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Evidence for a Genetic Component for Substance Dependence in Native Americans

Cindy L. Ehlers, PhD and

Department of Molecular and Integrative Neurosciences, The Scripps Research Institute, La Jolla, California, USA

Ian R. Gizer, Ph.D.

Department of Psychological Sciences, University of Missouri, Columbia, MO, USA

Abstract

Objective—Although tribes differ with regard to the use of alcohol and drugs, substance dependence is one of the most important sources of health problems facing Native Americans. Although substance dependence has shown a substantially heritable component (~50% of the risk resulting from genetic influences), in the general population, fewer studies have investigated the role of genetics in the risk for substance dependence in Native Americans.

Methods—A literature review of the evidence for a genetic component in the etiology of substance dependence in Native Americans is presented including studies on heritability, linkage analyses, and candidate genes.

Results—Evidence for the heritability of alcohol and drug dependence was found. Linkage analyses revealed that genes influencing risk for substance dependence and related phenotypes, such as body mass index, drug tolerance, EEG patterns and externalizing traits, reside on several chromosome regions identified in other population samples. Overlap in the gene locations for substance dependence and body mass index suggest a common genetic substrate may exist for disorders of consumption. Studies of the genes that code for alcohol metabolizing enzymes have not revealed any risk variants specific to Native American populations, although most Native Americans lack protective variants seen in other populations. Other candidate genes associated with substance dependence phenotypes in Native Americans include: *OPRM1*, *CRN1*, *COMT*, *GABRA2*, *MAOA*, and *HTR3-B*.

Conclusions—Substance dependence has a substantial genetic component in Native Americans, similar in magnitude to that reported for other populations. The high rates of substance dependence seen in some tribes is likely a combination of a lack of genetic protective factors (metabolizing enzyme variants) combined with genetically mediated risk factors (externalizing traits, consumption drive, drug sensitivity/tolerance) that combine with key environmental factors (trauma exposure, early age of onset of use, environmental hardship/contingencies) to produce increased risk for the disorder.

Keywords

Alcohol dependence; drug dependence; Native Americans; heritability; linkage analyses; population genetics

Address correspondence to Cindy L. Ehlers, Department of Molecular and Integrative Neurosciences, The Scripps Research Institute, 10550 N. Torrey Pines Road, SP30-1501, La Jolla, CA, USA, 92037. cindy@scripps.edu.

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INTRODUCTION

Although tribes differ with regard to the use of alcohol and drugs, the U.S. Indian Health Service has cited alcohol, tobacco and drug dependence as one of the most urgent health problems facing Native Americans [1]. Large scale U.S. epidemiological studies, demonstrate that compared to other U.S. ethnic groups Native Americans have the highest rates of alcohol and other drug dependence [2] and Native American adolescents have been shown to have the highest rates of substance use and substance-related disorders [3]. Lifetime rates of alcohol dependence, in the small number of individual tribal groups studied, have been reported as 20%–70% [4–6], higher than the epidemiological rate of DSM-IV alcohol dependence of 13% in the U.S. general population [7]. The causes for increased rates of alcohol and drug dependence in Native Americans are thought to have both environmental and genetic determinants.

Early socio-cultural theories posited that Native American alcohol use and abuse was a result of loss of traditional community lands, cultures and ties coupled with the stress of acculturation; however, there has been little direct evidence to support such theories [8]. More recent theories have presented data to support an association between alcohol dependence and such factors as personal and historical trauma (see [9–10]), early age of onset of drinking [11] as well as lack of contingency between access to basic life reinforcers (employment, housing, education and health care) and sobriety [12].

There have also been psychobiological theories developed to explain the excessive drinking seen in some Native Americans. One theory of problem drinking, called the “firewater myth,” hypothesized that Native Americans are physiologically unable to handle alcohol and thus experience “loss of control” following alcohol consumption and problem drinking [13]. However, recent empirical studies of alcohol drinking in the laboratory in Native Americans provide no support for such theories [14]. Additionally, the “firewater” theory is inconsistent with an extensive literature demonstrating that a *diminished* response to alcohol is predictive of the future development of alcohol-related problems in most populations [15], including Native Americans [14].

The contribution of genetic factors to the development of alcohol and other drug dependence has been consistently supported by numerous family, twin, and adoption studies in general population samples. Although the mode of transmission of this increased risk is unclear, most investigators favor a model where a genetic predisposition interacts with environmental variables to produce an overall risk for the disorder. It is also likely that complex disorders like substance dependence are influenced by a large number of genes of small effect. While many of these genes may be specific to the etiology of these disorders, others likely overlap with other psychiatric and metabolic disorders. For example, substance dependence and obesity both occur more frequently in some Native American populations. One theoretical assumption concerning Native people is that the long history of dependence on foraging and subsistence agriculture may have led to selective enrichment of traits that improve genetic fitness, so called ‘thrifty’ or ‘fat sparing’ genes. It has been suggested that this same selective pressure may have enriched for genetic variants that increase the risk for consumption of alcohol and perhaps other drugs of abuse providing another potential pathway that could give rise to shared genetic influences between these traits [16–17].

The present report presents a review of the findings supporting a substantial genetic component contributing to the development of substance dependence in Native Americans. Such findings have the potential to yield important insights into the genetics of substance dependence given that genetic epidemiology studies conducted in well-defined populations, such as Native American tribes, can be particularly informative given the relative

environmental and genetic homogeneity of some these populations compared to larger, more stratified general population samples.

METHODS

A review of the evidence for a genetic component in the etiology of substance dependence in Native Americans was conducted. A literature search was conducted using the PubMed and Google Scholar databases and keywords related to Native Americans, alcohol and substance abuse and dependence. The reference sections of identified studies were reviewed to identify additional studies. Because the present review was qualitative in nature, all identified studies that reported either qualitative or quantitative results for a Native American sample were included in the present review. Reviewed studies were primarily conducted in three populations, a California Indian population (Mission Indians), a Southwest American Indian population, and a Plains Indian population. The names of the tribes included in this review are not formally identified in order to avoid potential stigma to the populations studied. The three primary sources of genetic studies (California, Southwest, Plains) utilized community samples. Studies estimating the heritability of substance dependence diagnoses and related phenotypes are reviewed first, followed by reviews of genetic linkage studies examining these phenotypes, thirdly with a review of candidate gene studies, and finally a summary.

RESULTS

Evidence for heritability of substance use and dependence in Native Americans

The heritability of drug and alcohol dependence and related phenotypes has been studied in at least 3 Native American populations. In these studies, heritability (h^2) estimates were obtained from data collected in large extended families. The earliest study was conducted in the Southwest American Indian population and found that DSM-III-R alcohol dependence was heritable, though exact heritability estimates were not presented [18]. Alcohol dependence in the California Indian population showed some evidence of heritability (DSM-III-R: .19, DSM-IV: .38) [19], and was also found to be associated with degree of Native American Heritage [20]. However, little evidence was found for the heritability of alcohol dependence in the Plains Indian population (David Goldman personal communication, 2008). In contrast, twin studies of alcohol dependence have consistently yielded significant evidence of heritability, ranging from .50-.65 using general population samples with participants of predominantly Caucasian origin [see 21].

One potential explanation for these discrepant findings is that high prevalence rates of the disorder among Native Americans may make it difficult to detect genetic influences. Alternatively, the heritability of disorders like alcohol dependence may be reduced or difficult to detect, in some populations, because only some aspects of the diagnosis may be heritable. Two symptoms that have been long associated with severe alcohol dependence are withdrawal and tolerance, specified in DSM-IV as alcohol dependence with a “physiological component.” In the California Indian population, evidence for the heritability of DSM-III-R symptoms of alcohol dependence with withdrawal (.71) and symptoms of alcohol dependence associated with heavy drinking (.37) were found to be heritable [20-21] whereas psychosocial problems associated with alcohol dependence were not. These findings are consistent with those of a previous general population twin study demonstrating that some specific alcohol dependence symptoms, including withdrawal symptoms, are more heritable than others, but also differ in that the latter study reported that heritability estimates of specific symptoms did not exceed that of the alcohol dependence diagnosis [22]. These studies suggest that specific facets of alcohol dependence most likely have a genetic

component whereas others, particularly those associated with psychosocial impairment but not heavy drinking, may not.

Evidence for the heritability of the use of and dependence on other illicit drugs has also been investigated in the California Indians. Heritability for initiating use was found to be high for marijuana (0.59), opiates (0.58), PCP (0.51), sedatives (0.49), and stimulants (0.38). Heritability was only modest for initiation to cocaine (0.14), hallucinogens (0.26), and solvents (0.13). The heritabilities of drug dependence diagnoses and symptoms were also estimated in that population and found to be significant for marijuana dependence with antisocial traits [23], stimulant dependence with craving [24], and heavy tobacco usage [25]. Taken together, these studies suggest that both initiation of drug use and transition to dependence have a significant genetic component. These findings are largely consistent with findings from general population twin studies suggesting substantial genetic influences, in the same numerical ranges, in the liability for the initiation of illicit drug use as well as the transition to dependence [see 26].

Genome scans for substance use and dependence in Native Americans

The first whole autosomal genome scan for genetic linkage to alcohol dependence was conducted in the Southwest American Indian population. In that study highly suggestive evidence for linkage, expressed as the log of the odds (LOD score) of a locus being linked to the phenotype rather than unlinked, emerged for two genomic regions. The best evidence was seen on chromosome 11p15.5 (LOD score: 3.1) near the D4 dopamine receptor (*DRD4*) and tyrosine hydroxylase (*TH*) genes, with secondary evidence on chromosome 4p11-p13 near the alpha 2 and beta 1 GABA receptor genes (*GABRA2* and *GABRB1*, respectively) and 4q23-q25 near the alcohol dehydrogenase gene cluster [18]. Evidence for linkage has also been demonstrated for three alcohol dependence phenotypes in California Indians. The strongest result was reported for chromosome 5q21.2-q21.3 in a study of an alcohol craving phenotype (LOD score 4.5) [16]. Chromosomes 4q22.1 and 12q24.32 yielded LOD scores exceeding 2 for an alcohol use severity phenotype, and chromosomes 6p21.1, 15q22.2-q25.3, and 16p13.3 yielded LOD scores that exceeded 2 for a withdrawal phenotype [20]. The evidence for linkage to chromosomes 4, 15, and 16 have been reported previously for alcohol related phenotypes in the collaborative study on the genetics of alcoholism (COGA), suggesting these regions of the genome confer risk and protection for alcohol dependence in Native Americans as well as general population samples.

Evidence for linkage has also been demonstrated in genome scans for other drugs of abuse in Native Americans including marijuana, stimulants, and tobacco. A genome scan using a marijuana dependence phenotype that also included externalizing traits uncovered a LOD score of 4.4 on chromosome 16q24.1, as well as a LOD score of 6.4 on chromosome 19q13.33 [23]. Genome scans have also been conducted to map loci associated with stimulant dependence (amphetamine, cocaine) phenotypes in California Indians. In that study linkage analysis revealed a locus with a LOD score of 3.02 on chromosome 15q22.3 near the nicotinic receptor gene cluster. A genome scan for loci associated with tobacco usage in California Indians identified a region with a LOD score that exceeded 3.0 on chromosome 4q22.1 in a bivariate analysis with an alcohol drinking severity phenotype [25]. This finding suggests that a region of chromosome 4q22.1 harbors a gene(s) that jointly influences alcohol dependence and tobacco use phenotypes.

In order to test the theory that dependence on drugs of abuse may have similar genetic underpinnings to other consumptive disorders such as obesity, the results of the genome scan for “any drug dependence” was compared to a genome scan for body mass index (BMI). Evidence for linkage was found on chromosome 6q25.2-q25.3 for both the ‘any drug’ (LOD score = 3.3) and BMI (LOD score = 2.3) phenotypes. Bivariate analyses of the

two phenotypes revealed a combined LOD score of 4.1 at that location with evidence of pleiotropy (i.e., a single genetic locus influencing more than one trait). This result provides preliminary data suggesting that ‘consumption phenotypes’ may share common genetic determinants thus providing a potential explanation for the elevated rates of substance dependence and obesity in some Native American populations [17].

Genome scans for substance use-related phenotypes in Native Americans

There are a number of environmentally and genetically influenced risk factors that could potentially enhance the development of substance dependence. One set of factors is the presence of co-morbid internalizing (anxiety and depression) and externalizing (antisocial personality/conduct) disorders. One theory of the cause of the increased rates of substance use disorders seen in some Native American tribes is that memories of historical and current trauma, conditions on reservations, prejudice, economic hardship, etc. may lead to increased rates of anxiety and depression leading to increased substance use and dependence, a hypothesis called “self medication”. However, a number of investigators have studied the co-morbidity of substance use and dependence with internalizing disorders and do not find increased rates of internalizing disorders [see 27].

In contrast, higher rates of externalizing disorders and substance dependence have been reported in several studies of Native American communities and clinic samples [28-29]. Only one study has examined the evidence for shared genetic influences between these diagnostic categories in Native Americans [30]. In that study, antisocial personality disorder (0.76) and antisocial personality disorder/conduct disorder (0.56) were found to be highly heritable and co-morbid with drug and alcohol dependence. Additionally, suggestive evidence for linkage (LOD score > 2.0) was found on chromosomes 1q43, 3q27, 4q12, 14q31.3, 17q25.3, and 20p11.23. Each of these linkage peaks have been related to alcohol and other substance use phenotypes in studies of other ethnic groups, and the loci identified on chromosomes 1 and 3 have been related to conduct symptoms in other linkage studies using general population samples [31]. Again, these studies suggest that the regions of the genome that influence externalizing disorders and substance dependence in Native Americans are most likely similar to those found in the general population.

A second set of factors specifically hypothesized to improve the power to identify genetic variants related to substance use disorders are collectively referred to as endophenotypes. Electrophysiological measures provide one example of an endophenotype for substance use disorders. Electrophysiological measures are highly heritable indices of brain function shown to be relevant to the processes involved in the development of substance dependence both in the general population [32], as well as in Native Americans [33]. Evidence that EEG measures represent specifically promising endophenotypes for substance use disorders has been presented in a number of studies published using the COGA dataset [see 34]. Similar findings in Native American populations have now been described in several studies [35-39]. In one study of the California Indian population [38], EEG alpha phenotypes were found to be heritable (0.67), and in a second study [37] linkage analysis revealed two loci that had a LOD score of 3.0 or above for the fronto-central scalp region on chromosomes 1p36.31-p36.22 and 6p21.1. Additionally, 4 locations were identified with LOD scores above 2.0 on chromosomes 4q22.1, 11p14.1, 14q32.2, 16q12.2 for the fronto-central location and one on chromosome 2p12 for the centro-parietal-occipital location. These results corroborate the importance of regions on chromosome 4 and 6 highlighted in prior segregation studies in this and other populations for alcohol dependence-related phenotypes, as well as areas that overlap with other substance dependence phenotypes identified in previous linkage studies. Notably, further research is needed to determine whether the described linkage peak on chromosome 4 can be explained by polymorphisms in *GABRA2* as reported by COGA [40] or polymorphisms in another gene. Nonetheless, these results

support the general use of EEG traits and specifically support EEG alpha recorded from fronto-central scalp areas as important endophenotypes for alcohol and other substance dependence [37-38].

Two additional studies using EEG frequency measures as endophenotypes for substance use disorders were conducted in the Plains Indian population. In the first study, the authors conducted a genomewide linkage study that yielded significant evidence of linkage to a region of chromosome 5q13-14 containing the corticotropin releasing hormone-binding protein gene (*CRHBP*). Follow-up association studies suggested a relation between polymorphisms in this gene and alcoholism in a Caucasian sample but not in the Plains Indian population. In the second study, the authors conducted a genomewide association scan of EEG power phenotypes. Significant associations were observed between theta power and polymorphisms in the SH3-domain GRB2-like (endophilin) -interacting protein 1 gene (*SGIP1*) on chromosome 1p31.3 that also yielded an association with alcohol dependence in this sample [39]. Notably, this was not replicated in the COGA dataset [41]. Though preliminary, the studies conducted in the California Indian and Plains Indian populations demonstrate the utility of EEG phenotypes in identifying genetic loci that confer risk for these disorders.

Another endophenotype that has been described is related to an individual's sensitivity to a given substance. A lowered individual sensitivity to alcohol has been demonstrated to be an inherited factor that affects the likelihood of drinking and mediates, in part, the disposition for developing alcoholism [15]. In one empirical study, California Indian participants, like Caucasian sons of alcoholics, were found to have less intense objective and subjective effects of alcohol in an alcohol challenge paradigm. Additionally, participants with at least 50% Native American heritage reported less intense effects of alcohol than did those with less than 50% Native American heritage, despite equivalent blood alcohol concentrations [14]. Further, Ehlers and colleagues [42] asked participants in the California Indian population to provide retrospective reports of their responses to alcohol during the first five times they had ever drank alcohol using the Self-Rating of the Effects of Alcohol (SRE) questionnaire. A linkage analysis using these responses as the phenotype, revealed loci on chromosomes 6q25.2 and 9p24.1 that had a LOD score greater than 3.0. Like the EEG studies previously described, these studies provide support for the use of an individual's sensitivity to a given substance as an important endophenotype for alcohol and other substance use disorders in Native Americans as well as in general population samples [42].

A summary of the linkage findings for substance use phenotypes in Native Americans is provided in table 1.

Candidate gene studies for alcohol and other drug dependence in Native Americans

The genes involved in alcohol metabolism represent obvious candidate genes for alcohol misuse disorders, and thus, have been the focus of much research in a number of different ethnic populations. The seven alcohol dehydrogenase (ADH) genes, *ADH7*, *ADH1C*, *ADH1B*, *ADH1A*, *ADH6*, *ADH4*, and *ADH5*, are located in a single cluster on chromosome 4q21-24 with each gene coding for a unique isozyme. The relation between this chromosomal region and alcohol dependence has been reported in a number of linkage studies of diverse ethnic groups including Native Americans [20], and association studies have now produced replicable evidence of association between polymorphisms in these genes and alcohol-related phenotypes in Native Americans. For example, two functional polymorphisms were identified in the *ADH1B* gene that have been used to describe the presence of three alleles, *ADH1B**1, *ADH1B**2 (identified by rs1229984), and *ADH1B**3 (identified by rs2066702). The *ADH1B**2 and *ADH1B**3 alleles have demonstrated a protective relation with alcohol dependence and related phenotypes in Asian and Caucasian

samples and African-American samples respectively, and both alleles have been observed in the studied Native American populations. The *ADH1B**2 allele was observed in both the California Indian and Southwest American Indian populations. The *ADH1B**3 allele, which has only been observed in the California Indian population has been associated with reduced risk for alcohol dependence, reduced alcohol consumption, and reduced risk for alcohol withdrawal [43-44]. Studies of other Native American samples, however, have not observed the presence of the *ADH1B**3 allele in their samples [45]. Additionally, a polymorphism in the promoter region of *ADH4* (rs3762894) that has been shown to produce a more active version of the ADH enzyme [46] has shown a protective association with alcohol misuse phenotypes in multiple Caucasian and Native American populations. This polymorphism has shown evidence of association with reduced risk for alcohol withdrawal in the California Indian population [43] and with reduced risk for alcohol dependence in the Southwest American Indian and Plains Indian populations [45]. Although an initial study suggested a relation between a functional polymorphism in *ADH1C* (rs698; [47]), subsequent studies have failed to detect a relation between alcohol misuse phenotypes and *ADH1C* polymorphisms [43, 45], including a proline-threonine substitution in codon 351 of *ADH1C* (rs35719513) that has been observed almost exclusively in Native American populations [48].

The two aldehyde dehydrogenase (ALDH) genes involved in alcohol metabolism are *ALDH1A*, located on chromosome 9q21.13, and *ALDH2*, located on chromosome 12q24.2. The *ALDH2* enzyme is the primary enzyme responsible for acetaldehyde metabolism, and a mutation in *ALDH2* (commonly referred to as the *ALDH2**2 allele) produces a largely inactive aldehyde dehydrogenase enzyme that leads to elevated acetaldehyde levels when alcohol is consumed. This *ALDH2**2 allele has been shown to produce an aversive flushing reaction and an increased level of response to alcohol that is associated with lower rates of alcohol use and alcoholism in Japanese and Chinese samples demonstrating its protective effect against the development of alcoholism [46]. Nonetheless, this allele does not appear to be present in Native American populations [49].

The second ALDH gene, *ALDH1A1*, appears to play a lesser role in acetaldehyde metabolism relative to *ALDH2*, but a growing number of studies suggest that this gene contains one or more polymorphisms that influence alcohol related phenotypes in Native American populations. One of the earliest reported results involved a 17 base-pair (bp) deletion in the promoter region of *ALDH1A1* commonly referred to as the *ALDH1A1**2 allele. Similar to the reports for *ALDH2* in Far East Asian populations, this allele has been associated with a reduced risk of alcohol dependence, reduced alcohol consumption, and reduced risk of cigarette smoking [50]. Additional polymorphisms in *ALDH1A1* have shown relations with alcohol dependence in the Southwest American Indian and Plains Indian populations [45] and Caucasian [51] populations. Thus, *ALDH1A1* represents an interesting candidate gene with respect to alcoholism in several populations including Native Americans.

Investigations of candidate genes other than those coding for alcohol metabolizing enzymes in Native American populations have thus far included those genes involved in drug-reward pathways, serotonergic genes, and positional candidates based on previous linkage studies. For example, polymorphisms in the *CNR1* gene, which encodes for the cannabinoid receptor type 1, have been related to a number of alcohol, cannabis, and other substance use phenotypes in multiple populations including the COGA sample [52]. In the California Indian sample, *CNR1* polymorphisms were associated with a trait measure of impulsivity [53]. Trait impulsivity is hypothesized to underlie the lack of behavioral control associated with substance use disorders, and thus, this finding suggests that *CNR1* may act as a general risk factor for alcohol and drug misuse.

In the Southwest American Indian and Plains Indian populations, associations between alcohol-related phenotypes and polymorphisms in several GABA receptor genes have been tested. A region of chromosome 4p containing *GABRA2*, *GABRB1*, and the GABA 1G receptor gene (*GABRG1*) has been identified as a susceptibility locus in previous linkage scans of alcohol dependence and quantitative EEG traits in the COGA sample [34]. Additionally, polymorphisms in *GABRA2* and *GABRG1* have shown evidence of association with alcohol use phenotypes [40]. In the Plains Indian sample, *GABRA2* and *GABRG1* polymorphisms have yielded evidence of association with alcohol misuse diagnoses [54-55]. In the Southwest American Indian sample, a second GABA receptor gene cluster located on chromosome 5q34 containing the GABA 1A (*GABRA1*), GABA 6A (*GABRA6*), GABA B2 (*GABRB2*), and GABA G2 (*GABRG2*) receptor genes has also yielded evidence of association with alcohol dependence with evidence suggesting the association is due to a causal variant in *GABRA6* [56]. Studies of other ethnic groups including Caucasian [57] and Asian populations [58] have reported similar associations with *GABRA6* polymorphisms.

Other candidate genes that have shown evidence of association with alcohol and other drug misuse phenotypes in Native Americans includes *OPRM1*, which encodes for the mu opioid receptor and is the primary site of action for opioids such as morphine and heroin [59], the serotonin 1B receptor gene (*HTR1B*) [60], the catechol-O-methyltransferase gene (*COMT*), which encodes for an enzyme involved in synaptic dopamine metabolism, and the alpha-synuclein gene (*SNCA*), which encodes for a protein involved in dopamine neurotransmission. A summary of these and additional candidate gene studies of alcohol and other substance misuse phenotypes conducted in Native American samples is provided in Table 2. A review of this table highlights that with a few exceptions, these genes have been investigated in only a single study. Additionally, each of these genes have been studied in relation to alcohol and drug related phenotypes in other ethnic groups yielding a mix of both positive and negative results [21, 61]. Thus, given the low replication rate that has been noted for candidate gene studies of complex traits in general and for the relations between the described candidate genes and alcohol and substance use phenotypes specifically, it is important to note the preliminary nature of these findings and the need for additional studies in larger Native American samples.

Candidate gene studies of some substance related endophenotypes have also been conducted. For example, a study conducted in the Plains Indian sample suggested that EEG alpha power, which was related to co-morbid alcohol dependence and antisocial personality disorder, showed a significant relation with polymorphisms in the serotonin 3B receptor gene (*HTR3B*; [62]). EEG alpha power also demonstrated a relation with the same *COMT* polymorphism that was associated with alcoholism and smoking women in the Plains Indian sample [63]. Thus, these studies provide further support for the use of EEG measures as endophenotypes for alcohol and other substance use disorders.

A final area of study to be discussed in the context of candidate gene studies is gene-environment interaction studies. Several gene-environment interaction studies of substance use disorders have been conducted in Caucasian samples, but only one such study has been conducted in a Native American population. This study investigated whether a relation between a functional polymorphism in the monoamine oxidase A gene (*MAOA*) and alcoholism and antisocial personality disorder was moderated by childhood sexual abuse in the Southwest American Indian population [36]. The *MAOA* gene has been previously implicated in antisocial personality disorder, and in one of the first gene-environment interaction studies conducted, the relation between *MAOA* and antisocial behavior was moderated by childhood maltreatment such that individuals possessing the 'high-risk' genotype and were abused in childhood were more likely to exhibit antisocial behavior later

in life relative to the other groups [64]. A similar interaction was observed in females from the Southwest American Indian population in which women with the 'high-risk' genotype were more likely to develop co-morbid alcohol dependence and antisocial personality disorder but only if they were exposed to childhood sexual abuse. Though preliminary, this study highlights the potential impact of gene x environment interaction studies.

DISCUSSION AND CONCLUSIONS

This review began with a summary of quantitative genetic studies establishing the heritability of the substance misuse diagnoses as well as the increased heritability of a more severe form of alcohol and drug dependence characterized by symptoms of increased tolerance and withdrawal. The review then presented evidence from linkage analyses and candidate gene studies suggesting relations between specific genes and genomic regions and the substance misuse diagnoses. The reviewed linkage analyses suggest that the genes influencing risk for substance dependence and related phenotypes, such as body mass index, drug sensitivity/tolerance, EEG patterns and antisocial personality traits, are many and reside on several chromosomal regions (see table 1). It appears that these regions are not unique to Native Americans, as similar findings have been reported in studies in other ethnic (primarily Caucasian) groups. Some overlap in the gene locations for substance dependence and body mass index have been found suggesting the possibility of a common genetic substrate for disorders of consumption.

The review of candidate gene studies revealed a number of polymorphisms that have been found to be associated with substance dependence phenotypes in Native Americans. The strongest results were reported from studies investigating the genes that code for alcohol metabolizing enzymes, including variants in ADH1B (rs1229984 and rs2066702) and ADH4 (rs3762849). Notably, these results were not always consistent across tribal groups. Some of these differences may be the result of population differences such as the observed association of the ADH1B*3 allele (rs2066702) in the California Indian sample and the absence of this allele in the other tribal groups examined. Others, such as the ADH1B*2 allele (rs1229984) and rs3762849 in ADH4 were more likely the result of inadequate sample sizes given that the direction of effect was consistent across studies. Larger studies including a greater number of tribal groups will be needed to conclusively test these conclusions. Thus far, the reviewed studies suggest that some Native American tribes appear to lack protective variants in alcohol metabolizing enzyme genes that are seen in East Asian and some African population groups (e.g., ALDH2*2 and ADH1B*3), but they provide little overall support for the theory that Native American groups have an "unusual" metabolism of alcohol. Additional genes that code for neurotransmitter receptors and neuromodulators, including OPRM1, CRN1, COMT, GABRA2, MAOA, and HTR3-B, have shown preliminary evidence for association with substance use phenotypes in some tribal groups (table 2). Nonetheless, these associations have also been reported in other ethnic groups, and also provide little evidence to support a genetic association specific to a Native American tribal group or the Native American population as a whole.

Taken together, the results of genetics studies thus far conducted suggest that the genetic influences contributing to substance use, abuse, and dependence in Native American populations are likely similar in kind and magnitude to the genetic influences contributing to the liability for these phenotypes in other ethnic groups. One previous study has demonstrated that a correlation exists between degree of Native American ancestry and substance dependence phenotypes [20] but it remains to be seen if this relationship is due to genetic or environmental influences. Nonetheless, this is an important issue deserving of further study as genetic methodology has demonstrated an advantage in studying Native populations, even when recent admixture between the population isolate and outside

populations have occurred if the phenotype of interest is correlated with degree of ancestry from the population isolate [65]. It is likely that more advanced genetic techniques such as genomewide association studies, sequencing strategies, and investigations of copy number variation, combined with admixture analyses will shed further light on this issue. Additionally, a number of environmental factors could be targeted to potentially reduce rates of substance dependence. These include: general economic and educational conditions, personal and historical trauma [9-10], early age of onset of drinking [11] as well as lack of contingency between access to basic life reinforcers (employment, housing, education and health care) and sobriety [12]. Interventions that address underage drinking such as motivational interviewing [66], as well as tribal agreements to address social norms concerning drug and alcohol usage and associated trauma, have the potential to substantially reduce substance use in these populations. Additional studies in the genetics of substance abuse in Native Americans are recommended especially when key environmental variables are accounted for and gene-environment interplay can be assessed.

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Table 1
Summary of findings from Linkage Studies of Alcohol and Other Drug Dependence and Related Phenotypes

CHR	Trait(s)	LOC (cM)	LOD	Nearest Marker	Linkage Evidence in Native Americans
1	EEG Alpha Power	12	4.25	D1S214/D1S450	[37]
	ASPD/CD	256	2.0	D1S2670	[30]
2	EEG Alpha Power	92	2.66	D2S286	[37]
	EEG Beta Power	244	2.1	Not reported	[35]
3	Alcohol Craving	142	2.24	D3S1292	[16]
	ASPD/CD	193	2.3	D3S3609	[30]
4	EEG Theta Power	40	2.5	Not reported	[35]
	EEG Alpha Power	48	2.4	Not reported	[35]
	Alcohol Dependence	59	2.8	D4S3242	[18]
	ASPD/CD	66	2.0	D4S428	[30]
5	EEG Alpha Power	93	2.25	D4S2460	[37]
	Severe Alcohol Use	103	2.9	D4S414	[20]
	EEG Theta Power	76	2.2	Not reported	[35]
	EEG Beta Power	90	3.5	Not reported	[35]
6	EEG Alpha Power	93	3.5	Not reported	[35]
	Alcohol Craving	117	4.55	D5S2084	[16]
	Alcohol Craving	8	2.14	D6S309/D6S470	[16]
	Alcohol Withdrawal	47	3.26	D6S1610	[20]
7	EEG Alpha Power	50	3.9	D6S1575	[37]
	Regular Tobacco Use	50-75	2.0	D6S1575	[25]
	First Five SRE	147	3.86	D6S441	[42]
	BMI	151	2.3	D6S1577	[17]
8	Any Drug Dependence	157	3.3	D6S1581	[17]
	BMI	7	2.3	D8S277	[17]
	Regular Tobacco Use	110	2.0	D8S1762	[25]
	First Five SRE	11	4.5	D9S1810	[42]
10	First Five SRE	87	2.7	D10S581/D10S210	[42]

CHR	Trait(s)	LOC (cM)	LOD	Nearest Marker	Linkage Evidence in Native Americans
11	EEG Beta Power	110	2.5	Not reported	[35]
	Alcohol Dependence	4	3.1	D11S1984	[18]
	First Five SRE	13	1.97	D11S1760	[42]
	EEG Alpha Power	30	2.98	D11S4115	[37]
	EEG Alpha Power	114	2.2	Not reported	[35]
12	Stimulant Craving	5	2.11	D12S352/D12S1725	[24]
	Severe Alcohol Use	155	2.14	D12S1675/D12S1659	[20]
	First Five SRE	179	2.43	D12S1638	[42]
13	ASPD	19	2.1	D13S289	[30]
	ASPD/CD	86	2.2	D14S68	[30]
14	EEG Alpha Power	113	2.13	D14S65	[37]
	Alcohol Withdrawal	51-75	2.13/2.27	D15S1036/D15S152	[20]
	Heavy Stimulant Use	77	2.05	D15S979	[24]
	Stimulant Craving	83	3.02	D15S127	[24]
16	Alcohol Withdrawal	6	2.02	D16S3027	[20]
	EEG Alpha Power	69	2.07	D16S415/D16S3140	[37]
	Cannabis Dependence w/Externalizing Behavior	139	4.4	D16S520	[23]
	First Five SRE	101	2.87	D17S1807	[42]
17	ASPD/CD	129	2.1	D17S928	[30]
	BMI	14	2.2	D18S1132	[17]
	Stimulant Craving	113	2.55	D18S469	[24]
19	Cannabis Dependence w/Externalizing Behavior	74	6.4	D19S902	[23]
20	ASPD/CD	40	2.0	D20S912	[30]
22	EEG Theta Power	20	3.2	Not reported	[35]
	EEG Alpha Power	29	2.38	D22S280/D22S277	[37]

Table 2

Gene	Chrom.	Polymorphism	Phenotype	Population	Reference
ADH1B	4q23	ADH1B*3 (rs2066702)	Alcohol dependence, alcohol consumption	CI	[44]
			Alcohol withdrawal	CI	[43]
ADH1C	4q23	HaeIII (rs1693425), Ile349Val (rs698)	Alcohol dependence, binge drinking	SWI	[47]
ADH4	4q23	rs3762894	Alcohol dependence	PI, SWI	[45]
			Alcohol withdrawal	CI	[43]
ALDH1A1	9q21.13	ALDH1A1*2 allele	Alcohol dependence, alcohol consumption, cigarette smoking	CI	[50]
		rs1424482, rs8187876, rs2249978, rs1418187, rs4745209			
CNR1	6q15	AATn triplet repeat, rs1535255, rs2023239, rs1049353, rs806368	Alcohol Dependence	PI, SWI	[45]
			Impulsivity	CI	[53]
COMT	22q11.21	Val158Met (rs4680)	Alcohol Dependence among cigarette smokers (females only)	PI	[67]
GABRA2	4p12	rs279858, rs279863	Alcohol Dependence	PI	[54]
GABRA6	5q34	1519T>C (rs3219151)	Alcohol Dependence	SWI	[56]
GABRB2	5q34	1412C>T (rs2229944)	Alcohol Dependence	SWI	[56]
GABRG1	4p12	rs1497575, rs6824361, rs6813633, rs12511372	Alcohol Dependence	PI	[55]
GAL	11q13.3	rs4930241, rs4930241	Alcohol Dependence	PI	[68]
HTR1B	6q14.1	G861C (rs6296), D6S284	Alcohol Dependence with Antisocial Behavior	SWI	[60]
HNMT	2q22.1	Thr105Ile (rs11558538)	Alcohol Dependence	PI	[69]
OPRM1	6q25.2	Asn40Asp (rs1799971), IVS2+691G/C	No observed association	SWI	[70]
		rs553202, rs524731, rs3778148, rs1461773, rs2075572, rs548646, rs681243	Sensitivity to alcohol	CI	[59]
SINCA	4q22.1	rs2583978, rs356186, rs356198, rs3775423	Drug Dependence	SWI	[71]
		rs356163	Alcohol Dependence (males only)	PI	[71]