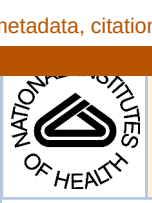

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Externalizing disorders in American Indians: comorbidity and a genome wide linkage analysis

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Abstract

Alcohol dependence is one of the leading causes of morbidity and mortality in Native Americans. Externalizing disorders such as conduct disorder (CD) and antisocial personality disorder (ASPD) have been demonstrated to have significant comorbidity with alcohol dependence in the general population. This study's aims were to: assess the comorbidity of DSM-III-R ASPD and CD with alcohol dependence, to map susceptibility loci for ASPD and CD, and to see if there is overlap with loci previously mapped for alcohol dependence phenotypes in 587 American Indians. Alcohol dependence was found to be comorbid with DSM-III-R ASPD but not CD. However, the amount of alcohol dependence in the population attributable to ASPD and/or CD is low. ASPD and the combined phenotype of participants with ASPD or CD were both found to have significant heritability, whereas no significant evidence was found for CD alone. Genotypes were determined for a panel of 791 micro-satellite polymorphisms in 251 of the participants. Analyses of multipoint variance component LOD scores, for ASPD and ASPD/CD, revealed six locations that had a LOD score of 2.0 or above: on chromosome 13 for ASPD and on chromosomes 1,3,4,14,17 and 20 for ASPD/CD. These results corroborate the importance of several chromosomal regions highlighted in prior segregation studies for externalizing diagnoses. These results also further identify new regions of the genome, that do not overlap with alcohol dependence phenotypes previously identified in this population, that may be unique to either the phenotypes evaluated or this population of American Indians.

Keywords

Native American; conduct disorder; antisocial personality disorder; alcohol dependence; genome scan; heritability

INTRODUCTION

Native Americans have the highest alcohol-related death rates of all ethnic groups, with age adjusted rates attributed to alcohol being five times higher than those for the general U.S. population (Shalala et al., 1999). Depending on the individual tribe sampled and their sanctions concerning alcohol use, prevalence rates of alcohol dependence of 20–80% for men and 10–55% for women have been reported (Beals et al., 2005; Gilder et al., 2004; Kinzie et al.,

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1992; Kunitz et al., 1999a; Robin et al., 1998; Wall et al., 2003). Despite the devastating impact that alcohol has had, the risk factors that may predispose a greater proportion of individuals in some Native American communities to develop alcohol use disorders remains unclear.

Explanations for increased drinking in some Native American communities have often focused on the hypothesis that disruption of their traditional cultures was associated with psychological states of anomie, depression, and/or anxiety which in turn led to increased use of alcohol and alcohol-related problems (see Brave Heart, 2003; Kunitz and Levy, 1994; Levy and Kunitz, 1974; Whitbeck et al., 2004). However, a relatively low prevalence of anxiety and affective disorders combined with a high prevalence of substance use disorders has been reported in SWC Indians (Gilder et al., 2004). Higher rates of substance use disorders and equal or lower rates of "other psychiatric illness" have also been reported in four other studies of Native Americans (Howard et al., 1996; Kasprow and Rosenheck, 1998; Walker et al., 1994).

It appears from the literature that some Native American tribes may experience an earlier age of onset of alcohol dependence than what has been reported for other non-Native samples of alcoholics (Ehlers et al., 2004a). One factor that could theoretically lead to an earlier onset of alcohol dependence in Native Americans is an earlier age of initiation of drinking. In some tribes of American Indians early age of onset of first intoxication was found to be significantly associated with both a shorter time to the onset of alcohol dependence as well as increased probability of developing the disorder in that population (Ehlers et al., 2006). It has been suggested that drinking alcohol at a young age acts as an environmental factor that disrupts the normal course of social and intellectual development leading to an increased risk for social and psychological pathologies including drug addictions (DeWit et al., 2000; York, 1999). An alternate hypothesis has been forwarded suggesting that drug addictions and psychopathology are in fact a reflection of a more general underlying susceptibility to disinhibitory behavior and/or behavioral under-control that may emerge at a young age and influence the initiation of substance use (Clark et al., 2005; Iacono et al., 2002; Jessor and Jessor, 1977; Mc Gue et al., 2006; Slutske et al., 1998, 2002; Wong et al., 1999).

A considerably large literature has clearly documented in the general population that substantial comorbidity exists between antisocial behaviors and substance abuse. Evidence for the covariation of substance use disorders and antisocial behavior is found in both clinical and epidemiological samples in both men and women and in both adolescents and adults (Bucholz, 1999; Compton et al., 2000; Dinwiddie and Reich, 1993; Fu et al., 2002; Goldstein et al., 2006; Holdcraft et al., 1998; Kessler et al., 1997; Regier et al., 1990; Simmons and Havens, 2006; Westermeyer and Thuras, 2005; Wong et al., 1999). In fact, it has been suggested that the relationship between antisocial behavior and substance abuse may be one of the best documented findings in the psychopathology literature (see Waldman and Slutske, 2000). However, documenting comorbidity between disorders does not necessarily imply a causal connection between them or a common etiological pathway.

Both substance dependence and behavioral control disorders, such as conduct disorder and adult antisocial personality disorder, have been shown to have a significant genetic component to their etiology (Button et al., 2005, 2006; Cloninger et al., 1981; Grove et al., 1990; Heath et al., 1997; Kendler et al, 1992, 2003; Prescott and Kendler, 1999; Slutske, 2001). Behavioral genetics studies have the advantage in being one of the strongest methods for determining whether the comorbidity among psychopathological conditions is due to common etiologies and or pathologies associated with the disorders or not. Complex disorders like substance dependence and behavioral under-control may be influenced by a number of genes that may be specific to the etiology of those disorders, or could overlap with other neurobehavioral disorders.

Genetic studies of complex diseases often have advantages when they are conducted in well-defined populations such as Native American tribes living on reservations (Lander and Schork, 1994). The present report is part of a larger study exploring risk factors for substance dependence among Native American Indians (Ehlers et al., 1998, 1999, 2001, 2004a,[b], 2006; Garcia-Andrade et al., 1997; Wall et al., 1997, 2003). The lifetime prevalence of substance dependence in this Indian population is high and evidence for heritability and linkage to specific chromosome locations has been demonstrated (Ehlers and Wilhelmsen 2005, 2006, 2007; Ehlers et al., 2004b; Wilhelmsen and Ehlers, 2005). The purpose of the present set of analyses was to explore the comorbidity of alcohol dependence and other externalizing disorders as well as to identify genetic loci associated with antisocial personality disorder/conduct disorder (ASPD/CD). To accomplish these aims autosomal linkage analysis of data from American Indian families was performed. These data are also discussed in the context of previously published data demonstrating linkage to alcohol and other substance related phenotypes in this population (Ehlers et al., 2004b).

MATERIALS AND METHODS

Participants

Participants who were of mixed heritage but at least one-sixteenth Native American, were recruited from eight geographically contiguous reservations with a total population of about 3,000 individuals. They were recruited using a combination of a venue-based method (Kalton and Anderson, 1986; Muhib et al., 2001), and a respondent-driven procedure (Heckathorn, 1997). The venues used as recruitment sites included tribal halls, health clinics, tribal libraries, and stores on the reservations. Fliers advertising the study were placed in each venue with the phone number of the tribal recruitment coordinator. The venues were also randomly visited by the tribal recruitment coordinator who approached potential participants in order to offer information about and enrollment in the study. Individuals who elected to participate were encouraged to inform other eligible participants, particularly family members, about the study (respondent-driven procedure) (see Ehlers et al., 2004a,c).

To be included in the study a participant had to be an American Indian from one of the four tribes living on one of eight contiguous reservations, between the age of 18 and 70, and to be mobile enough to be transported from their home by van to the General Clinical Research Center (GCRC) of The Scripps Research Institute (TSRI). The protocol for the study was approved by the Institutional Review Board of TSRI, the scientific advisory committee of the GCRC, and the Indian Health Council, a tribal review group overseeing health issues for the reservations where the recruitments were undertaken.

Psychiatric diagnoses

Potential participants first met individually with research staff to have the study explained, give written informed consent, and respond to a screening questionnaire that was used to gather information on demographics, personal medical history, ethnicity and detailed measures of substance abuse history (Schuckit, 1985) and weight & height. Each participant also completed an interview with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994) which was used to make diagnoses (American Psychiatric Association, 1994). The SSAGA is a fully structured, poly-diagnostic psychiatric interview that has undergone both reliability and validity testing (Bucholz et al., 1994; Hesselbrock et al., 1999). It has been successfully used in Native American populations previously (Gilder et al., 2004; Hesselbrock et al., 2000). Interviewers were all trained by personnel from the Collaborative Study on the Genetics of Alcoholism (COGA). All best final diagnoses were made by a research psychiatrist/addiction specialist, trained in the SSAGA. The three externalizing phenotypes were: 1) DSM-III-R Antisocial personality disorder (requires

childhood CD to make the diagnosis), 2) DSM-III-R conduct disorder with no diagnosis of adult ASPD, and 3) The combined phenotype of participants with either 1) or 2) e.g. DSM-III-R conduct disorder/or Antisocial personality disorder.

Analysis of the diagnostic data focused on investigating the frequencies of each disorder (ASPD, CD, ASPD/CD) in men and in women in the entire community sample assessed (n=587), and in the subsample that the linkage analyses were conducted (n=251) (see below). The same calculation was made for each disorder in the alcohol dependent and non-alcohol dependent groups. To determine if significant comorbidity existed between each disorder and alcohol dependence, the odds ratio and 95% confidence interval were calculated for both men and women.

Genetic analyses

One hundred pedigrees containing 885 individuals were used in the genetic analyses. Of these, 528 individuals were from 41 extended families where multiple family members were directly interviewed, data from these individuals were used to calculate heritability of the phenotypes. Fifty-nine families have only a single individual with direct interview data. The individuals in these 59 families were not included in the linkage analyses but were included in the comorbidity analyses and in the calculation of trait means and variance in order to determine the impact of covariates. Two hundred and fifty-one individuals from the 41 extended pedigree families have both genotype and phenotype data and were used in the linkage analyses. The family sizes for the 41 families ranged between 4 and 38 members (average 13.5±10) with between 2 and 15 individuals having both genotype and phenotype data (average 5.4±4.2). The 251 individuals within the 41 families that were genetically informative include: 77 parent-child, 212 sibling, 26 half sibling, 8 grandparent-grandchild, 151 avuncular, and 245 cousin relative pairs. Only sib, half-sib, avuncular and cousin pairs were included as being potentially genetically informative. Family structure and genotype consistency were verified and described previously (Ehlers and Wilhelmsen 2005, 2006, 2007; Ehlers et al., 2004b).

DNA was isolated from whole blood using an automated DNA extraction procedure, genotyping was done as previously described (Wilhelmsen et al., 2003). Genotypes were determined for a panel of 791 autosomal microsatellite polymorphisms (Weber and May, 1989) using fluorescently labeled PCR primers under conditions recommended by the manufacturer (HD5 version 2.0; Applied Biosystems). The HD5 panel set has an average marker-to-marker distance of 4.6 cM, and an average heterozygosity of greater than 77% in a Caucasian population. Allele frequencies were estimated from the entire Indian population with genotype data. Gender and age accounted for greater than 5% of the phenotypic variance for each of the phenotypes. Therefore, age and gender were included as covariates in the analyses.

Genotypes were ultimately determined for 251 subjects. The total additive genetic variance (heritability, h^2) and its standard error were estimated for the CD, ASPD, ASPD/CD phenotypes using SOLAR (http://www.sfbr.org/solar/). Two approaches to estimating heritability were used for the three traits. In the first approach the trait was modeled as a latent normally distributed variable with a threshold above which an individual is considered “affected”. Using a second approach, the same trait was modeled as if it was a normally distributed variable. In this case heritability is higher for the trait modeled as if it was a normally distributed variable. These methods can occasionally give very dissimilar results presumably because of factors related to convergence. In this analysis it was required that both methodologies provide support for heritability prior to linkage analyses. Variance component estimate methods were used to calculate LOD scores using SOLAR v2.0.4 (Almasy and Blangero, 1998) Genhunter 2 (Kruglyak et al., 1996) and Merlin (http://www.sph.umich.edu/csg/abecasis/Merlin/) with similar results. Results are presented

for SOLAR. Simulation analysis was used to estimate empirical LOD scores and make appropriate genome wide adjustments for non-normality when the trait was modeled as normally distributed trait (Blangero et al., 2000). Bivariate analyses of data on chromosome 12 for ASPD/CD and drinking severity, was performed using SOLAR (2.1.4). To test for pleiotropy, by excluding coincident linkage, the method proposed by Almasy et al. (1997) and as elaborated by North et al. (2005) was used. Briefly, the likelihood for the linkage model in which p_q was estimated was compared to the likelihood for the linkage model in which p_q was constrained to 1 (or −1 complete pleiotropy) or 0 (complete coincident linkage).

RESULTS

The demographic characteristics of the sample are virtually equivalent to the U.S. census data for these tribes and have been presented previously for the linkage subsample (see Ehlers et al., 2004b). Two hundred forty seven men and three hundred and forty women participated in the study. Demographic characteristics of participants are shown in Table 1. Demographic comparisons of men and women (not shown in Table 1) showed no significant differences ($p<0.05$) for years of education, economic status, employment, marital status, and Native American heritage. There were no significant differences in the demographics between the linkage sample and the entire sample except that individuals in the linkage sample were more likely to have income lower than $20,000 a year (55% linkage sample, 47% entire sample; $p<0.04$).

Prevalences of each of the externalizing disorders evaluated for men and women are shown in Table 2 for the entire sample (n=587) and the linkage sample (n=251). In the entire sample, 10.5% percent of men and 5% of women had CD. Seventeen percent of men and 7% of women had ASPD, and 28% of men and 11.5% of women had a diagnosis of either CD or ASPD. Similar prevalences were found for the linkage sample (see Table 2).

Comorbidity of each disorder was evaluated by comparing the frequencies of that disorder in the alcohol dependent and non-alcohol dependent groups of individuals. As shown in Table 3, odds ratios and 95% confidence intervals were calculated for each externalizing disorder group for the entire group and men and women separately. Alcohol dependence was found in 65% of the men and 54% of the women in the total sample. Alcohol dependence was found to be comorbid with: ASPD ($p<0.001$) ASPD/CD ($p<0.001$) but did not reach significance for CD alone ($p<0.1$). Alcohol dependence was also found to be comorbid with ASPD, and ASPD/CD in men and women when they were analyzed separately. However, CD was not found to be significantly comorbid with alcohol dependence in either men or women. Similar results were found in the linkage sample.

The estimated heritability (h^2) for the ASPD/CD phenotype was 0.56 ± 0.24 ($p<0.01$) and for ASPD was 0.76 ± 0.1 ($p<0.002$). Significant evidence for heritability was not found for the CD phenotype. Gender ($p=0.00002$ and 0.0009) and Age ($p= 0.007, 0.06$) accounted for 6%, and 5% of the variance observed for ASPD/CD, and ASPD, respectively. As seen in Figure 1 and Figure 2, several regions of interest were identified for the two significantly heritable phenotypes in a genome scan. Six areas were found with LOD scores of 2.0 or above. For ASPD a region on chromosome 13 at 19 cM, and for ASPD/CD on chromosome 1 at 256 cM, on chromosome 3 at 193 cM, on 4 at 66 cM, on 14 at 86 cM, 17 at 129 cM and 20 at 40 cM.

Table 4 presents all loci identified with LOD scores above 1.5 for comparison with other genetic studies that have identified loci for externalizing phenotypes in similar regions of the genome. One region of the genome, on chromome 12, was identified previously in a genome scan for a phenotype of “the severity of alcohol dependence drinking symptomatology” in this American Indian population (Ehlers et al., 2004c). Bivariate analysis of the ASPD/CD

phenotype with the severity of alcohol dependence drinking symptomatology phenotype (LOD score 1.7) produced a combined maximum LOD score of 2.7. Complete pleiotropy can be excluded by this analysis, but the analysis had insufficient power to exclude coincident linkage.

DISCUSSION

It appears that the prevalences of externalizing diagnoses may differ depending on the population sampled. Rates of ASPD in the Epidemiologic Catchment Area (ECA) Study (Regier et al, 1990) (2.6%) were lower than the National Co-morbidity Survey (NCS) (3.5%) (Agosti et al., 2002; Kessler et al., 1994). In the national epidemiologic survey on alcohol and related conditions (NESARC) the lifetime prevalences of ASPD, and CD were 1.1% and 3.6%, respectively (Compton et al., 2005). In that survey they found that Native Americans were more likely to have ASPD than any other ethnic group.

While there have been some well sampled large epidemiological studies of Native American tribes, prevalences of ASPD or CD in those populations have not been reported (Beals et al., 2005). However, there have been some smaller samples that have estimated rates within a specific tribe or a treatment subsample. In this American Indian sample, the lifetime prevalence's of ASPD (11.0%) and CD (7%) were high but were not higher than those reported by Hesselbrock and colleagues (2000, 2003) in Alaska Native alcoholics, in treatment, using the same diagnostic instrument as the present study (ASPD=35%; CD=39%). Duclos et al., (1998) reported that 16.7% of American Indian adolescent detainees on a Northern Plains reservation had a diagnosis of CD. In a southeastern American Indian tribe substance abuse treatment center, 74.2% of the adolescents sampled were found to have a CD diagnosis (Fiscenschjer and Novins, 2003; Novins et al., 2006). In the “Flower of Two Soils Project”, Canadian First Nations children were found to have high rates of CD but low rates of depression (Dion et al., 1998; Sack et al., 1993). Interestingly, low rates of depression and anxiety disorders have also been reported previously in this American Indian population (Gilder et al., 2004)

Perhaps the most informative data on conduct disorder and substance dependence in American Indians has been published by Kunitz and colleagues (1998, 1999a,b). In a study of the Navajo they reported that the prevalence of CD was 22.2% in men and 12.3% in women and the prevalence of alcohol dependence was 70% among men and 29% among women. (Kunitz et al., 1999a). They also reported that CD was not simply a risk factor for alcohol dependence but also for more extreme forms of alcohol- and non-alcohol related problems (Kunitz et al., 1999a). Risk factors for CD in that population were: histories of physical and sexual abuse in childhood; abusive maternal drinking, a small number of households per camp; younger age; and being male (Henderson et al., 1998; Kunitz et al., 1999b). They further speculate that the decline of the livestock economy and the development of a cash economy, and the movement from multiple household camps to agency and border towns causing the disruption of the network of obligations to kin, may have resulted in social structural risk factors for excessive drinking (Kunitz and Levy, 1994) and other externalizing disorders.

ASPD and ASPD/CD were both found to be highly heritable in this American Indian population. There have been few studies of the heritability of the diagnosis of ASPD published previously. In one study, of the Vietnam Era Twin Sample, a heritability of 0.67 was found, similar to the estimated heritability of that trait in this population of American Indians (0.76) (Slutske, 2001). However, significant evidence for a heritable component for CD was not found in this American Indian population. A number of authors have suggested that genetic influences may impact antisocial behaviors in adulthood more than during childhood or adolescence (Cloninger and Gottesman, 1987). Lyons et al., (1995) reported a lower heritability estimate for a CD symptoms scale than a scale of adult antisocial behavior symptoms. Additionally, Hesselbrock and Hesselbrock (1994) noted that among patients being treated for alcohol

dependence, associations of the clinical characteristics of alcohol dependence with CD were much less striking that those with ASPD. Thus, it appears that in some populations that a history of childhood conduct symptoms without subsequent adult antisocial symptomatology may be less associated with alcohol dependence and also may be less genetically regulated. While a larger sample size may uncover evidence for a genetic component for CD in this American Indian population, sources of environmental risk factors should also be considered in understanding the etiology of childhood CD.

Sack et al., (1993) has suggested that cultural disparity, minority status and poverty may be important factors in the genesis of CD in First Nations people, and further speculated that CD rates may be a “barometer of socio-cultural stress” akin to the way neonatal mortality rate is seen as a measure of the quality of overall healthcare. In this regard, Costello et al., (2003) reported on a natural experiment in an American Indian community in the Smoky Mountains where the opening of a casino provided an income supplement that moved 14% of their study families out of poverty. Children in the study were evaluated 4 years before and 4 years after the casino opened. The effect of moving out of poverty was found to be specific to reducing symptoms of conduct and oppositional defiant disorders, whereas anxiety and depression symptoms were unaffected. Taken together these studies provide some support for a social causation explanation of the high prevalence of CD seen in some American Indian communities.

A variety of genetically influenced characteristics may also contribute to the increased risk for substance dependence and other externalizing disorders seen in adulthood, such as ASPD. This study provides some support for this hypothesis through the identification of several sites in the genome that may harbor genes for antisocial behaviors. Analyses of multipoint variance component LOD scores for the dichotomous DSM-III-R phenotypes of ASPD and ASPD/CD revealed six locations, on chromosome 13 for ASPD and on chromosomes 1, 3, 4, 14, 17 and 20 for ASPD/CD that had a LOD score of 2 or above. Only some genetic loci were found to be in common for the two heritable phenotypes (ASPD, ASPD/CD) in this American Indian population. This may be somewhat explained by prior findings in twins where it was demonstrated that genetic influences that contributed to the risk for adult antisocial behaviors also contributed to those same behaviors in childhood but that additional genetics risk factors came into play in adolescence and adulthood that could ultimately result in ASPD and alcohol dependence (Jacobson et al., 2002; Lyons et al., 1995).

Although this is the first published genome scan for ASPD in any population, there are several reports of genome wide scans for “conduct symptoms” and CD that have been previously published (see Dick et al., 2004; Kendler et al., 2006; Stallings et al., 2005). One linkage study, in adolescents, found preliminary evidence for linkage on chromosomes 3 and 9 (Stallings et al., 2003, 2005) for both a “dependence vulnerability” phenotype that consisted of “the average number of dependence symptoms across all classes of substances divided by the number of substances used repeatedly” and a phenotype that indexed the number of DSM-III-R CD symptoms. In another study, evidence suggestive of linkage was identified on chromosomes 2 and 19 and other regions of interest on chromosomes 3 and 12 using the COGA pedigrees (Dick et al., 2004), and in a third study, of Irish alcohol affected sibpairs, evidence suggestive of linkage to CD was found on chromosome 1 and 14 (Kendler et al., 2006).

While it is difficult to compare data between studies, there are two loci of interest for the ASPD phenotype found in this American Indian study that were also identified within the same general chromosome locations in previously published linkage analyses of conduct disorder. A location on chromosome 2, found in the present study, was in the general location to regions on chromosome 2 reported previously for CD symptoms phenotypes in the COGA study (Dick et al., 2004) and in the Irish alcohol affected sibpairs study (Kendler et al., 2006). Another

locus on chromosome 10 seen in the present study is generally with a region previously identified in a linkage analyses conducted using the Irish affected sibpairs study (Kendler et al., 2006).

There are three loci of interest for the ASPD/CD phenotype found in this American Indian study that were in a similar location to those identified in previously published linkage analyses for externalizing behaviors. A broad region on chromosome 3 supporting evidence suggestive of linkage for ASPD/CD in these American Indians was found in a similar location (within 30 cM) by another study for conduct symptoms (Stallings et al., 2005) and drug abuse vulnerability (Stallings et al., 2003).

While the ASPD and ASPD/CD phenotypes were found to be highly significantly comorbid with alcohol dependence in these American Indians it should be noted that the amount of alcohol dependence in this population that is actually attributable to those phenotypes is low. This finding was also highlighted in the studies by Kunitz and colleagues in the Navajo where high rates of CD and alcohol dependence were found but the amount of alcohol dependence that was attributable to CD was low (Kunitz et al., 1999a). This suggests that while ASPD/CD may be highly associated with alcohol dependence and may explain risk for alcohol dependence in a segment of the population other risk factors most likely explain a larger amount of genetic and environmental variance for alcohol dependence in the larger aggregate population.

Only a few chromosome locations found to be associated with the ASPD and ASPD/CD phenotypes were also found to overlap with those reported previously for alcohol related phenotypes in this population (see Ehlers et al., 2004b). One site on chromosome 4 that was identified for the ASPD/CD phenotype in these American Indians was near to a locus previously reported by Long et al., (1998) for alcohol dependence in Southwest Indians. Additionally, a site on chromosome 12 that was reported by Ehlers et al., (2004b) in this American Indian population for the “severity of alcohol dependence drinking symptomatology” was found to be associated with ASPD/CD in the present genome scan. Bivariate analysis of ASPD/CD with severity of alcohol dependence drinking symptomatology (LOD score 1.7) produced a combined maximum LOD score of 2.7 at that site on chromosome 12, however, but was insufficient power to exclude coincident linkage. Taken together these studies suggest that current evidence does not support the existence of areas of the genome that have significant common influence on alcohol dependence and ASPD, CD, or ASPD/CD, in this American Indian population.

However, the concordance between studies in identifying general areas in the genome that are associated with externalizing phenotypes suggests that the search for candidate genes within those locations may be productive in identifying some general mechanisms that may underlie these behaviors. In one recent study, for instance, Dick et al., (2006) found that the *GABRA2* gene was associated with childhood conduct disorder symptoms in children and adolescents. *GABRA2* is located on chromosome 4 in the general region that an area of interest for the ASPD/CD phenotype in these American Indians was found, and which Long et al., (1998) found linked to alcohol dependence in Southwest Indians. One region that may be intriguing is the area on chromosome 3 reported by Stallings et al., (2003,2005) for conduct symptoms and drug abuse vulnerability. This general location was also uncovered in the present study and it harbors genes for the 5-hydroxytyrptamine receptor 3 (*HTR3D, HTR3E*). Preclinical studies have demonstrated the important role of serotonin pathways in drug abuse liability and as such 5-HT receptors may be an important target of study (see Barr and Goldman, 2006; Johnson, 2004). Unfortunately, at this time it is not possible to know what genes may actually be contributing to the linkage peaks identified in this study or in any other studies that have uncovered areas of the genome linked to externalizing phenotypes. However, future studies

employing whole genome association analyses may contribute to the identification of such genes.

In conclusion, these data represent the first genome-wide scan using ASPD as a phenotype. The results corroborated the possible importance of several chromosomal regions highlighted in prior linkage studies for conduct disorder and other externalizing phenotypes and identify new regions of the genome. The results of this study should be interpreted in the context of several limitations. First, the sample size was limited and replication of the findings in a larger sample within this population is necessary. Second, the findings may not generalize to other Native Americans. Third, comparisons of linkage findings to non-Indian populations may be limited by differences in a host of potential genetic and environmental variables. Fourth, the underlying assumption that these phenotypes are normally distributed, an assumption of variance component analyses, may not be warranted. Finally, because this population has significant admixture, estimates of allele frequencies may produce biased LOD scores. Despite these limitations, this report represents an important first step in an ongoing investigation to understand the genetic determinants associated with the development of substance use disorders in this high risk and understudied ethnic group.

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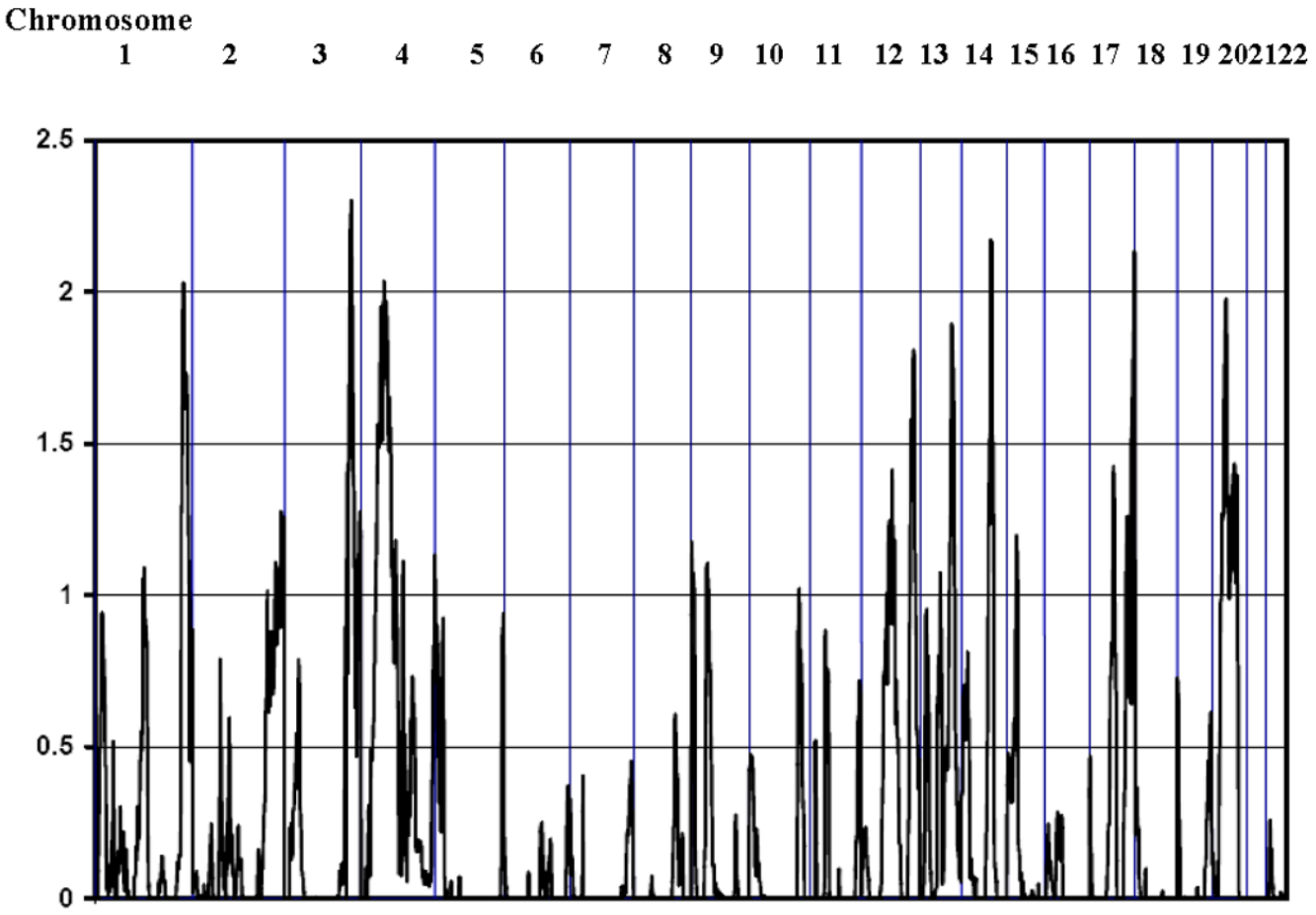

Figure 1.
Multipoint Linkage Analysis for the ASPD/CD phenotype for the entire genome. Results for each chromosome are aligned end to end with the p terminus on the left. Vertical lines indicate the boundaries between the chromosomes. The numbers above on the X-axis indicate the chromosome number.

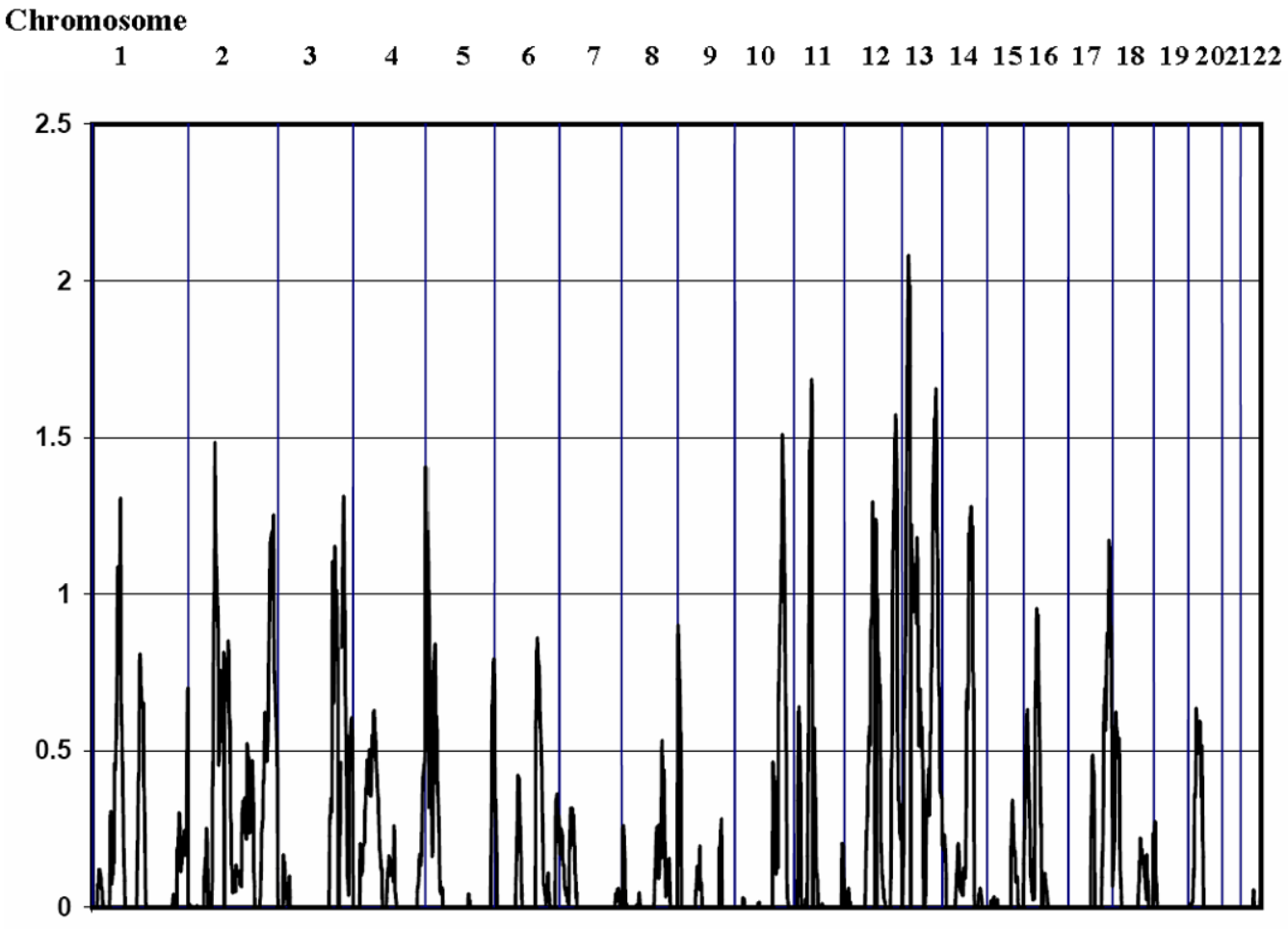

Figure 2.
Multipoint Linkage Analysis for the ASPD phenotype for the entire genome. Results for each chromosome are aligned end to end with the p terminus on the left. Vertical lines indicate the boundaries between the chromosomes. The numbers above on the X-axis indicate the chromosome number.

Table 1

Demographic Characteristics of American Indians Comparing the Full Sample (n = 587) to the Linkage Sample (n = 251)

Variable	Full sample (n = 587)	Linkage sample (n = 251)
Age (range, mean, SE)	18–76, 30.4 (0.5)	18–73, 30.2 (0.7)
Blood degree < 50%	61.3%	60.2%
Blood degree ≥ 50%	38.7%	39.8%
Gender	M = 247, F = 340	M = 110, F = 141
Education (years, mean, SE)	11.6 (0.1)	11.5 (0.1)
Income < $20,000/year	47.3%	55.4%
Income ≥ $20,000/year	52.7%	44.6%
Not married	82.4%	80.3%
Married	17.6%	19.7%

Table 2

Frequencies of Lifetime DSM-III-R Externalizing Disorders in American Indians

Externalizing Disorder	Linkage Sample (n=251) % (n)	Total Sample (n=587) % (n)
CD		
Men	12 (13)	10.5 (26)
Women	6 (9)	5 (16)
Total	9 (22)	7 (42)
ASPD		
Men	20 (22)	17 (43)
Women	6 (8)	7 (23)
Total	12 (30)	11 (66)
ASPD/CD		
Men	32 (35)	28 (69)
Women	12 (17)	11.5 (39)
Total	21 (52)	18 (108)
Alcohol Dependence		
Men	77 (85)	65 (162)
Women	53 (75)	54 (184)
Total	64 (160)	59 (346)

Table 3

Comorbidity of Lifetime DSM-III-R Externalizing Disorders with Alcohol Dependence in American Indians (n=587)

Externalizing Disorder	Alcohol dependent (n = 346) % (n)	Non-alcohol dependent (n = 241) % (n)	OR	95% CI	Fisher p-value
CD					
Men	12.4 (20)	7.1 (6)	1.85	0.72–4.81	0.275
Women	5.4 (10)	3.9 (6)	1.44	0.51–4.05	0.610
Total sample	8.7 (30)	5.0 (12)	1.81	0.91–3.61	0.104
ASPD					
Men	24.7 (40)	3.5 (3)	8.96	2.68–29.94	<0.001
Women	11.4 (21)	1.3 (2)	9.92	2.29–43.02	<0.001
Total sample	17.6 (61)	2.1 (5)	10.10	3.99–25.55	<0.001
ASPD/CD					
Men	37.0 (60)	10.6 (9)	4.97	2.32–10.63	<0.001
Women	16.9 (31)	5.1 (8)	3.75	1.67–8.42	0.001
Total sample	26.3 (91)	7.1 (17)	4.70	2.72–8.13	<0.001

Table 4

Genetic Loci for Externalizing diagnoses in American Indians

CHR	Trait	LOC (cM)	LOD	Nearest Marker	Supporting References, (phenotype), [proximity to peak]
2	ASPD	79	1.5	D2S337	Dick et al., 2004 (conduct symptoms) [20 cM]; Kendler et al., 2006 (conduct symptoms) [10 cM]
10	ASPD	141	1.5	D10S1693	Kendler et al., 2006 (conduct symptoms) [1 cM]
11	ASPD	52	1.7	D11S4102	
12	ASPD	152	1.6	D12S1675	
13	ASPD	19	2.1	D13S289	
1	ASPD/CD	256	2.0	D1S2670	Kendler et al., 2006 (conduct symptoms) [60 cM]
3	ASPD/CD	193	2.3	D3S3609	Stallings et al., 2003, 2005 (drug dependence vulnerability, conduct symptoms) [30 cM]
4	ASPD/CD	66	2.0	D4S428	Long et al., 1998 (alcohol dependence) [6 cM]
12	ASPD/CD	152	1.8	D12S1675	Ehlers et al., 2004b (severity of alcohol dependence drinking symptomatology) [2 cM]
13	ASPD/CD	91	1.9	D13S1322	
14	ASPD/CD	86	2.2	D14S68	
17	ASPD/CD	129	2.1	D17S928	
20	ASPD/CD	40	2.0	D20S912	