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Variation in the Gene Encoding the Serotonin Transporter is Associated with a Measure of Sociopathy in Alcoholics

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Abstract

The present study examined the association between a measure of sociopathy and 5-HTTLPR genotype in a sample of individuals from Project MATCH, a multi-center alcohol treatment trial. 5-HTTLPR, an insertion/deletion polymorphism in *SLC6A4*, the gene encoding the serotonin transporter protein, results in functionally distinct long (L) and short (S) alleles. The S allele has been associated with a variety of psychiatric disorders and symptoms including alcohol dependence, but it is unknown whether 5-HTTLPR increases the risk for co-morbid sociopathy among those with alcohol dependence.

Method—862 subjects diagnosed with alcohol dependence completed the California Psychological Inventory, a psychological assessment that includes a measure of socialization, which was used as a proxy measure of sociopathy. Subjects were genotyped for the insertion/deletion polymorphism, as well as a single nucleotide polymorphism (A→G) that is located in the inserted region.

Results—Regression analysis revealed that, after controlling for age, which was negatively related to socialization score, 5-HTTLPR genotype interacted with sex to determine socialization score ($p < 0.001$). Males with the L'L' genotype (i.e., those homozygous for the L_A allele) had lower socialization scores (i.e., greater sociopathy) than males who were carriers of the S' allele ($p = 0.03$). In contrast, women with the S'S' genotype had lower socialization scores than women with two L' alleles ($p = 0.002$) and tended to have lower CPI-So scores than women with one copy of the L' allele ($p = 0.07$).

Conclusion—Among individuals with AUDs, the tri-allelic 5-HTTLPR polymorphism had opposite effects on socialization scores in men than women. The basis for this finding is unknown, but it may have implications for subtyping alcoholics.

Keywords

5-HTTLPR; Antisocial Behavior; Behavioral Genetics; Sociopathy

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Introduction

Individuals diagnosed with an alcohol use disorder (AUD) show higher levels of antisocial behavior than the general population (Goldstein et al., 2007; Gough, 1994). In the National Epidemiologic Survey on Alcohol and Related Conditions, antisocial personality disorder (ASPD) was the disorder most closely linked to substance use disorders (Grant et al., 2004). Similarly, in the National Comorbidity Survey, the prevalence of comorbid ASPD ranged from 2.1% among women with alcohol abuse to 16.9% among men with alcohol dependence (Kessler et al., 1997). Ross, Glaser, and Germanson (1988) found that, in a clinical sample, up to 50% of patients with a diagnosis of alcohol abuse or dependence also met criteria for ASPD (Ross et al., 1988).

Serotonin (5-HT) has been shown to play a role in aggressive behavior (Brown et al., 1982; Giacalone et al., 1968; Linnoila et al., 1983; Valzelli and Garattini, 1968), thereby implicating it in the pathophysiology of ASPD. Low cerebrospinal fluid (CSF) levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been related to violent suicide attempts, impulsive fire-setting, violent and unprovoked aggression, and early-onset alcoholism (Brown et al., 1982; Mann et al., 1999; Virkkunen et al., 1994). These studies implicate 5-HT as a candidate neurotransmitter in the pathogenesis of psychiatric symptoms related to anger, lawlessness, and disregard for societal norms. Research also shows a role for 5-HT in alcohol drinking behavior (Naranjo and Bremner, 1993) and in Type II alcoholism, a subtype observed preponderantly in males and characterized by impulsivity, early age of onset, and antisocial features (Cloninger et al., 1982; von Knorring et al., 1985).

One gene in the 5-HT regulatory pathway that has received a great deal of research attention is *SLC6A4*, the gene that encodes the 5-HT transporter protein (5-HTT), a key regulator of 5-HT tone. A functional polymorphism identified in the 5-HTT linked promoter region (5-HTTLPR) of *SLC6A4* (Lesch et al., 1996) is characterized by a long (L) allele resulting from a 44-bp repeat insertion. The short (S) allele lacks the 44-bp insertion. The S and L alleles differentially modulate transcriptional activity of the serotonin transporter promoter, yielding differences in mRNA, protein density, and 5-HT uptake activity in human lymphoblastoid cells, platelets, and brain (Murphy et al., 2004). Greenberg and colleagues (1999) demonstrated that, in healthy individuals, 5-HT uptake was significantly higher in L allele homozygotes than in S allele carriers (Greenberg et al., 1999). Among individuals with treatment-resistant depression, S allele carriers had a significantly higher CSF concentration of 5-HIAA than L allele homozygotes (Kishida et al., 2007).

In addition to biochemical effects, the 5-HTTLPR polymorphism has been associated to behaviors relevant to both AUDs and ASPD. A meta-analysis of 17 published studies showed the S allele to be significantly more common among individuals with alcohol dependence (Feinn et al., 2005). The S allele has also been associated with impulsive aggressive behavior and extremely violent crimes (Lee et al., 2003; Liao et al., 2004). Taken together, these lines of research implicate the S allele as a risk factor for the development of both AUDs and sociopathic behaviors.

In this study, we examined the association of 5-HTTLPR alleles with scores on the Socialization Index (So) of the California Psychological Inventory (CPI), a measure of sociopathy, in a sample of individuals with an AUD. The CPI-So is a continuous psychological measure that was designed to measure social maturity and behavioral inhibition, with lower scores on this measure indicating greater sociopathy (Earleywine et al., 1990). We chose CPI-So score as our primary dependent measure because it is more informative than the binary diagnosis of ASPD, which is a heterogeneous disorder of complex etiology. We treated the 5-HTTLPR polymorphism as tri-allelic because the

functional effects of the 5-HTTLPR insertion-deletion polymorphism vary as a function of an A→G single nucleotide polymorphism (SNP; rs25531) located in the L-specific repeat of the gene (Hu et al., 2005; Wendland et al., 2006) with the L_G allele being similar to the lower activity S allele. We hypothesized that individuals with one or two of the lower-activity S or L_G alleles would have lower CPI-So scores (i.e., greater sociopathy) than individuals with two copies of the L_A allele. We controlled for age in the analysis, in light of work demonstrating that age was negatively related to traits characterizing Cluster B personality disorders, a rubric that includes ASPD (Reich et al., 1988). Because sex-specific effects of 5-HTTLPR have been reported (Limosin et al., 2005; Walderhaug et al., 2007), we also examined whether sex moderated the association between 5-HTTLPR and sociopathy.

Materials and Methods

Subjects and Materials

Subjects were 862 individuals participating in Project MATCH, a multi-center randomized clinical trial evaluating the efficacy of three types of psychosocial treatments for AUD (1993;1997). DSM-III-R (American Psychiatric Association, 1987) diagnoses of alcohol abuse or dependence were obtained using the Structured Clinical Interview for DSM-III-R (Spitzer and Williams, 1985). Diagnoses of ASPD were obtained using the computerized Diagnostic Interview Schedule (C-DIS-R). The vast majority of subjects ($n=829$ or 96.2%) met criteria for current alcohol dependence, with the remainder meeting criteria for current alcohol abuse. Subjects were also administered the Alcohol Use Disorders Identification Test (AUDIT), a ten-item instrument used to identify hazardous drinkers (Babor et al., 2001). Empirical research suggests that the AUDIT is a valid index of alcohol dependence severity (Donovan et al., 2006). A score of 8 or more on the AUDIT indicates hazardous alcohol use. AUDIT scores of 16 or higher represent a high level of alcohol problems, while individuals with scores of 20 or higher warrant further diagnostic evaluation for alcohol dependence (Babor et al., 2001). AUDIT scores in our sample ranged from 8 – 38 ($M=25.0$, $SD=6.3$), with most individuals (80%) scoring 20 or above. Similar to the larger Project MATCH sample, the typical subject in our sample met 6 of the 9 DSM-III-R criteria for a diagnosis of AD and 9.2% met full DSM-III-R criteria for ASPD. A higher proportion of males than females in the study sample received a diagnosis of ASPD [$\chi^2(1)=9.70$, $p<0.001$].

During a baseline assessment, Project MATCH subjects completed the CPI-So, a self-report inventory constructed using theory and clinical commonsense observations about the beliefs and attitudes of sociopathic individuals (Gough, 1994). The inventory consists of 46 true/false questions aimed at identifying individuals prone to deviance, rebelliousness, and defensiveness (Conway et al., 2003). Responses coded '1' for true and '0' for false (some reverse coded) were summed for an index of sociopathy such that lower scores represent greater sociopathy.

Subjects included in this report ($N=862$) were those with a complete CPI-So survey and for whom an adequate DNA sample was available to genotype the 5-HTTLPR polymorphism and a panel of 33 ancestry informative markers (Yang et al., 2005a). The sample was predominantly male (73.4%) with a mean age of 40.0 years ($SD=11.10$). We found no significant differences in age between men ($M=39.79$, $SD=11.62$) and women ($M=40.08$, $SD=10.82$) [$t(860)=0.34$, $p=0.74$]. European Americans (EAs) were the largest racial/ethnic group [$n=701$ (81.3%)] in our sample. Smaller proportions of the sample were African American (AA) [$n=79$ (9.2%)] or Hispanic [$n=82$ (9.5%)]. Table 1 summarizes sex, age, prevalence of ASPD, age of onset of problem drinking and AUDIT score for each of the major racial/ethnic groups. The Hispanic sample was eight years younger than the AA or EA

groups [$f(2,859)=22.53$, $p<0.0001$], had a higher representation of ASPD [$\chi^2(1)=5.2$, $p=0.03$] and a younger age of onset of problem drinking [$F(2,859)=8.65$, $p<0.001$].

Genotyping Procedure

We genotyped the 5-HTTLPR tri-allelic ($L_A/L_G/S$) polymorphism using a two-stage TaqMan™ 5'nuclease allelic discrimination assay modified from that originally described by Hu et al. (2005, 2006). This genotyping procedure identifies the presence of the 14 vs. the 16-repeat (i.e., S vs. L, respectively) alleles, as well as the A→G SNP located in the 16-repeat variant, which yields L_A and L_G alleles (Nakamura et al., 2000). The A allele variant (L_A) has a 2-fold higher level of gene expression than either the L_G or S allele variants (Hu et al., 2006).

A 25 μ L PCR reaction utilized 200 nM each of forward and reverse primers (5'GCAACCTCCCAGCAACTCCCTGTA-3' and 5'GAGGTGCAGGGGGATGCTGGAA-3'), 1M Betaine, 1 $\times$ ABI TaqMan Universal master mix (Applied Biosystems Inc., Foster City, CA), 25 ng of genomic DNA, and 120nM of an L allele-specific Fam-labeled probe (6FAM-TGCAGCCCCCCCAGCATCTCCC-MGB) and 60 nM of a Vic-labeled control probe (VIC-TCCCCCCTTCACCCCTCGCGGCATCC-MGB) complementary to a sequence contained in both S and L allele samples. The PCR samples were heated to 95°C for 10 min, cycled 40 times at 98°C for 15 sec, followed by 62.5°C for 90 sec. Examination of scatter plots of endpoint Fam vs. Vic fluorescence levels captured using an ABI 7500 Sequence Detection System was used to determine the number of L alleles (0, 1, or 2) for each subject. Using the same primers and amplification conditions as for the L vs. S allele assay, a second TaqMan™ 5'nuclease allelic discrimination test served to distinguish L_A from L_G alleles using L_A vs. L_G allele-specific probes (6FAM-CCCCCCTGCACCCCCAGCATCCC-MGB and VIC-CCCCTGCACCCCCGGCATCCCC-MGB, respectively).

A subset of our clinical sample ($n=300$) was genotyped for the 5-HTTLPR insertion-deletion polymorphism using the traditional agarose gel-based method, with 100% agreement between methods. Additionally, we sequenced 8 samples for each of the genotypes (L_A/L_A , L_A/L_G and L_G/L_G) with 100% agreement between direct sequencing and the TaqMan L_A vs. L_G assay. Genotyping completion rate was 97% for the L vs. S TaqMan assay and 95.5% for the L_A vs. L_G TaqMan assay. Subjects with incomplete L vs. S genotyping data were not included in the sample of 862 subjects, while the 39 of the 862 included samples (34 EAs, 3 Hispanics and 2 AAs) with failed or missing L_A vs. L_G assay data were coded by their primary S vs. L genotype data. Due to use of this genotyping method, other allelic variants (e.g. the uncommon “extra long” 5-HTTLPR) could not be detected.

Statistical Analysis

Because the L_G and S alleles are functionally equivalent in terms of in vitro promoter activities, they were grouped together as S' (the lower expression allele) and the L_A allele was designated as L' (the higher expression allele). While we and others have clumped L_g with S-alleles due to prior in vitro work indicating that both alleles have lower transcriptional activity in defined in vitro cell conditions, we have chosen not to substitute low, intermediate and high for the perhaps more awkward designations of S'S', S'L' and L'L' as it is not clear during what developmental epoch the transcriptional differences between the alleles is relevant to the psychological measures.

Our results did not indicate the presence of the G allele in samples from S allele homozygotes, consistent with the findings of Hu *et al.* (2006). In our sample, 55 (13%) of 422 LS individuals had the L_GS genotype and were recoded as S'S'. Six (2%) of the 275

individuals with two L alleles had the $L_G L_G$ genotype and were recoded as S'S'. Sixty-one $L_A L_G$ subjects or (22%) of the 275 LL individuals were recoded as L'S'. Altogether, 208 individuals were classified as L'L, 428 as L'S, and 226 as S'S'. 5-HTTLPR S vs. L genotypes for all three racial/ethnic groups were in Hardy Weinberg Equilibrium [EA: $\chi^2(1) = 0.63, p = 0.42$, AA: $\chi^2(1) = 3.05, p = 0.08$, Hispanic: $\chi^2(1) = 0.02, p = 0.99$]. The distribution of S' vs. L' 5-HTTLPR genotypes incorporating the L_A/L_G SNP rs25531 was also in Hardy Weinberg Equilibrium for all three racial/ethnic groups [EA: $\chi^2(1) = 0.26, p = 0.61$, AA: $\chi^2(1) = 3.24, p = 0.07$, Hispanic: $\chi^2(1) = 0.01, p = 0.99$]. Neither sex [$\chi^2(2) = 2.83, p = 0.24$] nor age [$F(2,859) = 0.50, p = 0.61$] were related to 5-HTTLPR genotype. Table 2 summarizes 5-HTTLPR genotype frequencies stratified by racial/ethnic group.

To estimate genetic ancestry proportions for each subject, DNA samples were also genotyped using a panel of 34 short tandem repeat ancestry informative markers (AIMs) as described previously (Covault et al., 2008; Luo et al., 2005; Stein et al., 2004; Yang et al., 2005b). These data were analyzed using the software program STRUCTURE v2.1 (Falush et al., 2003; Pritchard et al., 2000) to generate population $k=2$ estimates of the proportion of African vs. European genetic ancestry for each subject.

All statistical analyses were conducted using SPSS 15.0 (SPSS, Chicago, IL). Chi-square analysis was used to examine 5-HTTLPR allele frequencies in relation to the presence of ASPD. ANOVA was used to examine group differences for age, onset problem drinking and AUDIT score. Linear regression analysis was used to investigate the association between 5-HTTLPR and CPI-So score. The 5-HTTLPR genotypes L'L', L'S' and S'S' were coded 1, 0 and -1, respectively in the regression model. CPI-So scores were regressed hierarchically on the control variables (age, sex and genetic racial ancestry proportion), with the experimental variables (5-HTTLPR and 5-HTTLPR $\times$ sex) entered last in the model.

Results

CPI-So scores for the sample ranged from 8 to 40 ($M = 23.84$; $SD = 5.93$). As expected, individuals diagnosed with ASPD ($M = 18.39$; $SD = 4.29$) had significantly lower CPI-So scores (greater sociopathy) than individuals without that diagnosis ($M = 24.47$; $SD = 5.80$) [$t(862) = 9.04, p < 0.001$]. Men ($M = 23.98, SD = 6.06$) and women ($M = 23.44, SD = 5.53$) had comparable CPI-So scores [$t(862) = 1.165, p = 0.244$]. There was a significant correlation of age and CPI-So score [$r(862) = 0.344, p < 0.001$] such that older subjects had higher socialization scores. Because Hispanics ($M = 32.4, SD = 8.21$) subjects were significantly younger than either EA ($M = 41.5, SD = 8.7$) or AA ($M = 40.7, SD = 11.8$) subjects [$F(859) = 22.53, p < 0.001$], we controlled for age when examining CPI-So scores in relation to race/ethnicity. CPI-So scores did not differ as a function of race/ethnicity [$F(862) = 0.628, p = 0.52$] after controlling for age. There was no association of the ASPD diagnosis with 5-HTTLPR allele frequencies in any racial/ethnic group.

Table 3 shows the linear least squares regression models with CPI-So score as a function of sex, age, African vs. European genetic ancestry, 5-HTTLPR genotype, and sex $\times$ 5-HTTLPR genotype for each of the three racial/ethnic groups. We found no main effect of 5-HTTLPR genotype on CPI-So score; age predicted CPI-So score in EAs ($\beta = 0.32, p < 0.001$) and AAs ($\beta = 0.61, p < 0.001$), but not Hispanics ($\beta = 0.04, p = 0.695$) subjects. The interaction of 5-HTTLPR $\times$ sex in EAs ($\beta = 0.09, p < 0.02$) and Hispanics ($\beta = 0.47, p < 0.001$) was significantly related to CPI-So score, while the 5-HTTLPR $\times$ sex interaction trended towards statistical significance in AAs ($\beta = 0.20, p < 0.07$).

Table 4 shows the genotype differences in CPI-So scores separately by racial/ethnic group. A pattern in which men and women showed opposite effects was observed in all three

groups: males with the L'L' genotype and females with the S'S' genotype had the lowest mean CPI-So scores (i.e., greater sociopathy). These differences were greatest among Hispanics. As with the sample overall, there were no main effects of 5-HTTLPR genotype on CPI-So score in EAs [$\chi^2(2) = 1.849, p = 0.40$], AA [$\chi^2(2) = 0.26, p = 0.88$], or Hispanics [$\chi^2(2) = 2.85, p = 0.24$]. Inspection of the CPI-So mean data presented in Table 4 suggests that the S'-allele has a dominant effect in men and an additive effect in women. To examine this model for the overall sample, we compared men with the L'L' genotype with those having either the L'S' or S'S' genotype (L'L', L'S' and S'S' coded as 1, -1, and -1 respectively). For women to examine an additive gene effect model, genotypes L'L', L'S' and S'S' were coded as 1, 0, and -1 respectively. Men with the L'L' genotype had lower CPI-So scores than men with one or two S' alleles [$F(631) = 4.52, p = 0.03$] while for women the additive model was significant [$F(227) = 4.77, p = 0.009$] with S'S' genotype women having lower CPI-So scores than women with the L'L' genotype ($p = 0.002$), with a trend towards lower scores than women with the L'S' genotype ($p = 0.07$). Figure 1 illustrates the form of the 5-HTTLPR $\times$ sex interaction for the combined sample.

Discussion

We examined CPI-So scores as a function of age, sex, 5-HTTLPR genotype, and the interaction of sex $\times$ genotype in a sample of EA, AA and Hispanic subjects from a large multi-center study of psychotherapy to treat alcoholism. After controlling for age, we found a significant sex $\times$ 5-HTTLPR interaction. Men with the 5-HTTLPR L'L' genotype had greater sociopathy (i.e., lower CPI-So scores) than the other genotype groups. Conversely, women with the S'S' genotype had greater sociopathy (i.e., lower CPI-So scores) than the other genotype groups.

Existing literature suggests that males and females may respond differently to perturbations of the 5-HT system (Walderhaug et al., 2007). Although sex differences in serotonergic function are not well understood, multiple studies have shown such differences (Deakin et al., 1990; Delgado et al., 1989; Manuck et al., 1999; Soloff et al., 2003). Research is needed to identify the mechanism underlying the observed differences, which have implications for the sex differences observed among alcoholics, including substantial differences in the kinds of psychiatric symptoms and disorders that commonly co-occur in men compared with women alcoholics (Brady & Randall, 1999; Zilberman et al., 2003).

To our knowledge, no study has demonstrated a sex $\times$ 5-HTTLPR effect specifically on a measure of socialization, although there are multiple reports of differential effects of sex $\times$ 5-HTTLPR interaction on other psychological measures. Brummett et al. (2008a) reported that women with the S/S genotype who experienced early childhood stress had higher depression scores than those with at least one L-allele. Conversely, males with the L/L genotype who experienced early childhood stress had higher depression scores than males with one or more S-alleles (Brummett et al., 2008a). More recently, these investigators reported that during intravenous tryptophan infusion, men with two copies of the L'-allele and women with two copies of the S'-allele showed the greatest increases in negative affect compared with their sex peer group with the other genotypes (Brummett et al., 2008b). These reports are similar to our findings of opposite effects of the 5-HTTLPR polymorphism on CPI-So scores as a function of sex.

Age exerted the largest single effect on CPI-So scores. We suggest two at least two possible explanations for higher CPI-So score among older individuals. The first hypothesis is that by middle age, some extremely aggressive individuals may begin to internalize failures from their antisocial behavior, causing them to become more prosocial, which is sometimes termed "antisocial burnout" (Walker et al., 2003). Indeed, as observed in three studies

(Arboleda-Florez and Holley, 1991; Huchzermeyer et al., 2008; Robins and Price, 1991), only one-third of individuals diagnosed with ASPD still meet criteria after age 40. A second hypothesis for CPI-So score increasing with age is differential attrition. In this case, it is assumed that those who suffer the most severe cases of ASPD early in life sustain significant psychological and physical insults, which decrease their life span. Findings from a large epidemiological study ($N > 14,000$; Nabi et al., 2008) support differential attrition as a potential contributor for the age effect on socialization scores. Nabi et al. (2008) found that neurotic hostility, coronary heart disease-prone personality, and antisocial personality were all predictive of earlier mortality outcomes. If a similar effect holds in alcoholics, greater co-occurring sociopathy could be associated with premature death.

This study has a number of strengths. The study sample is large and recruited from inpatient and outpatient sites throughout the United States. We used the tri-allelic genotyping system for 5-HTTLPR, which provides a better measure of the functional effects of variation in this gene than does the bi-allelic genotype (Hu et al., 2006). The potential effects of population stratification were controlled for by inclusion of a measure of genetic ancestry. Finally, the interaction of sex $\times$ 5-HTTLPR was observed in all three racial/ethnic groups individually, consistent with a functional gene effect.

There are also study limitations that should be acknowledged. Although the mean CPI-So score of our alcoholic sample ($M = 24.0 \pm 5.9$) was similar to what Gough (1994) reported in two other alcoholic samples ($M = 23.8 \pm 5.4$ and $M = 22.49 \pm na$), making the findings relevant to understanding the serotonergic contribution to socialization among alcoholics, these findings may not generalize to healthy subjects. We did not validate our primary hypothesis of a main effect of 5-HTTLPR genotype on CPI-So score. Further, although the model was statistically significant, sex $\times$ 5-HTTLPR genotype differences explained only 1% of the total variation in CPI-So score, indicating that there are other important predictors of socialization among individuals with an AUD. In addition, sample sizes for Hispanics and AA were comparatively small, so results concerning the effects in those populations should be interpreted with caution. The smaller effect of the sex $\times$ 5-HTTLPR interaction on CPI-So scores in AAs may reflect the fact that for this population a larger portion of S'-alleles were comprised of the L_G-allele, as noted in Table 2.

In summary, we found significant effects of age and differential effects of 5-HTTLPR by sex on a measure of socialization in a large sample of individuals diagnosed with an AUD. Although further research is needed to investigate the mechanism by which sex influences the effects of the 5-HTTLPR polymorphism on socialization, these findings have important implications for understanding the well-described sex differences in the phenomenology of both sociopathy and alcohol dependence.

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Figure 1.

CPI-So score (Mean±S.E.) for 5-HTTLPR genotypes dichotomized by sex. Higher CPI-So scores indicated greater socialization (i.e., lower sociopathy). Men with the L'L' genotype had lower CPI-So scores than men with one or two S'-alleles ($p=0.03$) while women showed the opposite effect. Women with the S'S' genotype had lower CPI-So scores compared with S'L' ($p=0.07$), or L'L' genotypes ($p=0.002$).

Table 1

Sample descriptive features.

	Ethnicity				Statistic
	European American	Hispanic	African American	Total	
N	701	82	79	862	
Sex (% male)	74%	78%	64%	73%	n.s.
Age (M±SD)	40.7±11.3	32.4±8.2	41.5±8.7	40.0±11.1	p<0.0001 H<W or AA
ASPD (%)	8.9%	16.7%	8.3%	9.2%	p=0.03 H>W + AA
Age of onset problem drinking (M±SD)	26.5±10.6	21.7±7.8	27.5±9.6	26.0±10.4	p<0.001 H<W or AA
AUDIT Score	25.1±6.2	23.9±6.1	25.5±6.8	25.0±6.3	n.s.

*

n.s. = not significant

Table 2

Genotype count and percent frequency stratified by race/ethnicity.

Ethnicity	5-HTTLPR Genotype						
	S/S	S'/S'	S/Lg	Lg/Lg	S'/L'	Lg/La	L'/L'
EA	135 (19%)	42 (6%)	3 (0.4%)	314 (45%)	43 (6%)	164 (23 %)	701
Hispanic	22 (27%)	4 (5%)	1 (1%)	37 (45%)	3 (4%)	15 (18%)	82
AA	8 (10%)	8 (10%)	3 (4%)	16 (20%)	15 (19%)	29 (37%)	79
Total	165 (19%)	54 (6%)	7 (0.8%)	367 (43%)	61 (7%)	208 (24%)	862

Note: The frequency of Lg alleles (EA- 0.065; Hispanic- 0.055; AA - 0.18) was greater in AA compared with either EA ($\chi^2(1)= 28.1$, $p<0.0001$) or Hispanic ($\chi^2(1)= 12.8$, $p<0.001$), EA, European-American; AA, African-American

Linear least squares regression of CPI-So regressed onto age, genetic ancestry, 5-HTTLPR, sex, and sex $\times$ 5-HTTLPR for each racial/ethnic group.

Table 3

Model	Dependent Variable: CPI-So	Unstandardized Coefficients			Standardized Coefficients		
		B	Std. Error	Beta	t	p-value	
Total sample	(Constant)	17.189	1.120		15.344	.000	
	Age	.182	.017	.340	10.654	.000	
	Proportion EA ancestry	-.026	.699	-.001	-.037	.971	
	5-HTTLPR	-.415	.298	-.050	-1.391	.165	
	Sex	-.507	.429	-.038	-1.182	.238	
	Sex × 5-HTTLPR	.972	.299	.116	3.254	.001	
EA	(Constant)	4.899	5.491		.892	.373	
	Age	.168	.019	.322	9.040	.000	
	Proportion EA ancestry	12.359	5.537	.079	2.232	.026	
	5-HTTLPR	-.406	.329	-.048	-1.235	.217	
	Sex	.399	.244	.060	1.639	.102	
	Sex × 5-HTTLPR	.767	.333	.091	2.302	.022	
Hispanic	(Constant)	26.048	4.260		6.115	.000	
	Age	.026	.066	.041	.394	.695	
	Proportion EA ancestry	-6.060	3.883	-.161	-1.561	.123	
	5-HTTLPR	-.586	.894	-.079	-.656	.514	
	Sex	.594	.650	.095	.915	.363	
	Sex × 5-HTTLPR	3.477	.878	.472	3.958	.000	
AA	(Constant)	4.235	3.137		1.350	.181	
	Age	.470	.072	.613	6.522	.000	
	Proportion EA ancestry	8.529	5.454	.150	1.564	.122	
	5-HTTLPR	-.181	.814	-.021	-.223	.824	
	Sex	1.065	.770	.154	1.383	.171	

Model	Unstandardized Coefficients			Standardized Coefficients		
	Dependent Variable: CPI-So	B	Std. Error	Beta	t	p-value
	Sex $\times$ 5-HTTLPR	1.679	.917	.201	1.831	.071

Table 4

Mean CPI-So score by 5-HTTLPR genotype grouped by sex and race/ethnicity.

CPL-So Score (Mean $\pm$ SD)					
	S'S'	L'S'	L'L'	Total	Test Statistic*
Total sample	Total (n = 862)	23.8 $\pm$ 6.0 (n=226)	24.0 $\pm$ 5.9 (n=428)	23.5 $\pm$ 5.8 (n=208)	23.8 $\pm$ 5.9 (n=862) $F(2,861)=0.48, p=0.57$
	Men (n = 633)	24.3 $\pm$ 6.2 (n=170)	24.3 $\pm$ 5.9 (n=319)	22.9 $\pm$ 6.1 (n=144)	24.0 $\pm$ 6.1 (n=633) $F(2,630)=2.26, p=0.10$
	Women (n = 229)	22.1 $\pm$ 5.1 (n=56)	23.3 $\pm$ 5.9 (n=109)	24.9 $\pm$ 5.0 (n=64)	23.4 $\pm$ 5.5 (n=229) $F(2,228)=4.77, p=0.009$
Ethnic Group	Total (n = 701)	23.8 $\pm$ 6.1 (n=180)	24.3 $\pm$ 5.9 (n=357)	23.7 $\pm$ 5.7 (n=164)	24.0 $\pm$ 5.9 (n=701) $F(2,698)=1.15, p=0.32$
	Men (n = 518)	24.1 $\pm$ 6.3 (n=137)	24.6 $\pm$ 5.8 (n=268)	23.2 $\pm$ 5.8 (n=113)	24.1 $\pm$ 6.0 (n=518) $F(2,515)=1.92, p=0.15$
	Women (n = 183)	22.6 $\pm$ 4.8 (n=43)	23.3 $\pm$ 5.8 (n=89)	24.9 $\pm$ 5.2 (n=51)	23.6 $\pm$ 5.4 (n=183) $F(2,180)=2.06, p=0.13$
Hispanic	Total (n = 82)	23.4 $\pm$ 5.6 (n=27)	20.8 $\pm$ 4.5 (n=40)	21.6 $\pm$ 5.7 (n=15)	21.8 $\pm$ 5.2 (n=82) $F(2,79)=1.97, p=0.15$
	Men (n = 64)	24.1 $\pm$ 5.7 (n=22)	21.3 $\pm$ 4.8 (n=31)	20.3 $\pm$ 5.9 (n=11)	22.0 $\pm$ 5.4 (n=64) $F(2,61)=2.53, p=0.08$
	Women (n = 18)	20.0 $\pm$ 4.1 (n=5)	19.2 $\pm$ 2.9 (n=9)	25.3 $\pm$ 3.3 (n=4)	20.7 $\pm$ 4.0 (n=18) $F(2,15)=4.35, p=0.03$
AA	Total (n = 79)	24.7 $\pm$ 6.8 (n=19)	24.8 $\pm$ 6.8 (n=31)	23.2 $\pm$ 6.4 (n=29)	24.2 $\pm$ 6.7 (n=79) $F(2,76)=0.09, p=0.91$
	Men (n = 51)	27.7 $\pm$ 4.6 (n=22)	24.0 $\pm$ 6.9 (n=31)	22.6 $\pm$ 7.1 (n=11)	24.2 $\pm$ 6.8 (n=51) $F(2,48)=1.18, p=0.32$
	Women (n = 28)	20.5 $\pm$ 7.3 (n=8)	26.5 $\pm$ 6.7 (n=11)	24.4 $\pm$ 4.8 (n=9)	24.1 $\pm$ 6.6 (n=28) $F(2,25)=4.52, p=0.02$

^{*} Test statistic controlled for age

EA, European-American; AA, African-American