Evidence for a Genetic Component for Substance Dependence in Native Americans

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Objective: Although tribes differ with regard to the use of alcohol and drugs, substance dependence is one of the primary sources of health problems facing Native Americans. General population studies have demonstrated that substance dependence has a substantially heritable component (approximately 50% of the risk resulting from genetic influences); however, fewer studies have investigated the role of genetics in the risk for substance dependence in Native Americans.

Method: The authors present a literature review of the evidence for a genetic component in the etiology of substance dependence in Native Americans, including studies of 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 (BMI), 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 BMI suggests that 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, and drug sensitivity or tolerance) that combine with key environmental factors (trauma exposure, early age at onset of use, and environmental hardship) to produce an elevated risk for the disorder.

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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 with other U.S. ethnic groups, Native Americans have the highest rates of alcohol and other drug dependence (2), and Native American adolescents have been reported 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 to be in the range of 20%–70% (4–6), which is higher than the epidemiological rate of DSM-IV alcohol dependence of 13% in the U.S. general population (7). The causes for higher rates of alcohol and drug dependence among Native Americans are thought to have both environmental and genetic determinants.

Early sociocultural theories posited that Native American alcohol use and abuse were a result of the 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). Data for more recent theories support an association between alcohol dependence and factors such as personal and historical trauma (9, 10) and early age at onset of drinking (11), as well as lack of contingency between access to basic-life reinforcers (e.g., employment, housing, education, and health care) and sobriety (12).

Psychobiological theories have also been 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, laboratory studies of

alcohol drinking 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 elevated risk is unclear, most investigators favor a model in which a genetic predisposition interacts with environmental variables to produce an overall risk for the disorder. It is also likely that complex disorders such as 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, the so-called thrifty or fat-sparing genes. It has been suggested that this same selective pressure may be 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).

In this study, we present 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 in view of the relative environmental and genetic homogeneity of some of these populations compared with larger, more stratified general population samples.

Method

We conducted a literature search using the PubMed and Google Scholar databases and keywords related to Native Americans and alcohol and substance abuse and dependence. The reference sections of identified studies were reviewed to identify additional studies. Because our review was qualitative in nature, all identified studies that reported either qualitative or quantitative results for a Native American sample were included. 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 are not formally identified in order to avoid potential stigma toward the populations studied. The three primary sources of genetic studies (California, Southwest, and Plains) used community samples. Studies estimating the heritability of substance dependence diagnoses and related phenotypes are reviewed first, followed by a review of genetic linkage studies examining these phenotypes, then 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 three Native American populations. In these studies, heritability (h^2) estimates were obtained from data collected from large extended families. The earliest study, conducted in the Southwest American Indian population, found that DSM-III-R alcohol dependence was heritable, although exact heritability estimates were not presented (18). Alcohol dependence in the California Indian population showed some evidence of heritability (DSM-III-R criteria: h^2=0.19, DSM-IV criteria: h^2=0.38) (19) and was also found to be associated with the degree of Native American Heritage (20). However, little evidence was found for the heritability of alcohol dependence in the Plains Indian population (D. Goldman, personal communication, 2008). In contrast, twin studies of alcohol dependence have consistently yielded significant evidence of heritability, ranging from 0.50 to 0.65, using general population samples with participants of predominantly Caucasian origin (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 such as 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 (h^2=0.71) and symptoms of alcohol dependence associated with heavy drinking (h^2=0.37) 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 the findings also differ in that the latter study reported that heritability estimates of specific symptoms did not exceed those 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 Indian population. Heritability for initiating use was found to be high for marijuana (h^2=0.59), opiates (h^2=0.58), phencyclidine (h^2=0.51), sedatives (h^2=0.49), and stimulants (0.38). Heritability was only modest for initiation of cocaine (h^2=0.14), hallucinogens (h^2=0.26), and solvents (h^2=0.13). The heritabilities of drug dependence diagnoses and symptoms were also estimated in this population and found to be significant for marijuana dependence with antisocial traits (23), stimulant dependence with craving (24), and heavy tobacco use (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 (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 (18). 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 D_4 dopamine receptor (*DRD4*) and tyrosine hydroxlyase (*TH*) genes, with secondary evidence on chromosome 4p11-p13 near the alpha 2 and beta 1 GABA receptor genes (*GABRA2* and *GABRB1*, respectively) and on 4q23-q25 near the alcohol dehydrogenase gene cluster. 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). Evidence for linkage to chromosomes 4, 15, and 16 was reported for alcohol-related phenotypes in the Collaborative Study on the Genetics of Alcoholism (COGA), suggesting that these regions of the genome confer risk and protection for alcohol dependence in Native Americans, as well as in general population samples.

Evidence for linkage has also been demonstrated in genome scans for other drugs of abuse, including marijuana, stimulants, and tobacco, in Native Americans. 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 phenotypes (amphetamine and cocaine) 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 (24). A genome scan for loci associated with tobacco use 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 one or more genes that jointly influence alcohol dependence and tobacco use phenotypes.

In order to test the theory that dependence on drugs of abuse may have genetic underpinnings similar to other consumption disorders such as obesity, the results of the genome scan for any drug dependence was compared with those of a genome scan for body mass index (BMI) (17). Evidence for linkage was found on chromosome 6q25.2-q25.3 for both the any drug dependence (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 pleiotrophy (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 and thus provide a potential explanation for the elevated rates of substance dependence and obesity in some Native American populations.

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 comorbid internalizing (anxiety and depression) and externalizing (antisocial personality/conduct) disorders. One theory of the cause of the elevated rates of substance use disorders seen in some Native American tribes is that factors such as memories of historical and current trauma, conditions on reservations, prejudice, and economic hardship may lead to elevated rates of anxiety and depression, which in turn lead to more substance use and dependence—the self-medication hypothesis. However, a number of investigators have examined the comorbidity of substance use and dependence with internalizing disorders and have not found elevated rates of internalizing disorders (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 (h^2=0.76) and antisocial personality disorder/conduct disorder (h^2=0.56) were found to be highly heritable and comorbid 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 has 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 in both the general population (32) and 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 data set (34). Similar findings in Native American populations have been described in several studies (35–39). In one study of the California Indian population (38), EEG alpha phenotypes were found to be heritable (h^2=0.67), and in a second study (37), linkage analysis revealed two loci that had a LOD score ≥3.0 for the frontocentral scalp region on chromosomes 1p36.31-p36.22 and 6p21.1. Additionally, four locations with LOD scores >2.0 were identified on chromosomes 4q22.1, 11p14.1, 14q32.2, and 16q12.2 for the frontocentral location and one on chromosome 2p12 for the centroparietal-occipital location. These results corroborate the importance of regions on chromosomes 4 and 6 highlighted in previous segregation studies of alcohol dependence-related phenotypes in this and other populations, 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 in COGA (40), or by polymorphisms in another gene. Nonetheless, these results support the general use of EEG traits and specifically support EEG alpha recorded from frontocentral 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 (35, 39). In the first study, the authors carried out a genome-wide linkage analysis 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 relationship between polymorphisms in this gene and alcoholism in a Caucasian sample but not in the Plains Indian population (35). In the second study, the authors performed a genome-wide 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 finding was not replicated in the COGA data set (41). Although preliminary, the studies conducted in the California 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 lower 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 (14), California Indian participants, similar to Caucasian male offspring of alcoholic parents, 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 those with less than 50% Native American heritage, despite equivalent blood alcohol concentrations. More recently, Ehlers et al. (42) asked participants in the California Indian population to provide retrospective reports, using the Self-Rating of the Effects of Alcohol questionnaire, of their responses to alcohol during the first five times they had ever drank. A linkage analysis using these responses as the phenotype revealed loci on chromosomes 6q25.2 and 9p24.1 that had a LOD score >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).

The linkage findings for substance use phenotypes in Native Americans are summarized 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 use disorders and thus have been the focus of much research in a number of different ethnic populations. The seven alcohol dehydrogenase genes (*ADH7*, *ADH1C*, *ADH1B*, *ADH1A*, *ADH6*,

TABLE 1. Summary of Findings From Linkage Studies of Alcohol and Other Drug Dependence and Related Phenotypes in Native Americans

Chromosome	Trait	Location (cM)[a]	LOD[a]	Nearest Marker	Linkage Evidence in Native Americans (Study)
1	EEG alpha power	12	4.25	D1S214/D1S450	Ehlers et al. 2010 (37)
	Antisocial personality disorder/conduct disorder	256	2.0	D1S2670	Ehlers et al. 2008 (30)
2	EEG alpha power	92	2.66	D2S286	Ehlers et al. 2010 (37)
	EEG beta power	244	2.1	Not reported	Enoch et al. 2008 (35)
3	Alcohol craving	142	2.24	D3S1292	Ehlers et al. 2005 (16)
	Antisocial personality disorder/conduct disorder	193	2.3	D3S3609	Ehlers et al. 2008 (30)
4	EEG theta power	40	2.5	Not reported	Enoch et al. 2008 (35)
	EEG alpha power	48	2.4	Not reported	Enoch et al. 2008 (35)
	Alcohol dependence	59	2.8	D4S3242	Long et al. 1998 (18)
	Antisocial personality disorder/conduct disorder	66	2.0	D4S428	Ehlers et al. 2008 (30)
	EEG alpha power	93	2.25	D4S2460	Ehlers et al. 2010 (37)
	Severe alcohol use	103	2.9	D4S414	Ehlers et al. 2004 (20)
5	EEG theta power	76	2.2	Not reported	Enoch et al. 2008 (35)
	EEG beta power	90	3.5	Not reported	Enoch et al. 2008 (35)
	EEG alpha power	93	3.5	Not reported	Enoch et al. 2008 (35)
	Alcohol craving	117	4.55	D5S2084	Ehlers et al. 2005 (16)
6	Alcohol craving	8	2.14	D6S309/D6S470	Ehlers et al. 2005 (16)
	Alcohol withdrawal	47	3.26	D6S1610	Ehlers et al. 2004 (20)
	EEG alpha power	50	3.9	D6S1575	Ehlers et al. 2010 (37)
	Regular tobacco use	50-75	2.0	D6S1575	Ehlers et al. 2006 (25)
	First five alcoholic drinks[b]	147	3.86	D6S441	Ehlers et al. 2010 (42)
	Body mass index (BMI)	151	2.3	D6S1577	Ehlers et al. 2007 (17)
	Any drug dependence	157	3.3	D6S1581	Ehlers et al. 2007 (17)
8	BMI	7	2.3	D8S277	Ehlers et al. 2007 (17)
	Regular tobacco use	110	2.0	D8S1762	Ehlers et al. 2006 (25)
9	First five alcoholic drinks[b]	11	4.5	D9S1810	Ehlers et al. 2010 (42)
10	First five alcoholic drinks[b]	87	2.7	D10S581/D10S210	Ehlers et al. 2010 (42)
	EEG beta power	110	2.5	Not reported	Enoch et al. 2008 (35)
11	Alcohol dependence	4	3.1	D11S1984	Long et al. 1998 (18)
	First five alcoholic drinks[b]	13	1.97	D11S1760	Ehlers et al. 2010 (42)
	EEG alpha power	30	2.98	D11S4115	Ehlers et al. 2010 (37)
	EEG alpha power	114	2.2	Not reported	Enoch et al. 2008 (35)
12	Stimulant craving	5	2.11	D12S352/D12S1725	Ehlers et al. 2011 (24)
	Severe alcohol use	155	2.14	D12S1675/D12S1659	Ehlers et al. 2004 (20)
	First five alcoholic drinks[b]	179	2.43	D12S1638	Ehlers et al. 2010 (42)
13	Antisocial personality disorder	19	2.1	D13S289	Ehlers et al. 2008 (30)
14	Antisocial personality disorder/conduct disorder	86	2.2	D14S68	Ehlers et al. 2008 (30)
	EEG alpha power	113	2.13	D14S65	Ehlers et al. 2010 (37)
15	Alcohol withdrawal	51-75	2.13/2.27	D15S1036/D15S152	Ehlers et al. 2004 (20)
	Heavy stimulant use	77	2.05	D15S979	Ehlers et al. 2011 (24)
	Stimulant craving	83	3.02	D15S127	Ehlers et al. 2011 (24)
16	Alcohol withdrawal	6	2.02	D16S3027	Ehlers et al. 2004 (20)
	EEG alpha power	69	2.07	D16S415/D16S3140	Ehlers et al. 2010 (37)
	Cannabis dependence with externalizing behavior	139	4.4	D16S520	Ehlers et al. 2009 (23)
17	First five alcoholic drinks[b]	101	2.87	D17S1807	Ehlers et al. 2010 (42)
	Antisocial personality disorder/conduct disorder	129	2.1	D17S928	Ehlers et al. 2008 (30)
18	BMI	14	2.2	D18S1132	Ehlers et al. 2007 (17)
	Stimulant craving	113	2.55	D18S469	Ehlers et al. 2011 (24)
19	Cannabis dependence with externalizing behavior	74	6.4	D19S902	Ehlers et al. 2009 (23)
20	Antisocial personality disorder/conduct disorder	40	2.0	D20S912	Ehlers et al. 2008 (30)
22	EEG theta power	20	3.2	Not reported	Enoch et al. 2008 (35)
	EEG alpha power	29	2.38	D22S280/D22S277	Ehlers et al. 2010 (37)

[a] cM=centimorgans; LOD=log of the odds.
[b] The first five alcoholic drinks trait refers to participants' retrospective reports on the Self-Rating of the Effects of Alcohol questionnaire of their responses to alcohol during the first five times they had ever drank alcohol.

ADH4, and *ADH5*) are located in a single cluster on chromosome 4q21–24, with each gene coding for a unique isozyme. The relationship 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 produced replicable evidence of association between polymorphisms in these genes and alcohol-related phenotypes in Native Americans. For example, two functional polymorphisms identified in the *ADH1B* gene 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 in 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 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). However, studies of other Native American samples did not report the presence of the *ADH1B*3* allele (45). Additionally, a polymorphism in the promoter region of *ADH4* (rs3762894) that has been shown to produce a more active version of the alcohol dehydrogenase enzyme (46) has demonstrated 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 and Plains Indian populations (45). Although an initial study (47) suggested a relationship between a functional polymorphism in *ADH1C* (rs698), subsequent studies have not detected a relationship between alcohol misuse phenotypes and *ADH1C* polymorphisms (43, 45), including a proline-theonin substitution in codon 351 of *ADH1C* (rs35719513) that has been observed almost exclusively in Native American populations (48).

The two aldehyde dehydrogenase 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. The *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 *ALDH1A1* gene 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 deletion in the promoter region of *ALDH1A1*, commonly referred to as the *ALDH1A1*2* allele. Similar to reports of *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 and Plains Indian populations (45), as well as in Caucasian populations (51). 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 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 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 $GABA_{G1}$ 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 use 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 that the association is due to a causal variant in *GABRA6* (56). Studies of other ethnic groups, including Caucasian (57)

TABLE 2. Summary of Candidate Gene Studies of Alcohol and Other Substance Misuse Phenotypes in Native Americans

Gene	Chromosome	Polymorphism	Phenotype	Population	Study
ADH1B	4q23	*ADH1B*3* (rs2066702)	Alcohol dependence, alcohol consumption	California Indian	Wall et al. 2003 (44)
			Alcohol withdrawal	California Indian	Gizer et al. 2011 (43)
ADH1C	4q23	HaeIII (rs1693425), Ile349Val (rs698)	Alcohol dependence, binge drinking	Southwest American Indian	Mulligan et al. 2003 (47)
ADH4	4q23	rs3762894	Alcohol dependence	Plains Indian, Southwest American Indian	Liu et al. 2011 (45)
			Alcohol withdrawal	California Indian	Gizer et al. 2011 (43)
ALDH1A1	9q21.13	*ALDH1A1*2* allele	Alcohol dependence, Alcohol consumption, cigarette smoking	California Indian	Ehlers et al. 2004 (50)
		rs1424482, rs8187876, rs2249978, rs1418187, rs4745209	Alcohol dependence	Plains Indian, Southwest American Indian	Liu et al. 2011 (45)
CNR1	6q15	AATn triplet repeat, rs1535255, rs2023239, rs1049353, rs806368	Impulsivity	California Indian	Ehlers et al. 2007 (53)
COMT	22q11.21	Val158Met (rs4680)	Alcohol dependence among cigarette smokers (female only)	Plains Indian	Enoch et al. 2006 (67)
GABRA2	4p12	rs279858, rs279863	Alcohol dependence	Plains Indian	Enoch et al. 2006 (54)
GABRA6	5q34	1519T>C (rs3219151)	Alcohol dependence	Southwest American Indian	Radel et al. 2005 (56)
GABRB2	5q34	1412C>T (rs2229944)	Alcohol dependence	Southwest American Indian	Radel et al. 2005 (56)
GABRG1	4p12	rs1497575, rs6824361, rs6813633, rs12511372	Alcohol dependence	Plains Indian	Enoch et al. 2009 (55)
GAL	11q13.3	rs4930241, rs4930241	Alcohol dependence	Plains Indian	Belfer et al. 2006 (68)
HTR1B	6q14.1	G861C (rs6296), D6S284	Alcohol dependence with antisocial behavior	Southwest American Indian	Lappalainen et al. 1998 (60)
HNMT	2q22.1	Thr105Ile (rs11558538)	Alcohol dependence	Plains Indian	Oroszi et al. 2005 (69)
OPRM1	6q25.2	Asn40Asp (rs1799971), IVS2+691G/C	No observed association	Southwest American Indian	Bergen et al. 1997 (70)
		rs553202, rs524731, rs3778148, rs1461773, rs2075572, rs548646, rs681243	Sensitivity to alcohol	California Indian	Ehlers et al. 2008 (59)
SNCA	4q22.1	rs2583978, rs356186, rs356198, rs3775423	Drug dependence	Southwest American Indian	Clarimon et al. 2007 (71)
		rs356163	Alcohol dependence (male only)	Plains Indian	Clarimon et al. 2007 (71)

and Asian (58) populations, 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 include the *OPRM1* gene, 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. These and additional candidate gene studies of alcohol and other substance misuse phenotypes in Native American samples are summarized in Table 2, which highlights that with a few exceptions, these genes have been investigated in only a single study. Additionally, each of these genes has 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 relationships 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 of the Plains Indian sample suggested that EEG alpha power, which was related to comorbid alcohol dependence and antisocial personality disorder, demonstrated 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 among 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 using Caucasian samples, but only one such study has been conducted in a Native American population. That study investigated whether a relationship 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 relationship 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 compared with individuals in the other groups (64). A similar interaction was observed in women from the Southwest American Indian population, in which those with the high-risk genotype were more likely to develop comorbid alcohol dependence and antisocial personality disorder but only if they were exposed to childhood sexual abuse. Although preliminary, that study highlights the potential effect of gene-by-environment interaction studies.

Discussion

We began this review with a summary of quantitative genetic studies establishing the heritability of 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. We then presented evidence from linkage analyses and candidate gene studies suggesting relationships between specific genes and genomic regions and substance use diagnoses. The reviewed linkage analyses suggest that the genes influencing risk for substance dependence and related phenotypes, such as BMI, drug sensitivity or tolerance, EEG patterns, and antisocial personality traits, are many and reside on several chromosomal regions (Table 1). It appears that these regions are not unique to Native Americans, since similar findings have been reported in studies of other ethnic (primarily Caucasian) groups. Some overlap in the gene locations for substance dependence and BMI has been found, suggesting the possibility of a common genetic substrate for disorders of consumption.

Our 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 are needed to definitively test these conclusions. Thus far, the reviewed studies suggest that some Native American tribes appear to lack protective variants in alcohol metabolizing enzyme genes (the *ALDH2*2* and *ADH1B*3* alleles) that are seen in East Asian and some African populations, 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). However, these associations have also been reported for other ethnic groups and also provide little evidence to support a genetic association specific to a Native American tribal group or to the Native American population as a whole.

Taken together, the results of genetics studies conducted to date suggest that the genetic influences contributing to substance use, abuse, and dependence in Native American populations are likely similar in kind and in magnitude to the genetic influences contributing to the liability for these phenotypes in other ethnic groups. One previous study demonstrated that a correlation exists between degree of Native American ancestry and substance dependence phenotypes (20), but it remains to be seen whether this relationship is due to genetic or environmental factors. Nonetheless, this is an important issue deserving of further study because genetic methodology has demonstrated an advantage in examining 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 genome-wide 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), and early age at onset of drinking (11), as well as lack of contingency between access to basic life reinforcers (e.g., 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 use and associated trauma, have the potential to substantially reduce substance use in these populations. Additional studies of 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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