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A genome-wide screen for genes influencing conduct disorder

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While behavioral genetic studies have suggested that childhood conduct disorder is under genetic influence, studies aimed at gene identification are lacking. This study represents the first genome-wide linkage analysis directed toward identifying genes contributing to conduct disorder. Genome screens of retrospectively reported childhood conduct disorder and conduct disorder symptomatology were carried out in the genetically informative adult sample collected as part of the Collaborative Study on the Genetics of Alcoholism (COGA). The results suggest that regions on chromosomes 19 and 2 may contain genes conferring risk to conduct disorder. Interestingly, the same region on chromosome 2 has also been linked to alcohol dependence in this sample. Childhood conduct disorder is known to be associated with the susceptibility for future alcohol problems. Taken together, these findings suggest that some of the genes contributing to alcohol dependence in adulthood may also contribute to conduct disorder in childhood.
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Introduction

Childhood conduct disorder involves a persistent pattern of rule-breaking behaviors, including bullying other children, stealing, vandalizing, and skipping school. Conduct disorder is one of the most prevalent childhood disorders. Although rates vary according to the population under study, approximately 6–16% of males, and 2–9% of females, are diagnosable with conduct disorder.[1] A substantial body of literature suggests that childhood conduct disorder is a strong risk factor for concurrent and future alcohol problems. Moreover, conduct disorder appears to carry a stronger risk for alcohol dependence than any of the other childhood behavioral disorders, such as attention-deficit/hyperactivity disorder (ADHD). Several studies of adolescents who have been diagnosed with alcohol use disorders have concluded that of the childhood behavioral disorders, conduct disorder has the strongest association with alcohol problems.[2–5] This finding also has been demonstrated in two longitudinal studies. In a 6-year investigation of >500 teenage boys, only childhood conduct disorder predicted linear growth in alcohol use over that period. Similarly, a longitudinal study of males who had received treatment for conduct and substance use disorders found that conduct disorder severity predicted conduct, crime, and substance use outcomes 2 years later.[6]

The problems in school and home functioning associated with childhood conduct disorder, as well as the established relationship between conduct disorder and alcohol use problems, underscores the need to better understand the causes of this disorder. Historically, the role of the family has been emphasized in the development of childhood behavioral problems, with blame placed on poor parenting, inconsistent, overly strict, or overly lax parental discipline, and parental problems, such as divorce or separation.[7–10] Although genetically informative studies have confirmed the importance of the family environment in the etiology of conduct disorder,[11] more recent studies suggest that conduct disorder may also be under a significant degree of genetic influence. In the Australian Twin Study, retrospectively reported conduct disorder was assessed by interview in >2600 male and female twin pairs; more than 70% of the variance in conduct disorder was

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attributable to genetic factors.[12] Data on >500 female–female twin pairs from the Virginia Twin Registry also showed significant, modest heritability (~40%) for retrospectively reported childhood conduct disorder.[13] In a recent study of conduct disorder assessed prospectively among a sample of >1500 interviewed 14-year old Finnish twins, genetic influences played a significant role in conduct disorder in both boys and girls.[14] A meta-analysis of a related phenotype, antisocial behavior, is also worth noting: evidence from 51 twin and adoption studies suggested that genetic influences accounted for 32% of the variance in antisocial behavior.[15] Despite the consistent evidence of genetic effects on conduct disorder from a number of studies, heritability estimates have varied substantially in different populations. In addition, at least one study has found no significant evidence for genetic effects.[16] Thus, it is difficult to quantify the influence of genetic factors on conduct disorder.

As alcohol use is known to be under genetic influence,[17] and there is mounting evidence that conduct disorder is also under some genetic influence, it is possible that the association between conduct disorder and alcohol use may be due to a shared genetic liability. Family studies have suggested shared familial transmission, as indicated by the presence of higher rates of conduct disorder and substance use in the relatives of adolescents in treatment for substance abuse.[18] Twin studies are able to more precisely distinguish between genetic and environmental liabilities. In the Australian twin study, a bivariate analysis of childhood conduct disorder and adult alcohol dependence found that genetic factors largely contributed to the covariation observed between these disorders.[19] These findings suggest that some of the genes that contribute to alcohol dependence in later life may be contributing to conduct disorder in childhood and adolescence, although not all twin studies have reached that conclusion.[16]

While twin studies have demonstrated genetic influence on conduct disorder and have used latent modeling to suggest that these influences may overlap with those impacting alcohol dependence, studies aimed at identifying the actual genes involved in childhood conduct disorder have been lacking. Here, we report results from genome-wide linkage analyses of retrospectively reported conduct disorder in a genetically informative sample of families collected for the purpose of identifying genes involved in alcohol dependence and related disorders. To our knowledge, this represents the first genome scan for genes influencing conduct disorder.

Materials and methods

Sample

The Collaborative Study on the Genetics of Alcoholism (COGA) is a multisite collaboration with the goal of identifying genes contributing to alcoholism and related phenotypes. Alcoholic probands were recruited for the COGA project through in-patient and outpatient treatment facilities. Alcoholism was defined by the presence of a DSM-IIIR alcohol-dependence diagnosis,[1] plus definite alcoholism according to Feighner Criteria.[20] Alcoholic probands were invited to participate in the study if they had at least two additional first-degree relatives who lived in a COGA catchment area.[21] A total of 1227 families of alcohol-dependent probands were recruited for the first stage of the study.

All individuals aged 18 or older were interviewed using the semi-structured assessment for the genetics of alcoholism (SSAGA).[22,23] The SSAGA makes a diagnosis of childhood conduct disorder through retrospective report of behavioral problems evidenced before the age of 15. Symptoms include stealing (with or without confrontation of the victim); running away from home; lying; fire–setting; truancy from school; breaking into a house, building, or car; destroying property; cruelty to animals or people; forcing sexual activity on others; use of a weapon; and initiating physical fights. Symptom counts ranged from 0 to 11 in this sample; the mean number of symptoms reported was 1. Diagnoses were made by the presence of three or more symptoms; 13% of the sample of individuals with SSAGA data met criteria for a childhood diagnosis of conduct disorder. The 1 week interrater test–retest reliability for conduct disorder assessed using this method was approximately 0.65, and the correlations in liability for conduct disorder were 0.80–0.82.[24] The 15-month stability of childhood conduct disorder assessed in this manner has been reported by the Australian Twin Group to be as high as the short-term reliabilities reported in the COGA data.[12]

An initial subsample of 987 individuals from 105 families of alcohol-dependent probands was selected on the basis of their informativeness for genetic linkage analyses of alcoholism. Individuals from these families participated in a more extensive protocol, including the collection of blood samples for genotyping. A second sample has subsequently been ascertained and genotyped following identical procedures; it consists of 1295 individuals from 157 extended families.[25] Thus, a total of 2282 individuals from 262 families were available for genetic analyses.

Molecular methods and analysis

Microsatellite (simple sequence repeat) polymorphisms were genotyped throughout the genome as previously described.[25,26] The analyses reported here use 336 markers at an average intermarker distance of 10.5 cM. The genotypic data was stored using the GeneMaster Database Management System (J Rice, personal communication) and checked for Mendelian inheritance of marker alleles with the CRIMAP[27] and USERM13[28] option of the MENDEL linkage computer programs. Marker allele frequencies were estimated using maximum likelihood estimates from the USERM13 program. Marker recombination and

distance were estimated using CRIMAP. Families with an identified noninheritance were reviewed. If the apparent discrepancy was not resolved by review, the genotypic data from individuals incompatible with the remainder of the family were removed. Determination of allele sizes and the review of potential discrepancies were made blind to diagnostic phenotype.

Nonparametric, multipoint methods of linkage analysis for affected sibling pairs were employed. The DSM-III-R diagnosis of childhood conduct disorder was analyzed as a dichotomous trait, using the program ASPEX.[29] The linkage analyses were performed using all affected siblings regardless of parental genotyping (sib_phase), and using only those affected siblings with both parents genotyped (sib_ibd). Limiting the analyses to only those affected sibling pairs with genotyped parents (sib_ibd) allows for unambiguous estimation of identity-by-descent (IBD). While this type of analysis results in greater accuracy in the estimate of marker allele sharing among affected siblings, this occurs at the expense of a reduction in the sample size. Therefore, linkage analyses also were performed utilizing information from all available sibling pairs regardless of the availability of parental genotyping. While the sample size is maximized in these analyses, estimates of marker allele sharing are often based on identity-by-state (IBS) rather than IBD. Analyses were performed using all possible pairs of affected siblings (($n(n-1)$/2), where n = number of affected siblings in a nuclear family). There were 114 all possible sibling pairs (52 with both parents genotyped) concordant for childhood conduct disorder.

Additionally, secondary analyses of conduct disorder symptom counts as a quantitative trait were conducted. The program Mapmaker/SIBS[30] was used with the Haseman–Elston method. This method only assumes normality of the residuals of the quantitative trait, rather than normality of the trait itself.

Results

The lod scores for the entire genome are shown in Figure 1. Table 1 lists all regions of the genome that yielded lod scores ≥ 1.5 for conduct disorder diagnoses. Lander and Kruglyak[31] have suggested that a threshold of 2.2 indicates a lod score is suggestive of linkage; however, because lod scores are a measure of significance rather than effect size, they are necessarily influenced by sample size. Due to the smaller sample size of the present study, and because this is an initial, preliminary genome scan for conduct disorder, we chose to use a threshold of 1.5 for reporting lod scores of interest in the table. In addition, we report the IBD sharing, to indicate effect size and allow the reader to better assess the study findings. Chromosome 19 yielded the highest lod scores across both methods of analysis, with a maximum lod score of 2.8 at 35 cM. IBD sharing was nearly 75% when information was available from both parents and IBD estimation was exact. Chromosome 2 yielded a maximum lod score of 2.4, using the sib_ibd method of analysis; IBD sharing was nearly 65% among affected sib pairs in this region. There was weaker evidence for linkage on chromosomes 12 and 3. To estimate the effect size of the putative loci on chromosomes 19, 2, 12, and 3, we used the formula proposed by Risch[32] in which the estimated proportion of allele sharing among affected sibling pairs is compared to that expected under the null hypothesis. We used the larger sample size available for sib_phase analyses to estimate the risk ratios. The chromosome 19 locus had an estimated risk ratio of 1.9. The risk

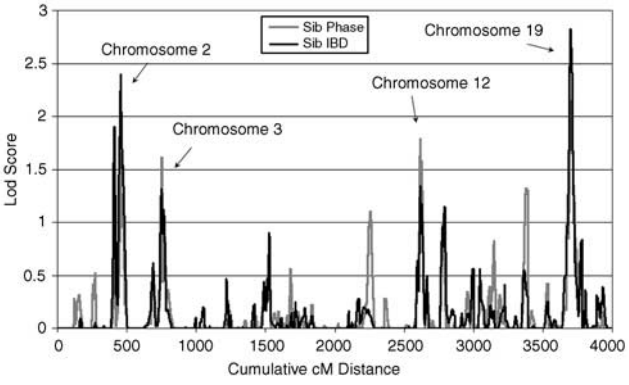

Figure 1 Lod scores for conduct disorder diagnoses across the genome.

Table 1 Genomic regions yielding lod scores ≥ 1.5 for conduct disorder diagnoses. Lod scores and % IBD sharing are shown from the sib_phase and sib_ibd analyses for all possible pairs

			Sib_phase		*Sib_ibd*	
Chromosome	*Position (cM)*	*Marker*	*Lod score*	*% IBD*	*Lod score*	*% IBD*
19	35	D19S714	2.14	65.5	2.82	74.3
2	136	D2S1331	1.65	60.0	2.4	64.8
12	78	D12S390, D12S398	1.79	61.8	1.35	61.0
3	134	D3S2459	1.6	59.7	1.32	60.9

The location of the maximum lod score and nearest markers are also shown

Table 2 Genomic regions yielding lod scores $\geqslant 1.5$ for quantitative conduct disorder symptom counts

Chromosome	*Position (cM)*	*Marker*	*Lod Score*
1	34	D1S1606	2.17
19	46	D19S433	2.10

Lod scores yielded by Mapmaker/SIBS

ratio for the three other putative loci was estimated at 1.6. The magnitude of these effect sizes is comparable to reported risk ratios for putative loci identified in linkage scans of other complex disorders.[25]

Analyses of conduct disorder symptoms as a quantitative trait yielded two regions with lod scores ≥ 1.5 (Table 2). One of these regions overlapped with findings for the conduct disorder diagnosis: a maximum lod score of 2.1 was found on chromosome 19 at 46 cM near the marker D19S433. Additionally, a maximum lod of 2.2 was found on chromosome 1 at 234 cM by the marker D1S1606.

Discussion

Since previous twin studies have suggested that genetic influences play a role in the susceptibility for developing childhood conduct disorder, and that some of these genetic factors may be shared with alcohol dependence, we conducted linkage analyses of retrospectively reported childhood conduct disorder in our genetically informative COGA sample. These analyses identified several regions of interest that may contain genes playing a role in childhood conduct disorder. Chromosome 19 yielded the strongest evidence of linkage with the conduct disorder diagnosis phenotype, with a maximum lod score of 2.8 near the marker D19S714. When we subsequently ran linkage analyses using a count of conduct disorder symptoms, analyses on chromosome 19 further supported a conduct disorder susceptibility locus in this chromosomal region.

Chromosome 2 yielded the next strongest linkage findings in the genome, with a maximum lod score of 2.4 at the marker D2S1331. This result is particularly interesting, because this region of chromosome 2 also has been linked to alcohol dependence[25] and suicidality[33] in the COGA sample. Taken together, these findings suggest that a gene in this region may contribute to a variety of impulsive, acting out behaviors. Alcohol dependence yielded a maximum lod score of 1.8 near the marker D2S1790.[25] This marker is adjacent to, and located 3 cM from, the marker D2S1331 that yielded the maximum lod score on chromosome 2 for conduct disorder. It does not appear to be the case that these findings coincide simply due to overlap in the individuals used for the two separate analyses: although retrospectively reported childhood conduct disorder and adult alcohol dependence do show the expected association in this sample (OR = 5.84, 95% CI (5.09–6.71)), only 25% of the individuals with alcohol dependence have childhood conduct disorder. Thus, the samples used in each analysis do not substantially overlap. However, while this finding has interesting implications, more definitive evidence for a potential susceptibility gene contributing to conduct disorder in this region necessitates replication in a sample ascertained expressly for the purpose of studying conduct disorder, rather than through alcoholic probands.

The other regions that emerged in our genome scans as being of some interest, on chromosomes 12 and 3 for conduct disorder diagnoses, and chromosome 1 for the symptom count, are not near regions that have previously been linked to alcoholism or any related behavioral disorders of which we are aware. It is interesting that we find somewhat different regions of linkage when using the conduct disorder diagnosis *vs* a conduct disorder symptom count. This is likely due in part to variations in the samples used in the analyses. Analyzing conduct disorder as a dichotomous phenotype uses information only from affected sibling pairs, whereas analysis of the conduct disorder symptom count uses information from all siblings in the sample by targeting the whole spectrum of conduct disorder symptomatology, not just individuals who meet diagnostic criteria. The fact that one region linked to conduct disorder symptoms overlapped with a region linked to conduct disorder diagnosis may suggest that some genes contribute both to a diagnosis of conduct disorder and to normal variation in conduct disorder symptomatology in the population. At least one previous twin study has suggested that the diagnosis of conduct disorder may be an extreme of normal variation in behavioral problems among individuals, rather than a discrete disorder.[12] However, our analyses also suggest that some genes may contribute specifically to the conduct disorder diagnosis without influencing normal behavioral variation in acting out behaviors.

To our knowledge, these analyses represent the first genome screen for genes influencing conduct disorder. Very little genetic work has been conducted using the phenotype of conduct disorder. Rather, most of the molecular genetic work that has been conducted on childhood behavioral disorders has focused on ADHD.[34,35] Some of these studies have also investigated aspects of conduct disorder. One study found that DRD4 was related to greater levels of conduct disorder symptoms among the fathers of ADHD children.[36] Another study conducted multivariate linear regression analyses to test the relationship of more than 40 candidate genes in ADHD, ODD, and conduct disorder symptomatology in a case–control sample of patients with Tourette syndrome.[37,38] Genes were studied in the dopaminergic, serotonergic, adrenergic, and GABAergic pathways, as well as hormone/neuropeptide genes, opioid genes, and other neurotransmitter genes. Associations

were found with many genes from each of the above categories; however, conduct disorder was more likely to be associated with hormone/neuropeptide genes than either ADHD or ODD.[37] Interestingly, the authors concluded that ADHD and ODD shared more genes with each other than either condition shared with conduct disorder. None of the regions implicated in our genome scan contain any candidate genes that have been implicated in ADHD. Perhaps this is not entirely surprising, as it is not clear whether ADHD and conduct disorder share a genetic etiology.[39,40] However, a more conclusive test regarding potential overlap between ADHD and conduct disorder would involve genotyping the candidate genes associated with ADHD in this sample and specifically testing for association with conduct disorder.

This study has several limitations, and the results should be interpreted cautiously. The sample used was ascertained through alcoholic probands. Although the strong association between conduct disorder and alcohol dependence would suggest that some genes may contribute to both phenotypes, a sample ascertained expressly for the purpose of studying conduct disorder will yield more definitive evidence of genetic loci contributing to the conduct disorder phenotype. Additionally, the sample size used in these analyses was modest and did not have sufficient power to detect small to moderate genetic effects. However, it is to be noted that the estimated risk ratio of the loci detected in this study ranged from 1.6 to 1.9. Finally, the regions of linkage that were detected in this study would only meet the lod score threshold for suggestive evidence of linkage; replication in independent samples is necessary to better evaluate the potential role of the nominated chromosomal regions.

Despite these limitations, this study has several interesting results, which deserve greater attention in future studies. The overlap of the linkage findings for alcoholism and conduct disorder on chromosome 2 supports the suggestion from twin studies that conduct disorder and alcohol dependence partially share a genetic liability. It is possible that conduct disorder may be a childhood manifestation of some of the genes that later contribute to alcohol dependence. Also, as would be expected when two disorders have only a partially shared genetic liability, we found suggestion of linkage to a region on chromosome 19 that may contain a gene or genes contributing to conduct disorder that has not been implicated in any studies of alcohol dependence. This genome scan represents a first step toward better understanding of the genetic etiology of conduct disorder. The strong relationship between conduct disorder and alcohol dependence, and the possibility that conduct disorder and alcohol dependence share a genetic liability, suggest that further research in this area will help clarify not only the genetic contributions to this important childhood behavioral disorder, but also genetic influences on alcohol dependence itself.

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