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### Permalink

<https://escholarship.org/uc/item/61t3112j>

### Journal

American Journal of Medical Genetics Part B Neuropsychiatric Genetics, 186(3)

### ISSN

1552-4841

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### Publication Date

2021-04-01

### DOI

10.1002/ajmg.b.32805

Peer reviewed

## RESEARCH ARTICLE



WILEY

# Genome-wide admixture mapping of DSM-IV alcohol dependence, criterion count, and the self-rating of the effects of ethanol in African American populations

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## Funding information

National Institute of Health, Grant/Award Number: HHSN268201200008; National Institute on Drug Abuse, Grant/Award Number: DA032573; the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse, Grant/Award Number: U10AA008401

## Abstract

African Americans (AA) have lower prevalence of alcohol dependence and higher subjective response to alcohol than European Americans. Genome-wide association studies (GWAS) have identified genes/variants associated with alcohol dependence specifically in AA; however, the sample sizes are still not large enough to detect variants with small effects. Admixture mapping is an alternative way to identify alcohol dependence genes/variants that may be unique to AA. In this study, we performed the first admixture mapping of DSM-IV alcohol dependence diagnosis, DSM-IV alcohol dependence criterion count, and two scores from the self-rating of effects of ethanol (SRE) as measures of response to alcohol: the first five times of using alcohol (SRE-5) and average of SRE across three times (SRE-T). Findings revealed a region on chromosome 4 that was genome-wide significant for SRE-5 ( $p$  value = 4.18E-05). Fine mapping did not identify a single causal variant to be associated with SRE-5; instead, conditional analysis concluded that multiple variants collectively explained

the admixture mapping signal. *PPARGC1A*, a gene that has been linked to alcohol consumption in previous studies, is located in this region. Our finding suggests that admixture mapping is a useful tool to identify genes/variants that may have been missed by current GWAS approaches in admixed populations.

#### KEYWORDS

admixture mapping, African American, criterion count, DSM-IV alcohol dependence, response to ethanol

## 1 | INTRODUCTION

Alcohol dependence is one of the most common and costly diseases worldwide. In the United States, 12.5% of the population meets criteria for alcohol dependence during their lifetime (Hasin & Grant, 2015), and about 88,000 deaths and 2.5 million years of potential life lost annually are attributable to excessive alcohol use (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014). The estimated economic cost attributable to excessive drinking is almost \$250 billion (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015).

It has been long observed that drinking behavior and drinking-related problems differ among ethnic groups (Chartier & Caetano, 2010; Delker, Brown, & Hasin, 2016; Gibbs et al., 2013; Hasin, Stinson, Ogburn, & Grant, 2007; Vaeth, Wang-Schweig, & Caetano, 2017; Witbrodt, Mulia, Zeng, & Kerr, 2014; Zapolski, Pedersen, McCarthy, & Smith, 2014). Compared to European Americans (EA), African Americans (AA) drink less frequently; are more likely to stop drinking; have fewer heavy drinking episodes, later onset of drinking, and slower progression to alcohol dependence (Alvanzo et al., 2011; Dawson, Goldstein, & Grant, 2013; Klima, Skinner, Haggerty, Crutchfield, & Catalano, 2014). As a result, AA have significantly lower prevalence of alcohol dependence (Hasin & Grant, 2015). Notably, this is despite the increased exposure to stressful experiences in AA, which is an important factor associated with progression to alcohol dependence (Gibbs et al., 2013; Ransome & Gilman, 2016). However, when alcohol dependence occurs, AA have higher rates of recurrent and persistent alcohol dependence than EA (Breslau, Kendler, Su, Gaxiola-Aguilar, & Kessler, 2005; Chartier & Caetano, 2010; Dawson et al., 2005). In addition, AA reported a sharper increase in stimulation in an alcohol administration study (Pedersen & McCarthy, 2013), and experienced different neuroendocrine and inflammation responses due to alcohol misuse (Ransome, Slopen, Karlsson, & Williams, 2017, 2018). Furthermore, rates of alcohol-related diseases, mortality, and consequences are higher in AA (Chartier & Caetano, 2010; Flores et al., 2008; Polednak, 2007; Russo, Purohit, Foudin, & Salin, 2004; Sempos, Rehm, Wu, Crespo, & Trevisan, 2003; Shield et al., 2013; Yang, Vadavkar, Singh, & Omary, 2008).

The reasons for the disparities in drinking and alcohol-related problems between AA and EA are not fully understood (Hasin & Grant, 2015; Zapolski et al., 2014). Studies have suggested that both

environmental and genetic factors contribute to these differences (Chartier et al., 2014). Relevant to the current study, there is evidence for differential heritability of problem drinking in EA and AA (Sartor et al., 2013). Genome-wide association studies (GWAS) of alcohol-related phenotypes have also identified variants that are only significant in AA or EA (Kranzler et al., 2019; Lai, Wetherill, Bertelsen, et al., 2019; Lai, Wetherill, Kapoor, et al., 2019; Walters et al., 2018). For example, different functional single nucleotide polymorphisms (SNP) in *ADH1B*, the gene encoding the main alcohol-metabolizing enzyme in liver, have been linked to alcohol dependence in various populations partially due to their population specific allele frequencies: rs2066702 in AA and rs1229984 in EA (Bierut et al., 2012; Edenberg & McClintick, 2018; Walters et al., 2018). Polimanti and colleagues studied functional variants in 24 genes related to alcohol dependence and found frequencies of these variants to vary between AA and EA (Polimanti, Yang, Zhao, & Gelernter, 2015).

There is a great need for identifying genes/variants specifically related to AA drinking behavior and problems (Zemore et al., 2018). The identification of population specific genes/variants can advance our knowledge of the etiology of alcohol dependence in AA and contribute to the development of novel prevention and therapeutic strategies. However, there are several methodological challenges specific to conducting genetic studies in AA. First, there are fewer and smaller studies of AA compared to EA. Of the 32 GWAS of alcohol dependence and related phenotypes in the NHGRI-EBI GWAS catalog (<https://www.ebi.ac.uk/gwas/home>), only 11 include AA and sample sizes are much smaller compared to other populations. Recently, in the largest GWAS of alcohol dependence, only 6,280 AA were included in an analysis of >52,000 individuals (Walters et al., 2018). In another recent GWAS using the Alcohol Use Disorders Identification Test (AUDIT) in the Million Veteran Project (MVP), there were about 57,000 AA samples, however, the EA population consisted of >209,000 participants (Kranzler et al., 2019). Second, people of African ancestry have more genetic variants and a faster decay of linkage disequilibrium (LD) with an increase in physical distance (Altshuler et al., 2015). Therefore, more independent tagging variants are needed to fully cover the entire genome in AA as compared with other populations. As a result, the traditional genome-wide threshold,  $5 \times 10^{-8}$ , may not be appropriate. Third, the proportion of African and European ancestries differ among AA populations in the United States (Dick, Barr, Guy, Nasim, & Scott, 2017). In genetic studies, this admixture is usually modeled by

including ancestral principal components (PCs) as covariates in analysis. However, these PCs are a genome-wide adjustment and may result in over- or under- adjustment in some chromosomal regions due to different proportions of local (i.e., region-specific) admixture.

Admixture mapping might provide novel insights into one potential source of the differential prevalence of alcohol dependence between EA and AA (Seldin, Pasaniuc, & Price, 2011). One study found that the degree of African admixture is correlated with alcohol dependence; and those with alcohol dependence have less African ancestry (Zuo et al., 2009). Since admixture in AA occurred relatively recently (usually <10 generations), only a small number of recombination events have likely occurred and the size of ancestry-specific regions is expected to be large. That is, the average size of an African ancestry block in AA is about 17 centimorgans (Patterson et al., 2004). Thus, a much smaller number of genetic markers would be needed to tag such regions than is required in a typical GWAS. Admixture mapping has been successfully applied to other traits, for example, blood pressure, obstructive sleep apnea, systemic lupus erythematosus, and so forth, (Molineros et al., 2013; Sofer et al., 2017; Wang et al., 2019; Winkler, Nelson, & Smith, 2010); however, to our knowledge, it has not been applied to the study of alcohol dependence and related phenotypes in AA.

In this study, we performed admixture mapping using AA individuals from the Collaborative study on the Genetics of Alcoholism (COGA) (Reich et al., 1998), Study of Addiction: Genetics and Environment (SAGE) (Bierut et al., 2010), Alcohol Dependence GWAS in European and African Americans (Yale-Penn) (Gelernter et al., 2014), and an African American cohort from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Duplicate individuals among those studies were removed. We focused on four phenotypes: DSM-IV (American Psychiatric Association, 1994) alcohol dependence diagnosis; DSM-IV alcohol dependence criterion count as a measure of alcohol dependence severity (Lai, Wetherill, Bertelsen, et al., 2019), and two scores from the self-rating of effects of ethanol (SRE) questionnaire (Schuckit, Smith, & Tipp, 1997) as measures of response to alcohol. In genome-wide significant (GWS) regions, we conducted fine mapping using genotyped and imputed data to identify potentially causal variants. Last, we performed conditional analyses to test whether the variants identified during fine mapping could explain the admixture mapping association signal.

## 2 | MATERIALS AND METHODS

### 2.1 | Samples

COGA recruited alcohol dependent probands and their family members from inpatient and outpatient AD treatment facilities in seven sites, and community comparison families were also recruited from a variety of sources in the same areas (Nurnberger et al., 2004; Reich et al., 1998). Institutional review boards from all sites approved the study and every participant provided informed consent or assent. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) and the child version of the SSAGA (Bucholz et al., 1994; Hesselbrock, Easton, Bucholz,

Schuckit, & Hesselbrock, 1999) were administered to individuals age 18 or over and younger than 18, respectively. SAGE (phs000092.v1.p1, [https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000092.v1.p1](https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1)) and Yale-Penn (phs000425.v1.p1, [https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000425.v1.p1](https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000425.v1.p1)) were downloaded from the database of Genotypes and Phenotypes (dbGaP). For the NIAAA cohort, participants were recruited using the NIH Institutional Review Board-approved screening and assessment protocols conducted at the National Institutes of Health Clinical Center (Bethesda, MD) from 2005 to 2015. All participants provided written informed consent.

### 2.2 | Phenotypes

Individuals who endorsed three or more of the seven DSM-IV criteria occurring within a 12-month period were diagnosed with DSM-IV alcohol dependence. Affected individuals were age 15 or older and met criteria for DSM-IV alcohol dependence. Unaffected individuals were defined as those who had consumed at least one full drink of alcohol, were  $\geq 21$  years old, endorsed <2 criteria for DSM-IV dependence, and did not meet criteria for abuse of alcohol, cocaine, opioids, marijuana, sedatives, and stimulants (Lai, Wetherill, Bertelsen, et al., 2019). For SAGE and Yale-Penn datasets, DSM-IV alcohol dependence diagnoses were downloaded from dbGaP; and unaffected individuals with alcohol abuse, or other substance dependence were excluded.

The seven DSM-IV alcohol dependence criteria were summed to create a criterion count. Individuals with comorbid use and misuse of other drugs were not excluded.

The SRE questionnaire is a retrospective, self-report instrument to measure the numbers of standard drinks required to produce four effects of ethanol (Schuckit, Tipp, Smith, Wiesbeck, & Kalmijn, 1997): (a) "how many (standard) drinks did it take for you to begin to feel an effect?"; (b) "how many drinks did it take for you to feel a bit dizzy or begin to slur your speech?"; (c) "how many drinks did it take you to begin to stumble or walk in an uncoordinated manner?"; (d) "how many drinks did it take you to pass out or fall asleep when you did not want to?". The SRE queries drinking at three time points: the first five times using alcohol (SRE-5); the period of heaviest drinking; and the most recent 3 months of consumption (Schuckit, Tipp, et al., 1997). In this study, we used SRE-5 as well as the average scores across the three time points (SRE-T). Individuals who drank  $\geq 2$  drinks on one occasion were included in the analysis with extreme observations winsorized at the mean plus 2 SDs. The natural logarithm of SRE-5 and square root of SRE-T were used in analyses based on their distributions (Lai, Wetherill, Kapoor, et al., 2019).

### 2.3 | Genotyping, ancestry and imputation

Detailed information about data processing and QC applied in each study was reported previously (Lai, Wetherill, Bertelsen, et al., 2019;

Lai, Wetherill, Kapoor, et al., 2019). To identify duplicate samples among studies, confirm the reported pedigree structure, and calculate PCs representing population stratification, all available data from COGA, SAGE, Yale-Penn, and NIAAA were combined. Then, variants meeting the following criteria: common (defined as minor allele frequency [MAF] >10% in the combined sample), independent (defined as  $r^2 < .5$ ), high quality (missing rate <2% and Hardy-Weinberg Equilibrium [HWE]  $p$  values > .001), were used to identify duplicate samples and confirm the reported pedigree structure using PLINK (Chang et al., 2015; Purcell et al., 2007). To remove the same individual included in multiple datasets, (i.e., between COGA and SAGE), duplicate samples were removed from the study with less phenotypic information and fewer family members (e.g., SAGE). Family structures were updated, as needed. Using genetically-confirmed pedigrees, Ped-check (O'Connell & Weeks, 1998) was used to identify Mendelian errors and inconsistencies were removed. The same set of variants were used to estimate PCs using Eigenstrat (Price et al., 2006) with 1,000 Genomes data serving as the reference (Phase 3, version 5). Only AA samples, designated based on the first two PCs (COGA  $N = 2,939$ ; SAGE  $N = 959$ ; Yale-Penn  $N = 2,044$ ; NIAAA  $N = 169$ ), were included in analyses (Lai, Wetherill, Bertelsen, et al., 2019; Lai, Wetherill, Kapoor, et al., 2019). For the purposes of fine mapping, all samples were imputed to 1,000 Genomes (Phase 3, version 5, hg19) separately by cohort using SHAPEIT2 (Delaneau, Howie, Cox, Zagury, & Marchini, 2013) followed by Minimac3 (Das et al., 2016). Only variants with non A/T or C/G alleles, missing rates <5%, MAF >3%, and HWE  $p$  values > .0001 were used for imputation. Imputed variants with imputation quality score  $r^2 < .30$  were excluded.

## 2.4 | Inference of African ancestry

Due to differences in genotyping arrays, RFMix (V1.5.4) (Maples, Gravel, Kenny, & Bustamante, 2013) was used to estimate local African ancestry in each cohort separately. RFMix is a discriminative modeling approach that uses random forests trained on reference samples. Ninety-nine CEU and 99 YRI samples from 1,000 Genomes Phase 3 were used as European and African reference samples, respectively, as recommended by RFMix. Only genotyped, high quality variants (defined as missing rate <0.05, Hardy-Weinberg  $p$  values > .001, and MAF >3%) were included to improve inference accuracy. SHAPEIT2 (Delaneau et al., 2013) was used for haplotype phasing, then RFMix was used to estimate the number of African alleles at each locus (i.e., 0, 1 or 2 copies of African alleles, referred as local African ancestry). For each individual, global African ancestry was also calculated as the average percentage of African ancestry across the entire genome.

## 2.5 | Admixture mapping

We used RVTESTS (Zhan, Hu, Li, Abecasis, & Liu, 2016) to perform admixture mapping within each dataset. For each phenotype, the association with the number of African alleles at each locus was

tested after adjusting for study specific covariates and a kinship matrix estimated by RVTESTS. For COGA and SAGE, sex and birth cohort were significantly associated with alcohol dependence, and were therefore used as covariates (Lai, Wetherill, Bertelsen, et al., 2019; Lai, Wetherill, Kapoor, et al., 2019). For Yale-Penn and NIAAA, birth cohort was not available, therefore, sex and age were included, as in previous studies (Lai, Wetherill, Bertelsen, et al., 2019; Lai, Wetherill, Kapoor, et al., 2019). Global African ancestry was included as a covariate in all tests, as suggested (Molineros et al., 2013; Parra et al., 2017). Results from each dataset were meta-analyzed with the effect size weighted by the inverse of the estimated SE using METAL (Willer, Li, & Abecasis, 2010). Since the block sizes were different for each cohort, only the overlapping part of the blocks from each cohort were included in meta-analysis.

The following procedure was used to determine the GWS threshold. First, matSpD was used to account for correlations across the four phenotypes by spectral decomposition of the correlation matrix (Li & Ji, 2005; Nyholt, 2004), resulting in 2.52 effective independent tests. Second, using the autocorrelation function of the R package CODA (Plummer, Best, Cowles, & Vines, 2005), 273.82 effective African ancestry blocks were estimated across the entire genome using a combined sample from all cohorts. Therefore, the GWS threshold was determined as  $0.05/(2.52 \times 273.82) = 7.25E-05$ .

## 2.6 | Fine mapping and conditional analysis

For GWS regions that were identified, all genotyped and imputed variants within that region that had a missing rate <0.05, Hardy-Weinberg  $p$  values > .0001, and MAF >3% were tested using the same model as in the admixture mapping, except the global African ancestry index was replaced by PCs (the first four PCs in COGA and the first three PCs in other samples as in the original studies (Lai, Wetherill, Bertelsen, et al., 2019; Lai, Wetherill, Kapoor, et al., 2019) to adjust for population stratification among AA. RVTESTS (Zhan et al., 2016) was used to perform association tests within each cohort separately, then results from each cohort were meta-analyzed using METAL (Willer et al., 2010). The significance threshold was determined by the estimated effective number of tests using the R package matSpDlite (Li & Ji, 2005; Nyholt, 2004), which decomposes the LD between variants to arrive at the approximate number of independent variants.

Conditional analysis was performed by including variants identified in fine mapping with the lowest  $p$  values as covariates in another round of admixture mapping in GWS regions. A conditional analysis  $p$  value > .01 indicated that the variants included as covariates in admixture mapping were the driving factors of an admixture mapping association signal. We first tested each variant individually. If single variants did not explain the admixture mapping signal, then we tested multiple variants following the framework proposed by Molineros et al. (2013). Starting with the variant with the lowest  $p$  value, we added the variant having the next lowest  $p$  value and not in LD (defined as  $r^2 < .5$ ) with variants that were already in the model, one at a time, until the conditional  $p$  value was greater than .01.

### 3 | RESULTS

Table 1 summarizes the study samples. COGA, SAGE, and Yale-Penn were used in the analysis of DSM-IV alcohol dependence diagnosis and DSM-IV alcohol dependence criterion count. In total, there were 2,872 alcohol dependence cases and 1,672 controls. A total of 5,942 individuals had data on DSM-IV criterion count. COGA and NIAAA datasets were used for SRE analysis; SRE-5 and SRE-T analyses included data on 1,546 individuals in total. In terms of variants, 632,882, 601,545, 637,753, and 580,705 SNPs were included in the COGA, SAGE, Yale-Penn, and NIAAA data respectively (Table 1). RFMix estimated 14,376, 14,958, 15,336, and 14,118 African ancestry blocks for COGA, SAGE, Yale-Penn, and NIAAA respectively (Table 1). Using the R package CODA (Plummer et al., 2005), 273.82 effective African ancestry blocks were estimated across these four cohorts.

One region on chromosome 4 reached genome-wide significance for SRE-5 ( $p$  value =  $4.18E-05$ ) (Table 2; Figure 1). The most significant blocks in this region were between 24,377,777 bp and 24,512,590 bp and were supported by both the COGA and NIAAA cohorts. The estimate of effect size is larger in NIAAA than in COGA due to the proportion of study participants with higher SRE scores and larger variation in the NIAAA sample. Individuals carrying African ancestry blocks in this region had higher SRE scores ( $BETA = 0.21$ ,  $SE = 0.05$ ), that is, lower the response to alcohol. No other region reached genome-wide significance for other phenotypes (Figure S1a–c).

There were 298 genotyped and imputed variants located in the SRE-5 chromosome 4 GWS region. Using matSpDlite (Li & Ji, 2005; Nyholt, 2004), the estimated number of effective tests was 132; therefore, the significance threshold for the fine mapping analysis was determined as  $p$  value  $<3.79E-04$ . None of the variants tested individually reached this significance threshold. Table 3 lists all variants with  $p$  values  $<.01$  in fine mapping; some, for instance, had  $p$  values  $<.01$  in COGA but  $p$  values  $>.05$  in NIAAA, possibly due to the much smaller sample size of the NIAAA cohort. These variants from both COGA and NIAAA had similar allele frequencies as the African sample in the genome aggregation database (genomAD, <http://gnomad.broadinstitute.org/>). However, they had dramatically different allele frequencies from the gnomAD non-Finnish European sample, indicating that they were ancestry informative, as expected. Carrying an effective allele increased SRE-5 scores (Table 3) and the effective allele frequencies were higher in Africans than in non-Finnish

Europeans for all of these variants, except rs79462764. This was consistent with the results of admixture mapping. All variants in Table 3 individually had conditional  $p$  values  $<.01$ , indicating that they did not individually explain the admixture mapping association signal. When conditioned collectively on rs76004436, rs3966916, rs11931595, and rs10018808 (four independent variants with the lowest  $p$  values), the conditional analysis had  $p$  value  $>.01$ , demonstrating that these four variants (or variants in LD with them) were driving the admixture mapping association signal. Figure S2 shows the regional association plots that those four variants were index variants. Variants that were in LD with those index variants were all located in a small region between 24.37 Mbp and 24.52 Mbp. Figure S3 depicts the proportion of African ancestry on chromosome 4 for all cohorts. As can be seen, the proportion of African ancestry differed dramatically at different locations for all four cohorts.

### 4 | DISCUSSION

In this study, we performed admixture mapping of DSM-IV alcohol dependence diagnosis, DSM-IV alcohol dependence criterion count, and two SRE scores in four cohorts of AA. To our knowledge, this is the first genome-wide admixture mapping analysis of any of those four alcohol-related phenotypes in AA. One region on chromosome 4 was genome-wide significant (i.e.,  $p$  value  $<7.25E-05$ ) for SRE-5.

For the chromosome 4 locus, carrying an African ancestry allele in this region increased the SRE-5 score, indicating a lower response to alcohol during the first five times the individual used alcohol. This might initially appear counterintuitive, because AA typically report faster rates of stimulation in response to alcohol compared to EA (Pedersen & McCarthy, 2013). Recent studies suggested that findings from admixture mapping need not conform to expectations regarding the direction of disease prevalence; that is, even though a disorder is more common in one ancestral group, admixture mapping may result in identification of variants of protective effect (Molineros et al., 2013; Sofer et al., 2017; Wang et al., 2019). As long as the disease-causing variants have different allele frequencies between different ancestries, these variants will be detected by admixture mapping (Patterson et al., 2004), regardless of their directions of effect on the phenotype. Other variants that cannot be detected in our current analysis might be responsible for the population-specific effect.

**TABLE 1** Summary of study samples

Cohort	DSM-IV alcohol dependence (#cs/#ctl)	# DSM-IV alcohol dependence criterion count	# SRE-5	# SRE-T	# Variants	# African ancestry blocks
COGA	875/840	2,939	1,377	1,377	632,882	14,376
SAGE	400/341	959	NA	NA	601,545	14,958
Yale-Penn	1,552/491	2,044	NA	NA	637,753	15,336
NIAAA	NA	NA	169	169	580,705	14,118
Total	2,827/1,672	5,942	1,546	1,546		

Abbreviations: COGA, Collaborative study on the Genetics of Alcoholism; NIAAA, National Institute on Alcohol Abuse and Alcoholism; SAGE, Study of Addiction: Genetics and Environment.

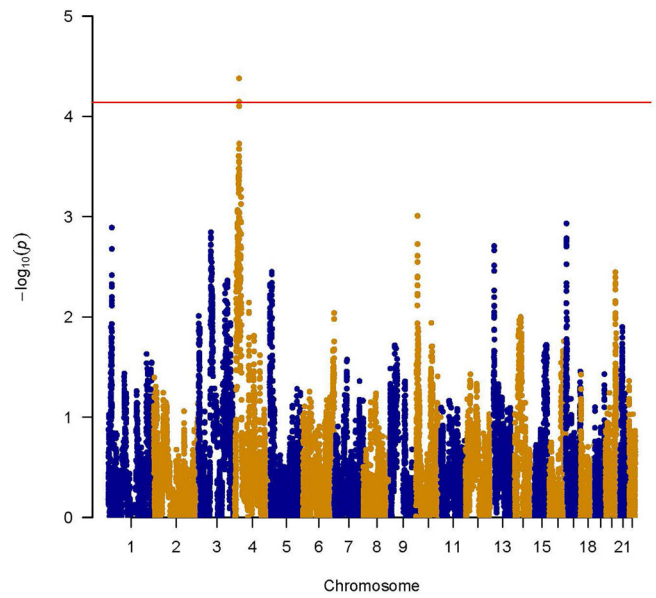


**TABLE 2** SRE-5 admixture mapping results of the chromosome 4 region

chr	Start	End	Ancestry tested	Meta-analysis			COGA			NIAAA		
				BETA	SE	p value	African ancestry frequency	BETA	SE	p value	African ancestry frequency	BETA
4	24,225,918	24,377,777	AFR	0.20	0.05	7.91E-05	0.78	0.06	2.08E-03	0.77	0.12	5.18E-03
4	24,377,777	24,439,865	AFR	0.20	0.05	7.15E-05	0.78	0.06	1.88E-03	0.77	0.12	5.64E-03
4	24,439,865	24,512,590	AFR	0.21	0.05	4.18E-05	0.78	0.06	9.02E-04	0.78	0.12	9.15E-03

Note: Genome-wide significant blocks are in bold. Abbreviations: AFR, African ancestry allele; COGA, Collaborative study on the Genetics of Alcoholism; NIAAA, National Institute on Alcohol Abuse and Alcoholism.

Multiple genes are located in the chromosome 4 GWS region.



**FIGURE 1** Genome-wide admixture mapping of SRE-5. Y-axis is the  $-\log_{10}(p)$  value for associations. X-axis is physical position of African ancestry blocks across the genome. The red horizontal line indicates genome-wide significance [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

One of them is *PPARGC1A* (PPARG coactivator 1 alpha). Among the 15 variants that have  $p$  values  $<.01$  in fine mapping (Table 3), 13 are in introns of *PPARGC1A*. This gene is broadly expressed in multiple tissues including liver and brain. The protein product of this gene interacts with cAMP response element binding protein (CREB) and nuclear respiratory factors (NRFs). Studies have found that the expression of the protein product of *PPARGC1A* was altered in post-mortem brain tissue from alcohol dependent individuals (Blednov et al., 2015; Ponomarev, Wang, Zhang, Harris, & Mayfield, 2012). Chronic alcohol exposure has also been shown to dramatically reduce cellular cAMP levels via a pathway involving *PPARGC1A* (Avila et al., 2016). In cultured neuronal cells, Liu et al. (2014) found that ethanol suppressed *PPARGC1A* expression, causing impaired mitochondrial functioning and increased cellular toxicity; while over-expression of *PPARGC1A* alleviated the alcohol-induced cellular toxicity (Liu et al., 2014). In a Spanish Mediterranean sample, *PPARGC1A* was found to be associated with alcohol consumption (Frances et al., 2008). Animal studies have reported that chronic alcohol treatment increased liver *PPARGC1A* expression levels in rats and this was reversed with an anti-oxidant *N*-acetylcysteine (Caro et al., 2014). In addition, *PPARGC1A* was related to reduced alcohol intake in mice (Blednov et al., 2015). Finally, while not studying SRE-5 as an outcome, one association study found that interactions between variants in *PPARGC1A* and alcohol consumption were significantly associated with obesity in AA but not EA (Edwards et al., 2012). Thus, there is persuasive evidence for a potential ancestry specific effect of this

**TABLE 3** Variants having  $p$  value  $<.01$  in fine mapping of chromosome 4 region for SRE-5

chr	bp	rs	Effective allele	Other allele	gnomAD		Meta-analysis			COGA			NIAAA			$p$ value	
					AFR	EAF	BETA	SE	$p$ value	EAF	BETA	SE	$p$ value	EAF	BETA		SE
4	24,509,859	rs76004436	T	C	0.05	1.00E-04	0.20	0.06	1.04E-03	0.04	0.21	0.06	9.20E-04	0.04	0.05	3.92	.86
4	24,506,961	rs376595619	T	C	0.05	6.67E-05	0.20	0.06	1.13E-03	0.04	0.20	0.06	1.02E-03	0.04	0.06	3.92	.85
4	24,377,799	rs3966916	G	A	0.09	9.00E-04	0.13	0.04	1.56E-03	0.08	0.14	0.04	1.15E-03	0.07	-0.04	2.89	.86
4	24,463,807	rs11931595	C	G	0.60	0.17	0.07	0.02	1.85E-03	0.55	0.07	0.02	1.38E-03	0.56	-0.01	1.41	.95
4	24,496,851	rs115697448	A	G	0.07	1.00E-04	0.16	0.05	2.34E-03	0.05	0.17	0.05	1.95E-03	0.05	0.01	3.61	.98
4	24,451,810	rs10018808	A	G	0.28	0.05	0.08	0.03	2.60E-03	0.25	0.08	0.03	3.76E-03	0.27	0.11	1.67	.39
4	24,454,550	rs10025734	G	C	0.37	0.12	0.07	0.02	2.81E-03	0.33	0.07	0.02	2.83E-03	0.35	0.04	1.59	.76
4	24,450,286	rs10034872	G	A	0.65	0.47	0.07	0.02	4.26E-03	0.62	0.07	0.02	2.37E-03	0.64	-0.06	1.49	.58
4	24,413,183	rs79462764	C	T	0.02	0.11	0.31	0.11	4.75E-03	0.01	0.36	0.11	1.48E-03	0.02	-0.39	5.43	.35
4	24,456,232	rs9992361	G	A	0.63	0.47	0.06	0.02	5.21E-03	0.60	0.07	0.02	2.96E-03	0.64	-0.07	1.48	.55
4	24,455,932	rs10026526	C	T	0.64	0.47	0.06	0.02	6.07E-03	0.61	0.07	0.02	3.56E-03	0.64	-0.06	1.49	.57
4	24,454,338	rs10025483	A	C	0.53	0.18	0.06	0.02	6.56E-03	0.49	0.06	0.02	5.55E-03	0.50	0.00	1.45	1.00
4	24,456,195	rs35429805	C	CA	0.62	0.47	0.06	0.02	6.58E-03	0.60	0.07	0.02	3.82E-03	0.63	-0.07	1.48	.56
4	24,466,090	rs6847029	A	G	0.48	0.15	0.06	0.02	7.91E-03	0.45	0.06	0.02	8.79E-03	0.49	0.05	1.49	.66
4	24,412,938	rs12331764	A	G	0.14	1.30E-03	0.09	0.03	9.28E-03	0.13	0.08	0.03	1.83E-02	0.08	0.40	2.90	.08

Note: Variants that are in bold were independent of each other and used in multi-variants conditional analysis.

Abbreviations: AFR, African; COGA, Collaborative study on the Genetics of Alcoholism; EAF, Effective allele frequency; gnomAD, the genome aggregation database; NFE, non-Finnish European; NIAAA, National Institute on Alcohol Abuse and Alcoholism.



gene on alcohol-related response. Other genes such as *DHX15* (DEATH-box helicase 15), *SOD3* (superoxide dismutase 3), *CCDC149* (coiled-coil domain containing 149), and *LGI2* (leucine rich repeat LDI family member 2) are also located within or near the chromosome 4 GWS region; however, none of them have previously been associated with alcohol dependence or related phenotypes.

The samples included in this study for SRE scores were also utilized in a previous GWAS (Lai, Wetherill, Kapoor, et al., 2019). In that study, no variant was genome-wide significant in meta-analysis of COGA and NIAAA cohorts, and that null finding was attributed to the relatively small sample size ( $N = 1,546$ ) (Lai, Wetherill, Kapoor, et al., 2019). In contrast, the current admixture mapping approach successfully identified a region on chromosome 4. Consistent with other studies, these findings corroborate the importance of applying admixture mapping for variant discovery in recently admixed samples, including those that might have been underpowered for detection using standard approaches. In that previous GWAS study of SRE, one variant (rs4770359,  $p$  value =  $2.92E-08$ , Beta = 0.16; SE = 0.03; effective allele: A) on chromosome 13 was genome-wide significant for SRE-5 in COGA only but not replicated in the NIAAA cohort ( $p$  value = .82), and meta-analysis has a  $p$  value of  $6.33E-08$  (Lai, Wetherill, Kapoor, et al., 2019). In the current admixture mapping analysis, this region was marginally associated with SRE-5 ( $p$  value = .08), with African ancestry increasing SRE-5 scores, which is in agreement with the prior GWAS result. This much higher  $p$  value could be due to the large size of the inferred African ancestry block: it is about twice the size of the identified region in previous GWAS, and included only one association signal; therefore, the regional effect size might have been too small to be detected by admixture mapping.

For DSM-IV alcohol dependence diagnosis and DSM-IV alcohol dependence criterion count, we did not find any genome-wide significant blocks. Most samples in this study were included in a GWAS meta-analysis of alcohol dependence in AA and the significant association of rs2066702 in *ADH1B* was identified (Walters et al., 2018). The protective role of rs2066702 was confirmed in a GWAS of alcohol dependence from the MVP (Kranzler et al., 2019). However, other variants in this gene, for example, rs1229984, also have protective effects in other ancestries, including EA. In the current admixture mapping, the inferred African ancestry block around this gene was large and included all known variants with protective effects; therefore, admixture mapping does not have sufficiently high resolution to detect association. We also examined the other AA-only finding from the MVP (rs72900220) (Kranzler et al., 2019) and found no evidence of association using the current admixture mapping approach. One possible explanation could be the low MAF of this variant (3.9%); therefore, even with admixture mapping, a much larger sample size may be required to detect the association with this variant.

Although admixture mapping can detect genes/variants that may not have been identified by current GWAS, it has several limitations. First, as shown in the *ADH1B* gene, multiple ancestry-specific disease-causing variants could be located in the same ancestry block, which limits the ability of admixture mapping to detect them. Second, ancestry blocks are determined by relatively common variants. If disease-causing

variants have low MAF, for example, rs72900220 identified by Kranzler et al. (2019), then larger sample sizes and much smaller blocks are needed to detect them in admixture mapping. Third, we performed a power analysis using QuantoV1.2.4 (Gauderman, 2002), assuming a MAF of 30% and the same sample size as in this study. We estimate 80% power to detect an odds ratio  $> 1.3$  and change of score  $> 0.4$  for binary and continuous traits, respectively. To detect variants with smaller effect, a larger sample size would be needed. Fourth, due to the design of admixture mapping and the complex LD patterns in admixed populations, no gene- or set-based tests could be performed. While large-scale GWAS will still be the major tool for genes/variants discovery, admixture mapping is a great complement to these mainstay methods. As shown in our chromosome 4 GWS region, all single variants had  $p$  values  $> .001$ . In GWAS, these variants would likely have been discounted; however, collectively these variants were associated with SRE-5 and explained the admixture mapping signal. Continued recruitment of participants from underrepresented and admixed populations are essential (Peterson et al., 2019) and we suggest that admixture mapping should also be performed to detect ancestry-specific disease genes/variants that may be missed by GWAS.

#### ACKNOWLEDGMENT

COGA: The Collaborative Study on the Genetics of Alcoholism (COGA), Principal Investigators B. Porjesz, V. Hesselbrock, T. Foroud; Scientific Director, A. Agrawal; Translational Director, D. Dick, includes 11 different centers: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, T. Foroud, J. Nurnberger Jr., Y. Liu); University of Iowa (S. Kuperman, J. Kramer); SUNY Downstate (B. Porjesz, J. Meyers, C. Kamarajan, A. Pandey); Washington University in St. Louis (L. Bierut, J. Rice, K. Bucholz, A. Agrawal); University of California at San Diego (M. Schuckit); Rutgers University (J. Tischfield, A. Brooks, R. Hart); The Children's Hospital of Philadelphia, University of Pennsylvania (L. Almasy); Virginia Commonwealth University (D. Dick, J. Salvatore); Icahn School of Medicine at Mount Sinai (A. Goate, M. Kapoor, P. Slesinger); and Howard University (D. Scott). Other COGA collaborators include: L. Bauer (University of Connecticut); L. Wetherill, X. Xuei, D. Lai, S. O'Connor, M. Plawecki, S. Lourens (Indiana University); L. Acion (University of Iowa); G. Chan (University of Iowa; University of Connecticut); D.B. Chorlian, J. Zhang, S. Kinreich, G. Pandey (SUNY Downstate); M. Chao (Icahn School of Medicine at Mount Sinai); A. Anokhin, V. McCutcheon, S. Saccone (Washington University); F. Aliev, P. Barr (Virginia Commonwealth University); H. Chin and A. Parsian are the NIAAA Staff Collaborators. We continue to be inspired by our memories of Henri Begleiter and Theodore Reich, founding PI and Co-PI of COGA, and also owe a debt of gratitude to other past organizers of COGA, including Ting-Kai Li, P. Michael Conneally, Raymond Crowe, Wendy Reich, and Robert E. Taylor, for their critical contributions. This national collaborative study is supported by NIH Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA). The authors acknowledge the Indiana University Pervasive Technology Institute for providing

[HPC (Big Red II, Karst, Carbonate), visualization, database, storage, or consulting] resources that have contributed to the research results reported within this article. A. Agrawal receives additional funding support from NIDA (DA032573). D. Goldman, M. L. Schwandt and V. A. Ramchandani are supported by the NIAAA Division of Intramural Clinical and Biological Research.

## CONFLICT OF INTEREST

Alison Goate is listed as an inventor on Issued U.S. Patent 8,080,371, "Markers for Addiction" covering the use of certain variants in determining the diagnosis, prognosis, and treatment of addiction. All other authors declare potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

Dongbing Lai, Arpana Agrawal, and Tatiana Foroud: Designed the study. Leah Wetherill, Melanie Schwandt, Vijay A. Ramchandani, David Goldman, and Marc Schuckit: Contributed to prepare the data. Dongbing Lai: Performed the analysis and drafted the manuscript. Manav Kapoor, Leah Wetherill, Melanie Schwandt, Vijay A. Ramchandani, David Goldman, Michael Chao, Laura Almasy, Kathleen Bucholz, Ronald P. Hart, Chella Kamarajan, Jacquelyn L. Meyers, John I. Nurnberger, Jay Tischfield, Howard J. Edenberg, Marc Schuckit, Alison Goate, Denise M. Scott, Bernice Porjesz, Arpana Agrawal, and Tatiana Foroud: Provided critical revision of the manuscript. All authors reviewed content and approved for publication.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Lai D, Kapoor M, Wetherill L, et al. Genome-wide admixture mapping of DSM-IV alcohol dependence, criterion count, and the self-rating of the effects of ethanol in African American populations. *Am J Med Genet Part B*. 2020;1–11. <https://doi.org/10.1002/ajmg.b.32805>