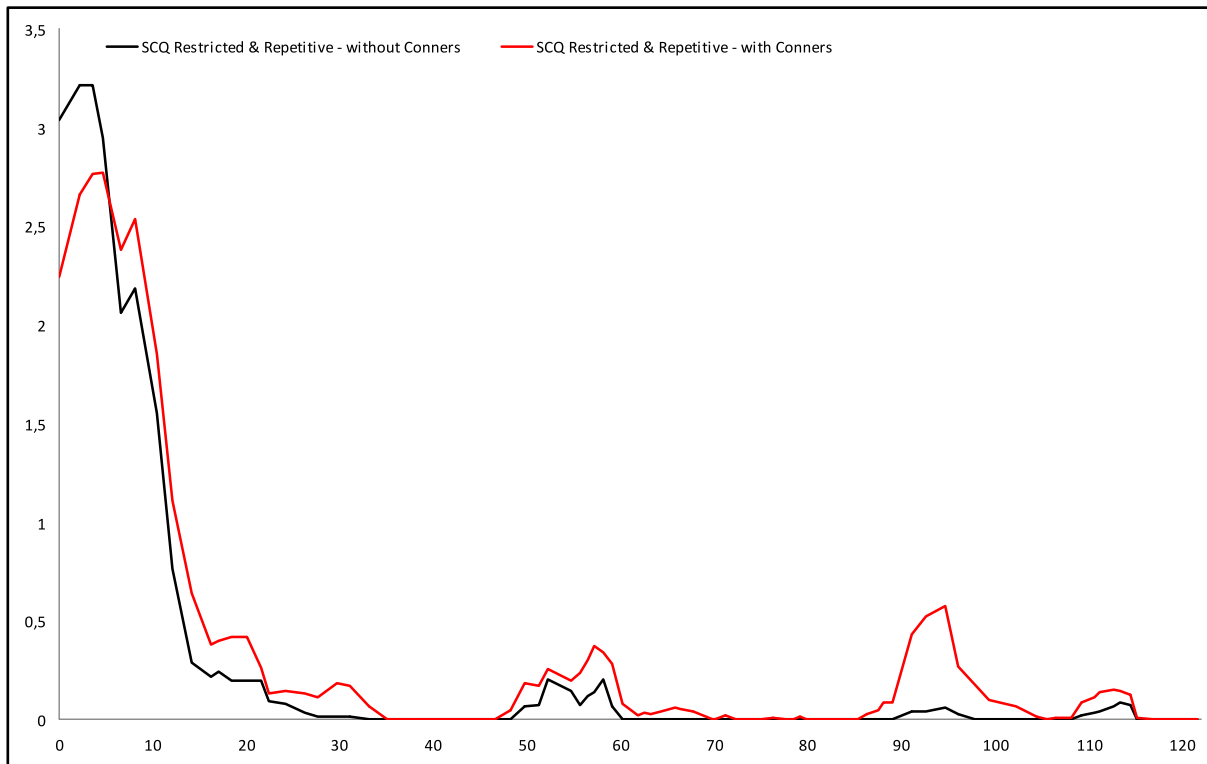
the fact that we did find overlap with previous linkage studies for ASD affection status, even though autistic cases were excluded from our sample, appears to confirm that similar genetic factors influence ASD symptoms along a continuum of severity, and supports the usefulness of the SCQ to measure this continuum. It should be remembered, however, that the study mostly excluded SCQ scores in the higher range. Nevertheless, further studies are needed to investigate whether our findings

pertain to narrowly defined autism as well. As another potential limitation, currently the SCQ has not yet been demonstrated to validly measure ASD symptoms as a continuous trait. Furthermore, the heritability figures used for the SCQ subscales were estimations based on previous ASD research, whereas ideally these should be derived from twin pair SCQ scores. However, it is unlikely that the heritability estimates have influenced the results importantly, as LOD scores were stable across a range of heritabilities (0.20 to 0.95; data not shown).

Finally, we did not adjust for testing multiple ASD dimensions, as a Bonferroni correction would have been overly conservative because of the high correlation between the ASD symptom scales. However, our simulation approach allowed us to take into account multiple testing resulting from analyzing several thousands of markers, and produced conservative LOD scores for suggestive linkage. Replicating the QTLs identified in the present study with genome-wide significance will likely require larger samples, as our data suggest that effects are not large.

TABLE 2   Thresholds for Suggestive and Significant Linkage (Logarithm of the Odds Scores)

SCQ Scale	Suggestive Threshold	Significant Threshold
Total	1.85	3.76
Social	1.894	3.73
Communication	1.894	3.63
Restricted and repetitive	1.849	3.52

Note: SCQ = Social Communication Questionnaire.

TABLE 3 Linkage Results for the Total Number of Autism Spectrum Disorder (ASD) Symptoms and the Three ASD Symptom Domains

SCQ Scale	Chromosome	Position (cM)[a]	Location[b]	Marker	LOD	No. of Markers[c]
Total	12	167.2	12q24.3	rs1487602	0.772	1
Social	.	.	.	.	.	.
Communication	15	78.88	15q24.1	rs896588	2.278	2 (2.1)
Restricted and repetitive	7	177.27	7q36.2	rs1657290	1.689	2 (0.6)
	16	11.67	16p13.3	rs859302	1.992	2 (2.3)
	18	2.21	18p11.32	rs1557299	3.216	6 (8.1)
Conners Added to Covariates						
Total	12	167.2	12q24.3	rs1487602	1.86	1
Social	.	.	.	.	.	.
Communication	15	76.79	15q24.1	rs1348318	1.692	1
Restricted and repetitive	7	176.66	7q36.2	rs306278	2.311	3 (2.0)
	16	11.67	16p13.3	rs859302	2.105	3 (4.5)
	18	4.64	18p11.32	rs1371264	2.77	7 (10.5)

Note: LOD = logarithm of the odds; SCQ = Social Communication Questionnaire.
[a]DeCODE Genetic map position.
[b]Most likely cytogenic location.
[c]Number of consecutive single-nucleotide polymorphism markers with LODs above thresholds for suggestive linkage and (in brackets) the genetic distance that they span.

Ideally, in these samples, extremes of both the ADHD and ASD spectra would be represented, in which parent reports as well as a detailed developmental history and observational data would be collected to assess autistic and ADHD symptomatology.

To our knowledge, our findings represent the first attempt to identify QTLs underlying the occurrence of ASD symptoms in children with ADHD. The strengths of this study are the use of a well-defined combined type ADHD sample, and the relatively large sample size. This resulted in the identification of suggestive QTLs on chromosome 7q, 12q, 15q, 16p, and 18p. &

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