Published in final edited form as:

Am J Addict. 2017 August ; 26(5): 461–468. doi:10.1111/ajad.12420.

Genetic and Environmental Risk Factors for Alcohol Use Disorders in American Indians and Alaskan Natives

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Abstract

Background and Objectives—Genetic and environmental predictors for alcohol use disorder (AUD) are both important in the general population. As a group, American Indian and Alaskan Native individuals (AI/AN) are at increased risk for alcohol-related morbidity /mortality, early onset problem drinking and AUD.

Methods—Alcohol consumption behaviors amongst AI/AN tribes, environmental stressors and genetic studies in AI/AN and European-ancestry individuals are reviewed followed by an analysis of unique difficulties for undertaking research with AI/AN.

Results—Some AI/AN tribes have high rates of childhood trauma that predict psychopathology including AUD. The deleterious effects of historical trauma and forced placement in boarding schools cross generations to the present day. There are scanty numbers of genetic studies of AUD in AI/AN and these derive from only a few tribes. However, it is important to note that the results are largely similar to findings in European-ancestry individuals indicating that AI/AN do not have increased genetic risk for AUD. Conducting AI/AN genetic studies has been challenging, in part because of tribe disillusionment and mistrust over past experiences and unique hurdles in getting consent from tribes, each a sovereign nation. However, it is encouraging that a new way forward has been established – community-based participatory research with tangible health benefits and a focus on strength-based approaches.

Conclusions and Scientific Significance—Given the high prevalence of AUD in many AI/AN tribes and limited knowledge about genetic risk-resilience factors, it is important for our understanding of prevention and treatment that AI/AN research progresses and that more tribes are represented.

INTRODUCTION

Alcohol use disorder (AUD) is a complex multifactorial disease that is both genetically and environmentally influenced. An individual's environment can in theory be manipulated to diminish the risk for the development of addiction to alcohol. However, current approaches

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

to prevention and treatment of AUD are only moderately effective, as evidenced by significant rates of lifetime AUD in the general US population¹ and high rates of relapse under available treatment regimens.² This review will discuss current knowledge about genetic influences on AUD in American Indians and Alaskan Natives (AI/AN) in the context of all genetic research in this domain, and will focus on some of the environmental stressors that are common to all societies and those that are unique to AI/AN.

Individuals with American Indian or Alaskan Native ancestry account for 1.7% of the general US population.³ When considered as a group, AI/AN are at increased risk for alcohol-related morbidity and mortality. A Center for Disease Control survey showed that the age-adjusted alcohol-attributable death rate in AI/AN was twice that of the US general population⁴ but it varied by region. AI/AN in the Northern Plains had the highest death rates and Eastern AI/AN had the lowest.⁵ In line with this, AI/AN tend to start drinking early in life. For example, a study in 727 AI adolescents from eight reservations showed that 40% began drinking at least occasionally by age 14; of these, 59% had developed DSM-IV AUD by age 15 – 17 years in contrast to 17% of the abstainers.⁶ It is interesting to note that these drinking patterns are comparable to those in British adolescents who have some of the highest rates of alcohol use in Europe. A study of approximately 6,000 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) showed that 40% likewise began drinking at least occasionally by age 14 and at age 16 – 17 years, 60% of high frequency drinkers at age 14 had developed hazardous or harmful alcohol use in contrast to 24% of low frequency drinkers.⁷ Numerous studies have shown that AI/AN adolescents and adults tend to exhibit heavy episodic alcohol use⁸⁻¹³ and this pattern of drinking has been associated with risk for AUD and other psychiatric disorders as well as multiple behavioral problems including violence.¹¹ An adolescent history of heavy episodic drinking in AIs has been associated with reduction in self-reported levels of intoxication in early adulthood, a potential predictor for AUD.¹⁴

Studies have shown that some AI/AN tribes have higher rates of AUD.¹³ For example, the prevalence of lifetime AUD in men and women respectively was 83 - 51% in a Southwestern American Indian tribe,¹¹ 70 - 50% in a Southwest California Indian tribe,⁹ 70 - 40% in a Plains American Indian tribe¹⁰ and 47 - 13% in a Southeastern American Indian tribe (Enoch, unpublished data) as compared to 17 – 8% in the general US population.¹ These aforementioned tribes have been the focus of most of the published studies on genetic influences on AUD. However, it is important to note that there are currently 567 federally recognized AI/AN tribes that differ considerably by size, culture, customs, language, alcohol use and prevalence of addictions.^{13,15} Whether tribes may also vary significantly in genetic risk factors for AUD and genetic predictors for treatment outcomes will be discussed later.

ENVIRONMENTAL RISK FACTORS FOR AUD IN AI/AN

AI/AN are exposed to the environmental risk factors for AUD that are found in all societies, including childhood trauma and living in geographically isolated communities without economic opportunities, but also stressors that are unique to indigenous populations. These stressors include historical trauma, the cross generational transmission of the cumulative emotional and psychological trauma of cultural genocide, a coordinated plan of different

actions aiming at the destruction of the essential foundations of a cultural group. The forced placement of children in federally mandated boarding schools was a vehicle for this genocide.

Childhood trauma

Early life trauma, characterized as emotional abuse and neglect, physical abuse and neglect and sexual abuse, is unfortunately common in all societies and ethnic groups and is a predictor of adult psychopathology, including AUD and drug use disorders (DUD).¹⁶ Several studies have demonstrated high levels of childhood trauma in some AI/AN communities.^{15,17-19} A study in AI women attending a primary care setting showed that childhood trauma was common and that severity was associated in a dose dependent manner with lifetime psychiatric disorders including post-traumatic stress disorder and substance use disorders.¹⁷ In a Southwestern American Indian tribe, men and women exposed to severe childhood sexual abuse (CSA) were more likely to be diagnosed with more than three psychiatric disorders.¹⁹ CSA in women significantly increased the risk for lifetime AUD and DUD.¹⁹ A study in 1362 individuals from six AI tribes with a high lifetime prevalence of AUD found that in men, childhood physical abuse and CSA was associated with an increased risk of AUD whereas for women, all forms of abuse and neglect increased the risk of AUD.¹⁵ In this study, 29% of men had experienced 4 or 5 childhood trauma categories and these individuals had a 3 fold greater risk of AUD; 35% of women had experienced 4 or 5 childhood trauma categories and had a 7 fold greater risk of AUD.

Historical trauma

AI/AN have had a centuries-long legacy of unrelenting traumatic contact with non-Indians resulting in a massive loss of life, land and culture.²⁰ This started well before the wars of genocide that resulted in final defeat and subjugation, forced movement onto reservations and forced removal of children to boarding schools.²¹ In 1880 Congress passed legislation that outlawed Indian religions, the practices of 'so-called' medicine men, ceremonies such as the Sun Dance, and leaving the reservation without permission. These 'Civilization Regulations' were in place until 1936.

Historical trauma reflects a collective response to the denial of a culture's right to exist and the attempt to eradicate cultural identity²² and can be regarded as unresolved grief across generations.²³ Duran et al.²⁴ suggested that historical trauma becomes embedded and 'normalized' in the cultural memory of a people. A study on the prevalence and correlates of perceived historical loss among AI reported that nearly one-fifth of indigenous parents/caretakers of children aged 10–12 years thought at least daily about loss of land; more than one-third thought at least daily about loss of traditional language and traditional spirituality and more than one-half had such thoughts at least on a weekly basis.²² Moreover, their adolescent children reported that they had similar thoughts at least daily.²⁵

Reminders of historical loss for adults and children persist to this day, including economic disadvantage on rural reservations, national disrespect, perceived discrimination, and a sense of continual erosion of traditional cultures.²⁵ Even where children are protected from the traumatic stories of their ancestors, the effects of past traumas still have an impact in the

form of ill health, family dysfunction, community violence, psychological morbidity and early mortality. Historical trauma has been shown to have independent effects on depressive symptoms in adolescent AI children.²⁵ Moreover, perceived discrimination has been shown to influence early and problem alcohol use in AI adolescents.⁶ In contrast, enculturation (restoration of culture) increases resilience against the development of alcohol abuse in AI adults²⁶ and two components of enculturation, participation in traditional activities and traditional spirituality, have been shown to have positive effects on alcohol cessation.²⁷ Treatment for historical trauma includes interventions based on traditional AI ceremonies as well as modern treatment modalities for grieving.^{23,28-30}

Forced removal to off-reservation boarding schools

After 1883 the Federal government took over the entire responsibility for AI education and established off-reservation boarding schools, the objectives of which were to instill a work ethic, individualism, and other tenets of American 'civilization' and to suppress all that was Indian. Children were forcibly removed and sent to these schools where it was forbidden to speak a native language or make reference to native religion or any cultural folk practice. The Carlisle Indian School with its approach "Kill the Indian: Save the Man" through forced assimilation became the model for the 26 Bureau of Indian Affairs boarding schools in 15 states and territories. By 1930 nearly half of all AI/AN children enrolled in schools were in off-reservation boarding schools.³¹ Reports of child abuse and neglect at the schools were common.³² It was not until 1978 that the Indian Child Welfare Act allowed AI/AN tribes and AI/AN parents to determine where their children would go to school. Increased psychopathology, including alcohol/drug use and suicidal behavior has been associated with boarding school attendance, and children of boarding school attendees also have increased psychopathology.³¹ One study has found that among urban AI/AN individuals, boarding school attendance and foster care were predictors of AUD in male drinkers.³³ However it should be noted that another study in 1,000 individuals from a large AI tribe found that individuals with AUD were no more likely to have attended boarding school than individuals without AUD.³⁴

GENETIC RISK FACTORS FOR AUD IN AI/AN

Heritability

The heritability (the genetic component of the variance) of addictive disorders has been determined from many thousands of largely European-ancestry twin pairs and ranges from 40% to 60%; the heritability of AUD is around 50%.³⁵ The one published AI/AN heritability study which was in Southwest California Indians produced a heritability estimate of 0.38 for AUD³⁶ and 0.71 for AUD with symptoms of withdrawal.³⁷ Therefore genetic and environmental influences on the development of AUD are both important.

Genetically influenced predictors for AUD

Genetic variation can predict differing, ethnic specific, metabolic responses to alcohol consumption that influence the risk for developing AUD. Heritable personality traits such as impulsivity that predicts alcohol seeking behavior³⁸ and anxiety / dysphoria that predicts drinking maintenance behavior^{39,40} may be useful for detecting genetic influences on

vulnerability to AUD. Finally, genetic variation in neurobiological pathways, including stress-response systems, may influence vulnerability to the development of permanent neurological changes in response to heavy alcohol use. Likewise, genetic variation may determine increased vulnerability to relapse in response to stressors.⁴¹

Variation in genes encoding ethanol metabolizing enzymes—Worldwide, the most robust finding for genetic influences on AUD is for genes encoding ethanol metabolizing enzymes. Ethanol is largely metabolized in the liver by alcohol dehydrogenases (ADH) to toxic acetaldehyde which is then converted to acetate by aldehyde dehydrogenases (ALDH), primarily by the mitochondrial enzyme ALDH2. Since functional variants in these genes have a high prevalence in East Asians and some studies have suggested East Asian ancestry for the original Native Americans, these variants have been investigated in AI/AN. The ALDH2*2 allele, encoding the inactive ALDH2 enzyme which results in a severe flushing syndrome upon ethanol consumption, has not been found in Plains American Indians, Southwestern American Indians and Southwest California Indians^{42,43} and indeed appears to be unique to East Asians.

The higher ADH enzyme activity encoded by the polymorphisms ADH1B*2 (Arg48His, rs1229984), ADH1B*3 (Arg370Cys, rs2066702), and the ADH1C*1 haplotype (Arg272Ile350) enables more rapid conversion of ethanol to acetaldehyde, thereby also resulting in the flushing syndrome and also being protective against excessive alcohol consumption. The ADH1B*2 allele, occurring at a frequency of 0.75 in East Asians, is uncommon in AI with a frequency of 0.01.⁴³ The ADH1B*3 allele, occurring at a frequency of 0.04 in Southwest California Indians, has been associated with a protective effect on risk for alcoholism in this population.^{42,44} In summary, studies to date in AI/AN individuals have shown that variation in genes encoding ethanol metabolizing enzymes has little if any impact on risk for AUD.

Exploratory methods for identifying genetic influences on AUD: Linkage analysis—Over the past several years numerous whole genome linkage studies have been performed in which the inheritance of phenotypes and genetic markers is followed in families. Two influential linkage scans, one in a Southwestern American Indian tribe⁴⁵ and the other in the large, predominantly European-ancestry Collaborative Study on the Genetics of Alcoholism (COGA) dataset⁴⁶ found evidence for linkage of AUD near the chromosome 4 GABAA receptor subunit gene cluster. This finding led to the discovery of the association of the *GABRA2* gene with AUD, a widely replicated finding. Other more modest linkage findings for AUD and alcohol-related phenotypes in AI are comprehensively reviewed elsewhere.⁴⁷

Since AUD is a heterogeneous disorder, one approach has been to use intermediate phenotypes that reflect mediating factors in behaviors such as AUD, and are likely to be influenced by variation at fewer genes. The resting EEG is a dynamic index of cortical activation, cognitive function and consciousness and is therefore an intermediate phenotype for many behaviors in which arousal is implicated such as anxiety and AUD. A dense whole genome linkage scan in a large pedigree of Plains American Indians identified convergent genome-wide significant linkage peaks for EEG power on chromosome 5q13-14, at the apex

of which was located *CRHBP*, a gene that encodes the binding protein for CRH, a key regulator of the stress response.⁴⁸ *CRHBP* was significantly associated with EEG alpha power in the Plains American Indians and also in a replication sample of US Caucasians and was also associated with anxiety disorders in the Plains American Indians and AUD in the US Caucasians.⁴⁸ Interestingly, the chromosome 5q13-14 *CRHBP* location was close to a linkage peak for alcohol craving in Southwest California Indians.⁴⁹ The *CRHBP* gene has subsequently been associated with several stress-related disorders in different ethnic groups.⁵⁰ Other linkage findings for resting EEG, particularly alpha power, in different chromosomal regions in the Southwest California Indian population are reviewed elsewhere.⁴⁷

Genome-wide association studies (GWAS)—GWAS ask whether a phenotype might be associated with any of a very large number (usually millions) of common single nucleotide polymorphisms (SNPs) distributed across the genome. Unfortunately, use of such large numbers of SNPs requires stringent statistical corrections for false positive findings resulting in many negative studies. The strongest and most consistent GWAS findings for AUD are for SNPs in alcohol metabolizing genes in Asian samples. Another strong finding was for a meta-analysis of an alcohol consumption phenotype in 26,316 individuals from 12 European-ancestry population-based samples with replication genotyping in another 21,185 individuals for one SNP in the autism susceptibility candidate gene 2 (*AUTS2*).⁵¹ Furthermore, a GWAS for alcohol dependence in a discovery / replication dataset of 16,087 European and African ancestry individuals confirmed known risk variants and identified population specific novel variants but also cross population risk genes.⁵² There have been other major findings from GWAS for AUD, alcohol-related phenotypes and comorbid diseases, however other than for SNPs in the alcohol metabolizing genes there are few if any commonalities across studies,⁴¹ most likely due to insufficient sample sizes combined with small effects of individual variants.

There has been one AI GWAS using resting EEG power as an intermediate phenotype for AUD, performed in a sample of 322 Plains American Indians.⁵³ Although the diagnostic phenotype of AUD did not generate genome-wide significant statistical signals, the EEG GWAS identified three genes, one of which (*SGIP1*) was associated with AUD, an effect that might be mediated via the same brain mechanisms as for EEG power. Convergence of findings at the sub-threshold level with previous findings in genetic studies of addictions provided evidence that the intermediate phenotype approach can potentially identify genes that have a general effect on addiction even in datasets of modest size, notably of population isolates such as AI/AN.⁵³

Hypothesis-driven approach: candidate gene studies

It is now recognized that genetic risk for AUD is likely to be due to common variants in very many genes, each of small effect, although rare variants with large effects might also play a role. These genes are likely to encode proteins in many neurotransmitter systems and signal transduction pathways within the mesolimbic dopamine reward pathway as well as the interacting stress response systems. There have not been many candidate gene studies in

AI/AN however it is important to note that the results in AI/AN are often similar to findings in individuals of European ancestry.

The most robust candidate gene finding to date for AUD and related phenotypes is for *GABRA2*, initially identified by linkage scans.^{45,46} The GABAA gene cluster on chromosome 4 includes the *GABRA2*, *GABRG1* and *GABRB1* genes that together encode the $\alpha_1\beta_1\gamma_1$ GABA receptor that is almost exclusively found in the reward pathway. Numerous studies, nearly all in European-ancestry individuals but also one study in Plains American Indians, have replicated this association although there have also been negative studies, notably in African American samples.⁵⁴ One study with similar results in both Plains American Indians and Finnish Caucasians showed that there are likely to be independent, complex contributions from both adjacent genes *GABRG1* and *GABRA2* to AUD vulnerability.⁵⁵ A recent study showed an association between *GABBR1*, a GABAB receptor encoding gene, and AUD that was likewise replicated in Finnish Caucasians and Plains Indians.⁵⁶ Other AUD associations for both Plains American Indians and Finnish Caucasians have been found for *GAL*, a gene encoding the neuroendocrine peptide galanin⁵⁷ and *HNMT*, that encodes histamine N-methyltransferase, implicated in metabolism of histamine.⁵⁸ An earlier study found that *5-HTR1B*, encoding a serotonin receptor, was associated with antisocial alcoholism in both Finnish Caucasians and Southwestern American Indians.⁵⁹ Finally, a sufficiently powered study looking at association and sib-pair linkage analyses of the functional *OPRM1* polymorphism A118G Asn40Asp, rs1799971 with AUD produced similar negative findings in US Caucasians, Finnish Caucasians and Southwestern American Indians.⁶⁰ There have only been a few other candidate gene studies of AUD and intermediate phenotypes for AUD conducted in AI with mixed results.⁴⁷

Gene x Environment Interactive (G x E) Effects on Risk for AUD

As discussed earlier, childhood trauma, particularly in the first few years of life, is associated with psychopathology including early onset of problem drinking in adolescence and AUD and DUD in early adulthood.¹⁶ The risk-resilience balance for addiction may in part be due to the interaction between environment stressors and variation in stress and anxiety related genes (G x E). The X linked *MAOA* gene has a repeat promoter polymorphism (MAOA-LPR) that influences gene activity. This gene encodes the MAOA enzyme that plays an important role in the metabolism of the stress-related neurotransmitters norepinephrine and serotonin. There is an extensive literature, starting with Caspi et al, 2002⁶¹ showing a G x E effect between MAOA-LPR and childhood trauma on antisocial behaviors, particularly in males.⁶² There is one published G x E study in AI, specifically Southwestern American Indian women, that investigated the interaction between CSA and MAOA-LPR. This study showed that the MAOA-LPR low activity allele was associated with AUD, particularly antisocial alcoholism, but only in women exposed to CSA.⁶³ Thus women who were carriers of the genetic risk allele but had been spared CSA were resilient to the development of AUD.

There is clearly a need for further research on the impact of G x E on AUD in AI/AN, not only investigating childhood trauma but also the inter-generational impact of historical trauma.

Gene-Gene Effects within Biological Pathways

Biologically relevant combinations of functional variants within gene networks are likely to have additive effects on risk for addiction. However, even with high frequency variants very large sample sizes are required to detect differences between carriers of different genotype combinations. Recent exploratory studies in European-ancestry and African American samples, but not yet in AI/AN samples, indicate that these kinds of studies might result in pharmacogenetic therapeutics, i.e. the determination of individualized responses to medications for the treatment of AUD (reviewed in Enoch⁴¹).

Pharmacogenetics

Three medications are licensed in the USA for treatment of alcoholism: disulfiram (antabuse) since the 1940's, naltrexone since 1995, and acamprosate since 2004. Disulfiram is rarely prescribed since it has potentially serious side effects and acamprosate is largely used in Europe. Naltrexone, a μ opioid receptor antagonist, has been shown to have a modest effect on drinking outcomes (reviewed in Enoch²⁰¹⁴⁶⁴). Genetic studies have shown that the largest therapeutic response is found in A118G G allele carriers of the *OPRM1* gene. Since the frequency of the minor G allele varies markedly across ethnicity, ethnic group status is a predictor for naltrexone treatment response. G allele frequency data from HapMap shows that Japanese (0.49) and Chinese (0.36) individuals with AUD are likely to derive the most benefit from naltrexone since the G allele is common in these populations whereas the G allele is less common in European ancestry (0.17) and virtually absent in individuals of African ancestry (0.01). There are no AI/AN genotypes available in HapMap or the 1000 Genomes databases. Unpublished data from our laboratory shows that the G allele is common in the Southeastern American Indian (0.31) and Plains American Indian (0.25) samples whereas the frequency in the Southwestern American Indian sample (0.18) is the same as in Europeans. Therefore, about half of Southeastern American Indians, one third of Southwestern American Indians and three quarters of Japanese are likely to respond well to naltrexone if this medication is administered along with psychosocial treatments.

CHALLENGES INVOLVED IN UNDERTAKING GENETIC RESEARCH STUDIES IN AI/AN TRIBES

The majority of genetic studies to date have been conducted in European-ancestry individuals even though there has been a historical interest in studying risk / resilience factors for AUD in AI/AN populations. This is because research on AUD can be facilitated by studying large, extended families and/or well-defined populations, such as AI/AN, that are likely to be more genetically and environmentally homogeneous than the general US population. If clinical diagnosis is the phenotype, then low prevalence samples are more likely to reveal genes conferring susceptibility to AUD whereas in high prevalence samples, such as some AI/AN tribes, the tribal members without AUD are likely to be informative about genetic mechanisms of resilience.

However, as shown in this review, the genetic literature on AI/AN and AUD is scanty and only a few tribes are represented. There are several reasons for this including tribal disillusionment with past research experiences, mistrust of researchers' motives, concerns

over human migration theories and the identification of tribal ancestry by DNA testing. Several AI/AN communities have experience of research programs that have been culturally insensitive, tending to treat tribal members as 'subjects' with no feedback about the published data, and have even violated the terms of informed consent. The recent (2010) resolution of a law suit in favor of the Havasupai Tribe against Arizona State University concerning their research violation of informed consent is a good example of how mistrust of research spreads throughout the AI/AN community.

One of the key differences in setting up studies with AI/AN compared to other ethnic groups is that informed consent is required not only from individuals but also from tribes, each of which is a sovereign nation. The complexities of negotiating research programs can be challenging since this requires interaction with the bureaucratic officials of a sovereign government and its elected officials from small communities who may not only have little knowledge or interest in genetic research but may be wary of outsiders asking questions that may impact tribal member privacy and even cultural identity. Some of the immediate concerns can be: what is the underlying motive of the proposed research? What is the benefit to the research organization? Will there be any tangible benefits for the community that is being studied? Might the study result in a negative image of the tribe?

Genetics research, in particular population genetics, is currently a contentious issue in AI/AN tribal communities.⁶⁵ For example, thus far, no AI/AN sovereign nations have chosen to participate in the HapMap or 1000 Genomes Project. Consequently, this might lead to difficulties in SNP imputation for future AI/AN genetic studies. Nevertheless, there is now an online guide to participation in genetic research to assist decision making by individual tribal governments that has been developed by the National Congress of American Indians Policy Research Center with support from the National Human Genome Research Institute, NIH.⁶⁵

THE WAY FORWARD: COMMUNITY-BASED PARTICIPATORY RESEARCH: PARTNERSHIP, EDUCATION AND EMPOWERMENT

Successful research with AI/AN populations will only be achieved when the research participants see themselves as partners who share both the research responsibility as well as the knowledge and benefits of the outcome. This approach, 'community-based participatory research' (CBPR) is an applied collaborative approach that enables community residents to more actively participate in the full spectrum of research with a goal of influencing change in community health, systems, programs or policies.^{66,67} Academic/research and community partners join to develop models and approaches to building communication, trust and capacity, with the final goal of increasing community participation in the research process. For example, tribes may have their choice of local community partners and be able to include tribal specific questionnaires in the research. 'Partnership, 'Education and Empowerment' are key terms for the outcome expected for any community involved in community-based research. Thus the focus of research goals has shifted away from scientific discovery first and foremost to that which can be learnt about the individual community to improve health and quality of life. To this end, an increasing number of tribes now have their

own Institutional Review Boards. CBPR may range from research question origination by the community to entirely external investigator-controlled research however, most studies fall somewhere in between. The ultimate goal is of an equal academia – tribal partnership in the research and the dissemination of results to federal, community and academic constituencies.⁶⁸ However, the challenges of trust, informed consent, data ownership and sovereign rights should not be underestimated and misunderstandings on both sides can derail the research process.⁶⁸

It should also be noted that this research approach is likely to require additional time and result in increased costs. It takes time to build trusting relationships with community members, to provide education through organized community meetings and focus groups and to obtain permission from rural community leaders and the cooperation of formal and informal community organizations. Recruiting and training culturally appropriate researchers may also add to the cost of the research.

Strength-based approaches to research

More recently, there has been a shift within AI/AN research communities towards advocating strength-based approaches to research, i.e. studying resilience/protective factors rather than risk factors, with the aim of developing strength-based health programs, drawing on the positive basis of the existing family, tribal and community resources.⁶⁹ This is particularly relevant for research with tribes with a high prevalence of AUD since these populations are more likely to be informative about genetic mechanisms of resilience.

DISCUSSION

Genetic and environmental vulnerability factors for AUD are both important. Examining social determinants of health such as socioeconomic status, education levels and current trauma in individual tribes may lead to important variables on which prevention efforts should focus.

Although AUD is known to be moderately heritable, the search for genetic vulnerability factors has proven to be more difficult than originally thought and to date only a small proportion of the genetic variance has been accounted for. Over the past decade there have been tremendous advances in large scale SNP genotyping technologies and next generation sequencing, and these technologies, including GWAS arrays and whole genome sequencing, are now widely available. Results of GWAS suggest that numerous common variants with very small effect are likely to encode proteins within, or regulate, numerous biological pathways. However, GWAS findings have to date explained only a small portion of the genetic vulnerability to AUD, in part because many studies have been underpowered. Another explanation for the ‘missing heritability’ of AUD may be that there are rare variants clustered within genes or pathways that in aggregate yield large effects. The new technologies may help to unravel the complex genetics of AUD, a crucial advance in order to improve prevention and to develop, through molecular diagnostic methods, more effective, individually-targeted pharmacotherapies.

The vast majority of genetic studies in AUD have been conducted in European-ancestry individuals. However, studies are increasingly also being conducted in African and Asian ancestry individuals. As shown in this review and for the reasons discussed, there have been only a limited number of genetic studies of AUD in AI/AN individuals from only a handful of tribes. It is not clear whether the results of these studies are generalizable to the hundreds of other federally recognized tribes that differ in many ways including culture, customs, language, alcohol use and prevalence of addictions^{13,15} and may differ in frequencies of genetic variants. Indeed, we showed that the frequency of the *OPRM1* A118G G allele that predicts response to naltrexone varied from 0.18 to 0.31 amongst three AI tribes. Nevertheless, it is important to note that despite the fact that genetic variants have different frequencies in AI/AN and European-ancestry individuals, the results of candidate gene studies are largely similar in both groups. Extrapolating from these limited findings, it can be concluded that it is unlikely that the genetic backgrounds of AI/AN tribes make them more vulnerable to the development of AUD compared with European-ancestry individuals. Given that many AI/AN tribes continue to have a high prevalence of AUD accompanied by associated negative health and social consequences and there are still significant gaps in knowledge about etiology, including genetic risk and resilience factors, it is imperative that AUD genetic research progresses in AI/AN individuals and that many more tribes /sovereign nations are represented.^{69,70} Past difficulties and mistakes in undertaking research with tribal members have largely been recognized and understood. There is now a comprehensive guide to genetic research produced by the National Congress of American Indians Policy Research Center to assist with informed decision making by individual tribal governments.⁶⁵ It is now recognized that community-based participatory research is the way forward with a goal of influencing change in community health, systems, programs or policies. To this end it is encouraging that an increasing number of tribes now have their own Institutional Review Boards. Finally, the shift towards strength-based approaches to research, i.e. studying resilience/protective factors rather than risk factors, is relevant for research with tribes with a high prevalence of AUD.

ACKNOWLEDGEMENTS

This work was funded by the Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda MD, USA, grant number AA000306-10.

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