Published in final edited form as:

Am J Addict. 2017 August ; 26(5): 532–537. doi:10.1111/ajad.12585.

Conclusion - Special Issue on Genetic and Alcohol Use Disorder Research with Diverse Racial/Ethnic Groups: Key Findings and Potential Next Steps

Karen G. Chartier, PhD^{1,2}, Michie N. Hesselbrock, PhD³, and Victor Hesselbrock, PhD³

¹School of Social Work, Virginia Commonwealth University, Richmond, VA, USA

²Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

³Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA

Abstract

Background and Objectives—This special issue brings together papers focusing on a wide range of topics relevant to the research and understanding of the role of race/ethnicity and genetic variation for the susceptibility of developing an alcohol use disorder (AUD).

Methods—The key findings from the issue's ten articles are reviewed and organized around three topics: I: addictive behaviors and potential environmental influences; II: a focus on four racial/ethnic groups; and III: special methodologies.

Results—Several potential next steps in improving effective research strategies are highlighted: (1) implementing best practices for outreach and community engagement may reduce reluctance to participate; (2) recruiting adequately sized and racially/ethnically diverse samples will require new collaborations with investigators who successfully work in diverse communities; (3) identifying and assessing environmental influences that are both unique to, and common among, racial/ethnic groups may inform preventions for AUD; (4) use of standardized measures will facilitate the generation of larger samples and meta-analysis of research findings; and (5) use of better analytic approaches and experimental methods will improve replication in gene finding research and help advance new areas of research.

Conclusions—Genetic research of AUD in diverse racial/ethnic populations is advancing. The articles in this issue examined the general theme of including diverse population groups in genetic studies and offered potential strategies for addressing some common problems.

Scientific Significance—Greater inclusion of diverse racial/ethnic populations in this research is important to ensure that the benefits of new knowledge and technology are equally shared.

We conclude this special issue by offering a description of the key findings of each of its papers, as well as identifying several potential next steps. This is an area of research that

Corresponding Author: Karen G. Chartier, PhD, MSW, Virginia Commonwealth University School of Social Work, 1000 Floyd Avenue, P.O. Box 842027, Richmond, VA 23284-2027; phone: 804-828-2865; fax: 804-828-0716; kgchartier@vcu.edu.

Declaration of Interest

The authors report no financial or other conflicts of interest related to the paper. The authors alone are responsible for the content and writing of this paper.

reaches across multiple disciplines as it involves a focus on genetics, biology, advanced statistics, human behavior, and the social and physical environment. This interdisciplinary approach brings a strength to the breadth of studies being conducted and also allows for the potential for different interpretations and priorities to emerge. This is evident in the language that investigators use to refer to groups studied, e.g., race/ethnicity as census categories and fundamentally social constructs or ancestry groups based on either the 1000 Genomes Project populations, ancestral geography, or the use of statistical approaches¹. This issue's *Commentary by Scott*² identifies relevant historical and cultural factors as well as methodological issues that are associated with the dearth of genetic research among American Indians, African Americans, Latinos, and Asians. New directions and suggestions are offered to help address the varied challenges associated with the inclusion of racially/ethnically diverse groups in genetic studies. Genetic research for alcohol use disorder (AUD) in diverse populations is moving forward, although not as quickly as some would like. While important advancements in the knowledge generated and the methodological techniques being used continue, several gaps remain. This summary of each of the ten paper's key findings is organized around three topics. We start with the first topic immediately below.

I: The first three papers examine the prevalence of addictive behaviors and potential environmental influences

In the first paper, *Luczak et al.*³ were able to identify relatively few studies that examine the interrelationships of addictive behaviors among U.S. racial/ethnic groups, and those studies primarily focused on the comorbidity of substance use disorders (alcohol, nicotine, and illicit drugs) and gambling. They report gaps in the literature for the repetitive addictive behaviors of eating/food, internet, sex, love, exercise, work, and shopping. Based on available studies, there is evidence for race/ethnic group differences in rates of substance use and prevalence of addictions. For example, American Indians are consistently higher and Asians consistently lower on rates of alcohol, nicotine, and drug use disorders. African Americans, Latinos, and Whites fall in between, but at changing rank orders, depending on the addictive behavior, timeframe (lifetime or current) assessed, and the inclusion of covariates. There is also evidence that U.S. racial/ethnic groups vary in the co-occurrence and comorbidity of these addictive behaviors. However, the temporal order of onset of these comorbidities is not clear, which is important for understanding whether addictive behaviors represent different or similar underlying mechanisms. The authors note that group differences in the co-occurrence and comorbidity of addictive behaviors likely occur when ethnicities have some combination of differential: (1) accessibility, (2) genetic vulnerability, (3) socialization to an addictive behavior, and (4) expectations about the drug or behavioral effects. Studies that examine comorbidity rates and these other factors among ethnicities require large sample sizes in order to disaggregate groups beyond major U.S. racial/ethnic categories. When examining genetic influences, these analyses must also consider the issues of population stratification and genetic admixture.

*Agrawal et al.*⁴ use a twin model approach to examine a specific environmental influence, religious services attendance, and its association with alcohol involvement in African American and White female younger adults. Religious attendance is conceptualized as a

prosocial protective activity, as well as a family practice often initiated during childhood and one indicator of personal religious devotion in adulthood. As expected, the associations between religious attendance and alcohol involvement measures (ever drink, age of first drink, and DSM-5 AUD) were different depending both on the timing of religious attendance (i.e., childhood and/or adulthood) and on race/ethnicity. While African Americans reported higher religious attendance and lower drinking levels, the protective relationships between childhood religious attendance and alcohol involvement were observed in Whites only. Adult religious attendance was associated with lower odds of DSM-5 AUD in both African Americans and Whites, but the protective relationship in Whites extended to 'ever drinking' and 'first alcohol use prior to age 18'. The modeling of the relationships between monozygotic and dizygotic twins allows for the variance in and covariance between alcohol involvement and religious attendance to be decomposed into underlying latent genetic and environmental mechanisms. Findings suggest distinct mechanisms for the relationships between religious attendance and alcohol involvement in African American and White women. A notable strength of this study is that it was conducted in the largest cohort of African American twin pairs available, although the proportion of White female twin pairs (85% of the 3,787 total) was considerably larger.

*Chartier et al.*⁵ expand the focus on environmental influences in genetic studies of alcohol consumption by considering environmental exposures at three levels (social network, community, and society) and under two environmental mechanisms (social control and social trigger) that are thought to modify genetic predisposition to AUD. Overall, relatively few studies examine the interrelationships between measured genes based on molecular methods and environmental risk and protective factors for AUD in U.S. racial/ethnic minority groups. The authors characterize the identified studies by the racial/ethnic population, substance use phenotypes, genetic variants, and environmental features studied. Gaps in the literature are evident, including the challenges posed by small sample sizes and a focus on candidate genes. Most studies including non-European samples predominantly involve African American and Asian samples and younger subjects, with very few studying Latinos and American Indians or a range of adult ages to coincide with key developmental periods for alcohol use initiation and escalation/de-escalation in different racial/ethnic groups. Despite having broadly been shown to influence racial/ethnic differences in a variety of health outcomes, there is also a gap in studies that examine community- and societal-level environmental influences on alcohol use. Considerations for selecting environmental factors for inclusion in gene-environment (G-E) association studies are offered. Potential environmental exposures at higher-order levels include indicators of community drinking norms, alcohol availability (e.g., outlet density), socioeconomic disadvantage, and unfair treatment (e.g., in housing and employment) as social control and social trigger mechanisms.

II: The next four papers present issues relevant to select racial/ethnic groups

There are striking similarities across these papers by *Enoch and Albaugh*⁶, *Matsushita and Higuchi*⁷, *Martinez et al.*⁸, and *Dick et al.*⁹. Each paper raises concerns about the limited racial/ethnic diversity in genetic study samples, subjects' often distrust of investigators, and

the reluctance of some racial/ethnic groups to participate in genomics research. The history of eugenics and other historical traumas; limited exposure and access to genetic research findings and opportunities to participate in research; the stigma attached to psychiatric disorders; and concerns about privacy, the accuracy of testing, and misuse of information are presented. Although some of these issues can be common across all potential subject pools regardless of race/ethnicity, it is important to consider the differential cultural implications of genetic research for the community/population of interest when planning a study. Several suggestions are offered for future genetic studies. For example, understanding the relevance of genetic findings to the individuals and families in various communities could help increase their motivation to participate, and outreach by investigators to gather community input and to provide better and more relevant information is essential.

*Enoch and Albaugh*⁶ begin this section by describing the alcohol consumption patterns of American Indian and Alaskan Native (AI/AN) individuals. Both groups are at elevated risk for heavy episodic drinking and alcohol-related problems, although there are 567 federally recognized AI/AN tribes that are different in many ways, including the prevalence of addictions. Rates of substance use/abuse vary considerably by geographic region as well as place of residence (e.g., reservation compared to non-reservation living). The authors review environmental risk factors for AUD and AI/AN individuals, both those in common with other groups (e.g., childhood trauma) and unique to indigenous populations (e.g., historical trauma). The literature on AI/AN genetic studies is very small and few tribes are represented. Past research experiences have led to mistrust and the process of negotiating informed consent with individual tribes can be complex. Enoch and Albaugh recognize that no AI/AN sovereign nations participated in the HapMap or 1000 Genomes projects. Community-based participatory and strengths-based research approaches are presented as potential solutions with their focuses on partnership, education, and empowerment and resilience/protective factors. We also note that genetic studies involving indigenous groups in the U.S. can have additional challenges. Most tribes/bands/groups have significant levels of admixture that are, not only different from other tribal groups, but also from European, Asian, and African Americans. There are also federal as well as tribal criteria for determining tribal membership, often determined by blood quantum, issues not typically associated with other racial/ethnic groups.

*Matsushita and Higuchi*⁷ describe the use of Asian samples to investigate genetic variations of alcohol metabolizing enzymes. The inactive aldehyde dehydrogenase 2 (*ALDH2*) and highly active alcohol dehydrogenase-1B (*ADH1B*) are unique to certain Asian groups and are considered to be protective factors against the development of AUD. The strong effect of the *ALDH2* gene provides an excellent opportunity to also examine gene×environment interactions (G×E). However, many environmental and other social factors that may contribute differentially to Asian groups remain to be studied. Genetic studies conducted in Asian countries tend to focus on different environmental factors, sometimes unique to that country/culture, and have identified different environmental contributions from those studies conducted in the U.S.

*Martinez et al.*⁸ identify a very limited number of genetic studies of AUD that include Latino participants. The authors also describe Latinos in the U.S. as diverse, including in

their country of origin and degree of genetic admixture. The authors start with a literature review regarding the participation of African Americans and other underrepresented racial/ethnic groups in genetic research, to serve as a framework for understanding relevant issues for Latinos. This framework is applied to content from two focus groups with Mexican American men and women about participating in alcohol studies that involve the collection of biological samples like saliva and blood. The thematic analysis shows conflicting concerns regarding the potential misuse of findings and distrust in genetic testing results versus the importance of including Latinos in genetic research for alcoholism because of the significance of alcohol problems in their local communities. Some differences between men and women are noted. The results of the focus groups identify several questions and suggestions to be considered when planning for the recruitment and retention of Latinos that should improve the quality of research, genetic and otherwise, with this population.

*Dick et al.*⁹ discuss the importance of including African Americans in genetic studies because such samples may contain genetic variants that differentially impact the etiology of AUD compared to other racial/ethnic groups. For example, African Americans typically have greater genetic diversity and different allele frequencies based on ancestral history that could be absent in European Americans. Several factors are discussed that may contribute to the reduced participation of African Americans in genetic studies. First, African Americans constitute a small fraction of the overall U.S. population and are distributed differentially across the country. Further, the ancestral diversity/admixture among different African American groups increases the analytic complexity for genetic studies, limiting the utility of self-identified race/ethnicity. Unfortunately, many current genetic studies use existing data sets that are mostly European American, with poor representation of racial/ethnic minority groups, including African Americans.

III: The final three papers cover special methodological topics

*Peterson et al.*¹⁰ compare the commonly used self-reported racial/ethnic identity phenotype to an empirical approach that uses genetic data for assigning research subjects to genetically informed ancestry groups. Improved genetic analytics are needed as study samples become larger and more racially/ethnically inclusive. Given both recent and past migration patterns worldwide, ancestry can be difficult to determine, resulting in erroneous findings due to population stratification. Admixture is a well-known confounder in genetic studies, thus determining subjects' population membership through self-report may no longer be sufficiently accurate for gene identification or association studies. This paper has a number of strengths including use of a large racially/ethnically diverse sample, use of a powerful empirical method (principal components analysis (PCA)) designed specifically for such classification purposes, and the use of genome-wide single nucleotide polymorphism (SNP) weights from well-defined reference panels from the 1000 Genomes Project. While finding a very high concordance (~95%) between self-reports and extended-PCA defined racial/ethnic groups, the findings indicate that empirical clustering methods provide an incremental increase in racial/ethnic group homogeneity and reduce marker loss and sample loss due to 'unknown' race/ethnicity. While this is a 'methods' paper, it should be kept in mind that other such techniques exist and others will likely be developed as newer analytic methods emerge. The use of PCA derived ethnicity phenotypes has already been applied to data sets

from a variety of diseases in admixed populations, although rarely in psychiatric/addiction samples.

*Zhang and Gelernter*¹¹ review studies about the potential importance of DNA methylation as a potential risk factor for AUD, i.e., as an epigenetic mechanism possibly affecting CpG dinucleotides. Work in this area is just beginning, as both the technology to examine possible epigenetic changes and the experimental strategies used continue to evolve. As new chips are developed, better coverage of the genome will become available. Factors such as gender and ancestry may also play important roles in determining any epigenetic changes discovered. Zhang and Gelernter point to many methodological issues that remain to be addressed, e.g., do methylation changes result from chronic alcohol consumption or do they predate heavy alcohol use, is there tissue specificity for epigenetic changes, and are such epigenetic changes specific to AUD or the result of other co-morbid psychiatric disorders, including other substance use disorders? It is not clear how important studies using model organisms will be as many genomic regions of interest are not well conserved across species. The methodological issues that have plagued the discovery of ‘risk’ genes for AUD are also the nemesis of epigenetic studies. These issues include small sample sizes with inadequate representation of diverse populations. Longitudinal studies of both affected (e.g., persons in treatment) and unaffected subjects who have not yet initiated heavy drinking are needed.

*Cservenka et al.*¹² provide a review of pharmacogenetic studies of AUD treatment. Such studies are important for understanding the biological mechanisms of AUD medication treatments, with the goal of moving more aggressively towards personalized medicine. It is well known that allele frequencies vary by ancestral background so it is quite likely that different biological treatments will vary in effectiveness across racial/ethnic groups. To date only selected medicines – naltrexone, ondansetron, acamprosate, and topiramate – have been studied, but only in limited samples of racial/ethnic minorities. This review points to the need for studies of other medications (e.g., nalmefene, disulfiram, etc.) including novel compounds not yet used in addictions treatment that may target risk alleles. Given that many known risk genes are commonly associated across different substances of abuse and related comorbidities, it is likely that some compounds currently used for other addiction conditions may also be effective in treating AUD; however, efficacy may vary by racial/ethnic ancestry and/or gender. Cservenka et al. note that the genetics of combination pharmacological therapies (the norm in current addictions treatment) are not well studied, suggesting a need to move toward gene-gene investigations and more standardization in outcome measures. This review also points out a quandary for developing pharmacogenetic studies. While it is the case that diverse samples should be emphasized to increase representation and to enhance susceptibility gene finding, the resulting genetic diversity can also make interpretation of results from pharmacogenetic studies difficult. More racially/ethnically homogeneous sampling may be useful in pharmacogenetic studies to increase clinical relevance. They also point to the need to include pharmacogenetics in clinical practice as is being done in other areas of medicine.

Summary and some next steps

This special issue has assembled papers focusing on a wide range of topics relevant to understanding the role of race/ethnicity and genetic factors for the susceptibility to the development of AUD. While these papers are representative and not comprehensive, several issues and potential next steps have emerged and are highlighted below.

First, and importantly, the reluctance of some racial/ethnic minority communities to participate in genetic studies cannot be ignored. Potential solutions could include greater outreach to communities, distribution of relevant information about the potential value of genetic studies, and the engagement of community members and leaders in research. Best practices for community engagement are developing, including those that maximize the benefits and reduce the possible burdens for participants. These practices may vary across participant groups or over the course of a study¹³. Greater inclusion of diverse racial/ethnic population groups in genetic research is important for ensuring that the benefits of new knowledge and technology are equally shared. This has particular relevance for pharmacotherapy studies and their potential for advancements in the prevention and treatment of AUD, but also for broader personalized or precision medicine approaches that recognize the influence on health of differences in genetic, environmental, and lifestyle factors¹³. However, since racial/ethnic minority groups tend to reside in certain geographic areas and are not evenly distributed across the U.S., some investigators will have better opportunities to work with diverse groups while others will have very limited access. Addressing this problem will require some investigators with expertise in genetic research to develop collaborations with others institutions or investigators who have successfully worked in these communities in order to recruit adequately sized and racially/ethnically diverse samples.

Our focus on four major racial/ethnic groups illustrates that some environmental exposures may have differential effects between groups, whether in association with AUD or in G-E relationships. Some environmental influences may be unique or more relevant to a specific culture or to individuals living in a country or region, and the distribution of exposure to adverse and protective conditions in the U.S. can vary by race/ethnicity. Therefore, while it is an important goal, it may not always be possible to compare the relationships between environmental and genetic effects and AUD by race/ethnic groups, and identification of key environments for individual groups that are highly affected by alcohol problems holds importance for informing targeted intervention strategies. Exposure to heavy drinking is a particular environmental condition, and epidemiologic studies identify elevated rates of heavy drinking and AUD for some U.S. racial/ethnic groups. Early findings suggest that chronic alcohol consumption is associated with DNA methylation changes and that this mechanism is possibly associated with AUD risk and persistence. Technology advances and more rigorous experimental designs are required next steps to bolster our understanding of these epigenetic changes and their association with gender and ancestry.

We underscore the recommendation that investigators consider using standardized approaches to assessing phenotypes for AUD, as well as environmental features of interest for GxE studies. For example, while screening instruments are efficient in terms of time of

administration, they typically only approximate the detailed information that can be obtained via a standardized diagnostic interview. Similarly, different formal diagnostic systems do not provide an exact overlap when identifying ‘affecteds’, e.g., Diagnostic Statistical Manual (DSM) diagnoses versus International Classification of Diseases (ICD) diagnoses. These variations in phenotype introduce additional variance that can complicate direct comparisons across studies. Conversely, greater consistency offered by standardization of assessments can facilitate the merging of data sets and meta-analysis of genetic and environmental findings¹⁴. This is one feasible strategy for generating the larger sample sizes needed to study genetic effects for AUD and to disaggregate gender by race/ethnicity differences and major racial/ethnic groups into potentially important subgroups.

Genetic diversity also requires special attention by investigators to avoid the reporting of erroneous findings and to increase replication. Better methods for determining more homogenous population groups are required, given the rates of admixture among the U.S. population. While self-reported race/ethnicity provides a degree of accuracy of genetic homogeneity, this self-identification also includes considerable information about social factors and related environmental exposures. More precision in determining ancestral groups is, therefore, required as larger samples sizes and the inclusion of underrepresented racial/ethnic groups inevitably leads to samples characterized by greater genetic and environmental diversity. The use of PCA approaches and external reference panels to define ancestry groups does seem to provide an increase in accuracy and to improve the retention of markers and subjects. Investigators should also consider the strengths and limitations of other methods of analysis for admixed genetic data (e.g., Thornton and Bermejo¹⁵), and new approaches are sure to be developed.

Scientific significance

In conclusion, this special issue examined several topics relevant to the design and implementation of genetic research studies on AUD with diverse racial and ethnic populations. The articles examined the general theme of including diverse population groups in genetic studies and offered potential strategies for addressing problems common to such studies. The *Commentary by Scott*² identifies several historical events and other issues that may contribute to the reluctance of different racial/ethnic groups to participate in genetic research. Gene identification efforts have historically focused on individuals of European descent. The relevance of this work to other racial/ethnic groups is not well established, as there may be important allele frequency differences across ancestral groups related to genetic risk, alcohol-related consequences, and even treatment response. The inclusion of racial/ethnic minority groups in genetic research for AUD calls for best practices to increase subject participation and engagement, the development of collaborations among investigators, and improved research methodologies and technologies. These new practices promise to identify possibly novel genetic variants that may be absent in European Americans and a wider variety of relevant environmental exposures. Improved research practices should lead to new developments that better inform prevention and treatments for AUD that are effective across a range of diverse racial/ethnic groups. Thus, there is a need for more studies of genetic vulnerability to alcoholism with diverse populations to ensure that genetic advances are inclusive and equally beneficial to all groups. Further, studies of

diverse groups will also provide opportunities to identify the low frequency or population specific variants that underlie genetic protection and vulnerability for developing alcohol problems and the consequences of chronic heavy drinking.

Acknowledgments

This work was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health (K.C. K01AA021145; V.H. P60AA003150; and V.H., M.H. U10AA008401).

References

1. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature*. 2015; 526(7571):68–74. [PubMed: 26432245]
2. Scott MS. Commentary: Perspectives on alcohol-related gene and environment interplay in diverse populations. *Am J Addict*. 2017; 26(5):526–531. [PubMed: 28745447]
3. Luczak SE, Khoddam R, Yu S, et al. Review: Prevalence and co-occurrence of addictions in US ethnic/racial groups: Implications for genetic research. *Am J Addict*. 2017; 26(5):424–436. [PubMed: 27759944]
4. Agrawal A, Grant JD, Haber JR, et al. Differences between White and Black young women in the relationship between religious service attendance and alcohol involvement. *Am J Addict*. 2017; 26(5):437–445. [PubMed: 27749011]
5. Chartier KG, Karriker-Jaffe KJ, Cummings CR, et al. Review: Environmental influences on alcohol use: Informing research on the joint effects of genes and the environment in diverse U.S. populations. *Am J Addict*. 2017; 26(5):446–460. [PubMed: 28117924]
6. Enoch MA, Albaugh BJ. Review: Genetic and environmental risk factors for alcohol use disorders in American Indians and Alaskan Natives. *Am J Addict*. 2017; 26(5):461–468. [PubMed: 27599369]
7. Matsushita S, Higuchi S. Review: Use of Asian samples in genetic research of alcohol use disorders: Genetic variation of alcohol metabolizing enzymes and the effects of acetaldehyde. *Am J Addict*. 2017; 26(5):469–476. [PubMed: 28098394]
8. Martinez P, Cummings C, Karriker-Jaffe KJ, et al. Learning from latino voices: Focus groups' insights on participation in genetic research. *Am J Addict*. 2017; 26(5):477–485. [PubMed: 28376266]
9. Dick DM, Barr P, Guy M, et al. Review: Genetic research on alcohol use outcomes in African American populations: A review of the literature, associated challenges, and implications. *Am J Addict*. 2017; 26(5):486–493. [PubMed: 28240821]
10. Peterson RE, Edwards AC, Bacanu S, et al. The utility of empirically assigning ancestry groups in cross-population genetic studies of addiction. *Am J Addict*. 2017; 26(5):494–501. [PubMed: 28714599]
11. Zhang H, Gelernter J. Review: DNA methylation and alcohol use disorders: Progress and challenges. *Am J Addict*. 2017; 26(5):502–515. [PubMed: 27759945]
12. Cservenka A, Yardley MM, Ray LA. Review: Pharmacogenetics of alcoholism treatment: Implications of ethnic diversity. *Am J Addict*. 2017; 26(5):516–525. [PubMed: 28134463]
13. Sankar PL, Parker LS. The Precision Medicine Initiative's All of Us Research Program: an agenda for research on its ethical, legal, and social issues. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2016
14. Hamilton CM, Strader LC, Pratt JG, et al. The PhenX Toolkit: Get the Most From Your Measures. *Am J Epidemiol*. 2011; 174(3):253–260. [PubMed: 21749974]
15. Thornton TA, Bermejo JL. Local and global ancestry inference and applications to genetic association analysis for admixed populations. *Genet Epidemiol*. 2014; 38(Suppl 1):S5–S12. [PubMed: 25112189]