**Twin Research and Human Genetics**
Volume 17 ▌ Number 2 ▌ pp. 80–88 ▌ © The Authors 2014 ▌ doi:10.1017/thg.2014.11

# *CHRNA5* and *CHRNA3* Variants and Level of Neuroticism in Young Adult Mexican American Men and Women

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A lifetime history of alcohol dependence has been associated with elevations in neuroticism in Mexican American young adults. The identification of genetic markers associated with neuroticism and their influence on the development of alcohol use disorders (AUD) may contribute to our understanding of the relationship between personality traits and the increased risk of AUD in Mexican Americans. The purpose of this study was to investigate associations between neuroticism and 13 single nucleotide polymorphisms (SNPs) in the nicotinic acetylcholine (nAChR) α5-subunit (*CHRNA5*) and α3-subunit (*CHRNA3*) genes in young adult Mexican American men and women. Participants were 465 young adult Mexican American men and women who are literate in English and are residing legally in San Diego County. Each participant gave a blood sample and completed a structured diagnostic interview. Neuroticism was assessed using the Maudsley Personality Inventory. The minor alleles of four *CHRNA5* polymorphisms (rs588765, rs601079, rs680244 and rs555018) and three *CHRNA3* polymorphisms (rs578776, rs6495307 and rs3743078) showed associations with neuroticism. Several of these SNPs also displayed nominal associations with DSM-IV alcohol and nicotine dependence, but tests of mediation suggested that these relations could be partially explained by the presence of co-occurring neuroticism. These findings suggest that genetic variations in nicotinic receptor genes may influence the development of neuroticism, which in turn is involved in the development of AUDs and nicotine dependence in Mexican American young adults.

■ **Keywords:** Mexican Americans, neuroticism, gender, *CHRNA5*, *CHRNA3*, nicotinic acetylcholine receptor

Differences in drinking patterns and problems between different racial or ethnic groups highlight the importance of studying the etiology of alcohol involvement in Hispanics (Dawson, 1998; Grant et al., 2004; Nielsen, 2000). Mexican Americans are the largest subgroup of Hispanic Americans, with nearly two thirds of the total US Hispanic population. There is evidence to suggest that Mexican Americans are at higher risk for hazardous patterns of alcohol drinking (Ramisetty-Mikler et al., 2010), alcohol use disorders (AUD; Caetano et al., 2008a), and alcohol-related accidents (Caetano et al., 2008b). Studies in first generation (immigrant generation) Mexican Americans have demonstrated that alcohol use and other psychiatric disorders increase in frequency with time spent in the United States, and these disorders further increase in frequency in subsequent (US-born) generations of Mexican Americans. For example, US-born Mexican Americans have rates of alcohol use and psychiatric disorders that are 2 to 3 times higher than their Mexican-born ancestors (Burnam et al., 1987; Golding & Burnam, 1990; Grant et al., 2004; Kessler et al., 1994; Strunin et al., 2007; Vega et al., 1998, 2003). It has been hypothesized that this increase in prevalence rates is the result of a transgenerational process of adapting to living in the United States (Burnam et al., 1987; Escobar, 1998; Ortega et al., 2000), thus suggesting that environmental factors may increase the susceptibility to psychiatric disorders in this population. Nonetheless, a recent family study

RECEIVED 13 December 2013; ACCEPTED 5 February 2014. First published online 3 March 2014.

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of Mexican-Americans suggests that substantial genetic influences are also involved in the development of AUD in this population (Olvera et al., 2011). However, how genetic influences affect behavioral traits associated with the increased risk of AUDs in Mexican Americans is not well understood.

The expression of certain personality traits is a prominent factor associated with an increase in the risk for alcohol dependence and substance abuse (see Acton, 2003; Cloninger et al., 1988; Larkins & Sher, 2006; Pihl & Peterson, 1995; Sher & Trull, 1994; Sher et al., 1999, 2000). Neuroticism is a personality trait that has been shown to influence the use and abuse of alcohol (see Larkins & Sher, 2006; Read & O'Connor, 2006; Sher & Trull, 1994). High levels of neuroticism have also been associated with cigarette smoking, marijuana use, and polysubstance abuse (McCormick et al., 1998; Terracciano & Costa, 2004; Terracciano et al., 2008). There is considerable evidence that neuroticism is associated with an increased susceptibility to stressors in US-born Mexican Americans (Finch et al., 2000; Mangold et al., 2007, 2012; Romero & Roberts, 2003). We have previously shown that Mexican American participants with a lifetime history of alcohol dependence exhibited an increase in neuroticism scores, compared to age-matched controls (Criado & Ehlers, 2007).

While many studies have shown a relationship between AUD and neuroticism (e.g., Read & O'Connor, 2006; Sher et al., 2005), neuroticism may be a risk as well as a protective factor for alcohol use. Read & O'Connor (2006) suggested two distinct pathways leading from neuroticism to alcohol use. The first (direct) pathway defines neuroticism as a protective factor for alcohol use that biases attention toward the negative consequences of drinking, thus reducing use. The second (indirect) pathway defines neuroticism as a risk factor for alcohol use via increased positive expectancies regarding the effects of alcohol. Additional studies, however, have suggested a bidirectional relation between neuroticism and alcohol use, demonstrating that increases in neuroticism can result from long-term alcohol use (Sutherland, 1997). These findings suggest a more complex association between neuroticism and AUD. Further, the relationship between personality traits and genetic markers associated with the increased risk for alcohol dependence in Mexican Americans is not well understood. The identification of genetic markers associated with neuroticism and their influence on the development of AUD and drug dependence in Mexican Americans may help in determining the relationship between basic molecular processes and clinical phenomena associated with the disorder in the broader general population.

Neuronal nicotinic receptors (nAChRs) are important therapeutic targets for the treatment of AUDs (Chatterjee & Bartlett, 2010). Preclinical studies have shown evidence of a relationship between α5 and α3 nAChRs subunits and alcohol-seeking behaviors. A recent study found that pharmacological activation of α3β4 nAChRs selectively decreases ethanol, but not sucrose consumption, in animal models (Chatterjee et al., 2011). Moreover, studies in animal models have provided evidence that genetic variations of nAChR subunits, including the α5 and β4 nAChRs subunits, are associated with alcohol preference and consumption (see Tuesta et al., 2011).

In humans, the genomic region on chromosome 15q25 encoding the α5 (*CHRNA5*) and α3 (*CHRNA3*) nAChR subunits has been associated with vulnerability to nicotine addiction, with the strongest effects observed for a nonsynonymous SNP in exon 5 of *CHRNA5* and a highly correlated synonymous SNP in exon 5 of *CHRNA3* (e.g., Bierut et al., 2008; Saccone et al., 2009, 2010; Schlaepfer et al., 2008; Sherva et al., 2010; Tobacco and Genetics (TAG) Consortium, 2010; Wang et al., 2009b). Additional studies have reported evidence of association between these SNPs and alcohol consumption, level of response to alcohol, and alcohol dependence (e.g., Chen et al., 2009; Joslyn et al., 2008; Schlaepfer et al., 2008; Wang et al., 2009a). Associations independent of these SNPs may also be present in the region (e.g., Joslyn et al., 2008; Wang et al., 2009a) indicating that multiple variants in the chromosome 15 nicotinic receptor gene cluster may influence the development of AUD and related traits.

The present report is part of a larger study exploring genetic risk factors for AUD among Mexican Americans (e.g., Ehlers & Phillips, 2007; Ehlers et al., 2012). Understanding the relationship between neuroticism and genetic markers associated with an increased risk for alcohol and drug dependence may provide critical information on risk and protective factors for addiction in Mexican American men and women. Thus, the primary aim of the study was to determine if significant associations could be detected between 13 SNPs in the *CHRNA5* and *CHRNA3* genes (rs684513, rs588765, rs601079, rs680244, rs692780, rs555018, rs16969968, rs1979906, *LOC123688* rs8034191, rs578776, rs6495307, rs1051730 and rs3743078) and neuroticism in young adult Mexican American men and women. A secondary aim was to determine if significant associations could be detected between these SNPs and alcohol dependence, and if so, whether these observed associations were mediated by the presence of neuroticism. Although the primary focus of the present report was on the relations between the measured SNPs, neuroticism, and alcohol use, SNPs in *CHRNA3* and *CHRNA5* have shown strong relations with smoking behaviors as described. Thus, we also conducted a parallel set of mediation analyses between these SNPs, nicotine dependence, and neuroticism.

## Materials and Methods

### Participants

Mexican American participants ($n = 465$) were recruited using a commercial mailing list that provided the addresses



https://doi.org/10.1017/thg.2014.11 Published online by Cambridge University Press

**TABLE 1**

**Results for Association Tests Between *CHRNA3/CHRNA5* SNPs and Neuroticism and Alcohol and Nicotine Dependence**

| SNP | Position | Gene | Alleles | MAF | Neuroticism B (SE) | *p* | $R^2$ | Alcohol dependence B (SE) | *p* | $R^2$ | Nicotine dependence B (SE) | *p* | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs8034191 | 78806023 | LOC123688 | C*/T | 0.19 | -0.28 (0.43) | .509 | .00 | 0.19 (0.22) | .386 | .00 | 0.28 (0.30) | .355 | .00 |
| rs1979906 | 78842289 | CHRNA5 | C*/T | 0.26 | -0.72 (0.39) | .067 | .01 | -0.32 (0.18) | .086 | .01 | 0.54 (0.24) | .023 | .02 |
| rs684513 | 78858400 | CHRNA5 | C/G* | 0.42 | -0.79 (0.35) | .024 | .01 | -0.10 (0.17) | .548 | .00 | 0.37 (0.24) | .111 | .01 |
| rs588765 | 78865425 | CHRNA5 | C/T* | 0.23 | **1.12 (0.40)** | **.005** | **.02** | 0.34 (0.19) | .068 | .01 | 0.52 (0.24) | .029 | .02 |
| rs601079 | 78869579 | CHRNA5 | A/T* | 0.24 | **1.12 (0.39)** | **.004** | **.02** | 0.33 (0.18) | .075 | .01 | 0.48 (0.24) | .044 | .02 |
| rs680244 | 78871288 | CHRNA5 | C/T* | 0.24 | **1.10 (0.39)** | **.005** | **.02** | 0.32 (0.18) | .084 | .01 | 0.47 (0.24) | .046 | .02 |
| rs692780 | 78876505 | CHRNA5 | C*/G | 0.20 | -1.11 (0.42) | .009 | **.01** | -0.38 (0.20) | .685 | .01 | 0.54 (0.24) | .034 | .02 |
| rs555018 | 78879242 | CHRNA5 | A/G* | 0.23 | **1.12 (0.40)** | **.005** | **.02** | 0.34 (0.19) | .068 | .01 | 0.52 (0.24) | .029 | .02 |
| rs16969968 | 78882925 | CHRNA5 | A*/G | 0.19 | -0.26 (0.43) | .535 | .00 | 0.14 (0.21) | .501 | .00 | 0.19 (0.29) | .507 | .00 |
| rs578776 | 78888400 | CHRNA3 | A/G* | 0.41 | **1.00 (0.34)** | **.004** | **.02** | 0.13 (0.17) | .435 | .00 | 0.21 (0.22) | .351 | .00 |
| rs6495307 | 78890321 | CHRNA3 | C/T* | 0.24 | **1.20 (0.39)** | **.002** | **.02** | 0.37 (0.19) | .048 | .01 | 0.54 (0.24) | .023 | .02 |
| rs1051730 | 78894339 | CHRNA3 | A*/G | 0.19 | -0.19 (0.42) | 0.65 | .00 | 0.18 (0.21) | .404 | .00 | 0.23 (0.29) | .441 | .00 |
| rs3743078 | 78894759 | CHRNA3 | C/G* | 0.43 | **1.01 (0.34)** | **.003** | **.02** | 0.15 (0.17) | .352 | .00 | 0.31 (0.22) | .159 | .01 |

Note: * Indicates minor allele; bold text indicates nominally significant association; position indicates position of SNP in base pairs on chromosome 15 using Genome Reference Consortium Human Build 37/Human Genome build 19 (GRCh37/hg19); MAF = minor allele frequency.

of individuals with Hispanic surnames in 11 zip codes in San Diego County that had a population of at least 20% Hispanic heritage and were within 25 miles of the research site. The mailed invitation stated that potential participants must be of Mexican American heritage, must be between the ages of 18 and 30 years, must be residing in the United States legally, and must be able to read and write in English. Potential participants were requested to phone research staff for more information. During the phone interview, potential participants were screened for the inclusion criteria listed on the invitation. Participants were excluded if they were pregnant or nursing, currently had a major medical or neurologic disorder, or a head injury. All participants were asked to refrain from alcohol or any other substance use for 24 hours before testing. Participants were compensated for their time spent in the study.

### Psychiatric Diagnoses

On the test day, after a complete description of the study to the participants, written informed consent was obtained using a protocol approved by The Institutional Review Board of The Scripps Research Institute. During the screening period, the study coordinator noted whether the participant was agitated, tremulous, or diaphoretic. Participants also took an alcohol breathalyzer test to assess blood alcohol concentration. Participants were eliminated from the current data analyses if they were taking psychoactive medication or had a positive breath alcohol test on the day of the evaluation. Information on demography, personal medical and psychiatry history, drinking history, and other substance dependence was obtained using a Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999) administered by trained research assistants. Information on family history of alcohol dependence was collected using the Family History Assessment Module (FHAM) developed by COGA (Rice et al., 1995). The SSAGA is a highly reliable and valid instrument for use in studies of psychiatric disorders, including substance dependence (Bucholz et al., 1994; Hesselbrock et al., 1999). Diagnoses of lifetime alcohol dependence and nicotine dependence were made on the basis of DSM-IV criteria (without clustering) generated by the SSAGA. All best final diagnoses were made by a research psychiatrist/addiction specialist (DAG). The 24-item Neuroticism (N) subscale of the Maudsley personality inventory (MPI) (Eysenck & Eysenck, 1975) was used to determine neurotic tendencies.

### Genotyping

Genotypes were available for 465 participants based on protocols described in previous reports (Ehlers et al., 2010a, 2010b). A blood sample was obtained by venipuncture from each participant and DNA was isolated from leukocytes. SNP selection and genotyping was based on previous studies conducted by a co-author of the present report (HJE: Hartz et al., 2012; Wang et al., 2009a). This set of 13 SNPs associated with the *CHRNA5* and *CHRNA3* genes were genotyped (see Table 1); all SNPs were in Hardy Weinberg Equilibrium ($p > .86$).

### Data Collection and Statistical Analysis

This study investigated the relationship among neuroticism, and polymorphisms in the *CHRNA5* and *CHRNA3* genes in young adult Mexican American men and women. A higher N-score in the MPI indicated a greater neurotic tendency. To divide participants into two groups with low and high neurotic tendencies, a median split was made of the MPI N-score for the entire sample. Comparisons between demographics, levels of neurotic tendencies, lifetime history of alcohol and nicotine dependence, and family history of alcohol dependence were conducted using ANOVA for continuous variables and Fisher's Exact Test for dichotomous variables.

Tests of association between individual SNPs and neuroticism were conducted using hierarchical regression. Specifically, age and gender were entered as covariates in an initial step, and genotype was entered as a predictor



https://doi.org/10.1017/thg.2014.11 Published online by Cambridge University Press

**TABLE 2**

**Demographic Characteristics of Participants as Function of Low and High Neuroticism**

| Demographic variable | Total sample | Low neuroticism | High neuroticism |
|---|---|---|---|
| Age, in years, mean (SEM) | 23.6 (0.2) | 24.1 (0.2) | 23.2 (0.2)* |
| Men | 23.6 (0.3) | 24.1 (0.4) | 23.0 (0.4) |
| Women | 23.6 (0.2) | 24.1 (0.3) | 23.3 (0.3) |
| Gender, *n* (%) | | | |
| Men | 194 (42) | 104 (54) | 90 (46) * |
| Women | 271 (58) | 120 (44) | 151 (56) |
| Years of education (SEM) | 13.3 (0.1) | 13.4 (0.1) | 13.2 (0.1) |
| Marriage status, *n* (%) | | | |
| No | 377 (81) | 178 (47) | 199 (53) |
| Yes | 88 (19) | 46 (52) | 42 (48) |
| Employed, *n* (%) | | | |
| No | 164 (35) | 81 (49) | 83 (51) |
| Yes | 300 (65) | 142 (47) | 158 (53) |
| Yearly family income, *n* (%) | | | |
| ≤ $20k | 87 (20) | 40 (46) | 47 (54) |
| ≥ $20k | 349 (80) | 169 (48) | 180 (52) |
| Family history of alcohol dependence, *n* (%) | | | |
| No | 278 (60) | 149 (54) | 129 (46) ** |
| Yes | 186 (40) | 75 (40) | 111 (60) |
| Lifetime history of alcohol dependence, *n* (%) | | | |
| No | 367 (79) | 196 (53) | 171 (47) *** |
| Yes | 98 (21) | 28 (29) | 70 (71) |
| Lifetime history of nicotine dependence, *n* (%) | | | |
| No | 418 (90) | 210 (50) | 208 (50)* |
| Yes | 47 (10) | 14 (30) | 33 (70) |

Note: [a] The low neuroticism group versus the high neuroticism group was compared using Fisher's Exact Test for dichotomous variables and analysis of variance (ANOVA) for continuous variables (* = $p < .05$; ** = $p < .005$; *** = $p < .001$). Values are $\bar{x} \pm$ SEM.

in a second step. The test of the regression coefficient for genotype and the associated increase in explained variance attributable to genotype were used to evaluate evidence for association. A similar approach using logistic regression was used to test for association between individual SNPs and DSM-IV alcohol and nicotine dependence. For SNPs exhibiting nominal evidence of association with alcohol or nicotine dependence ($p < .05$), a test of mediation was conducted to evaluate whether the relation between a given SNP and alcohol or nicotine dependence could be explained by the presence of neuroticism. Tests of mediation were conducted in MPlus (Muthén & Muthén, 2012) using methods described by Baron & Kenny (1986).

To minimize the probability of a Type I error occurring due to multiple comparisons, a correction for multiple testing of SNPs was performed according to Nyholt (2004) and critical *p* set at .006. Power analyses indicated that there was sufficient power (0.80) at $\alpha = 0.05$ to detect differences in our primary analyses, for a medium effect size (Faul et al., 2009).

## Results

Demographic data on the 465 participants are presented in Table 2. The sample had a mean age of 23.6 years (SEM = 0.2) and contained more women participants ($n =$ 271, 58%) than men ($n = 194$, 42%). Twenty-one percent ($n = 98$) of participants had a lifetime diagnosis of alcohol dependence, 40% ($n = 186$) had a family history of alcohol dependence, and 10% of participants ($n = 47$) had a lifetime diagnosis of nicotine dependence. Participants with low and high neuroticism scores showed no significant differences in the number of years of education, marriage status, employment, and yearly family income. Compared to participants with low neuroticism scores, participants with high neuroticism scores were more likely to be younger, to have a higher level of acculturation stress, a family history of alcohol dependence, and lifetime history of alcohol and nicotine dependence. The high neuroticism group had more women ($n = 151$; 56% of females) than men ($n = 90$; 46% of males).

Four hundred and sixty-five unrelated individuals were used to calculate linkage disequilibrium (LD) statistics between all pairwise SNPs genotyped as part of the present report. The degree of LD between SNPs and the haplotype block structure are shown in Figure 1. Consistent with previous reports (e.g., Wang et al., 2009a), we observed three correlated sets of SNPs as indicated by the lettered superscripts in Figure 1. These included sets of SNPs correlated with rs16969968, rs578776, and rs588765, respectively.

Regression analyses suggested a number of associations with neuroticism that remained significant after correction for multiple comparisons (Table 1). The most significant association was observed with the T allele of rs6495307 in *CHRNA3* (B = 1.20, SE = 0.39, $p = .002$, $R^2 = .02$), though this SNP is in strong LD with a number of SNPs in *CHRNA5*, including rs588765. A significant association was also observed with rs578776, which is located in *CHRNA3* and shows minimal levels of LD with rs6495307 (see Figure 1). For DSM-IV defined alcohol dependence, rs6495307 was



https://doi.org/10.1017/thg.2014.11 Published online by Cambridge University Press

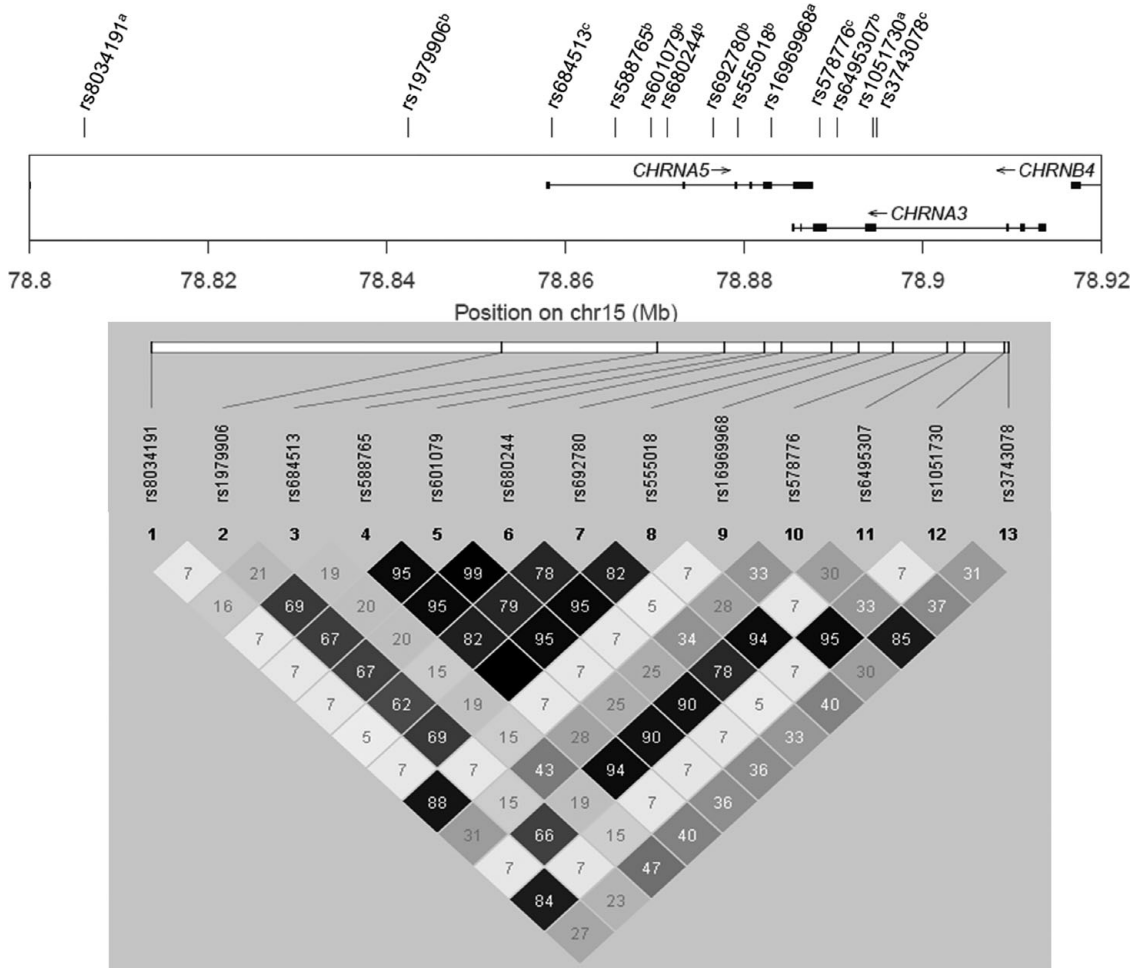


**FIGURE 1**

**LD structure of the genotyped *CHRNA5* and *CHRNA3* SNPs. Note: The top half of the figure provides the physical locations of the genotyped SNPs in relation to the *CHRNA5* and *CHRNA3* genes. Superscripts indicate SNPs in LD with each other as indicated by the $R^2$ values depicted in the shaded boxes that comprise the bottom half of the figure. This portion of the figure and the $R^2$ values were generated using Haploview (Barrett et al., 2005).**

the only SNP to reach nominal significance (B = 0.37, SE = 0.19, $p = .048$, Nagelkerke $R^2 = .01$), whereas several SNPs showed nominal associations with nicotine dependence.

A secondary aim of the present study was to examine whether any observed associations with alcohol dependence could be explained by the presence of neuroticism. Given that the only nominal association with alcohol dependence was observed for rs6495307, we constructed a mediator model in which the significance of an indirect path from rs6496307 to alcohol dependence with neuroticism as the mediator was tested. The indirect effect was significant ($t = 2.74$, $p = .006$) with the direct relation between rs6495307 and alcohol dependence becoming non-significant (B = 0.13, SE = 0.10, $p = .198$). Additionally, a constrained model in which the indirect path was dropped by fixing the regression of alcohol dependence on neuroticism to zero exhibited a significant decline in fit, $\Delta\chi^2(df = 1) = 28.51$, $p < 0.0001$, providing further support for neuroticism as a mediator of the relation between rs6495307 and alcohol dependence. A similar pattern of results was observed for mediator models constructed for the nominal associations reported for nicotine dependence (data not shown).

## Discussion

The identification of genetic markers associated with neuroticism may help determine the molecular mechanisms contributing to the interactions between this personality trait and AUDs, drug dependence, and other psychiatric disorders. There is considerable evidence to suggest that at least three distinct loci found in the chromosome region 15q25, encoding the α5 (*CHRNA5*), α3 (*CHRNA3*) and β4 (*CHRNB4*) nAChR subunits, have a strong association with smoking behavior and nicotine dependence (Saccone et al., 2009, 2010; TAG Consortium, 2010; Thorgeirsson et al., 2010; Wang et al., 2009b), and these findings have



https://doi.org/10.1017/thg.2014.11 Published online by Cambridge University Press

been extended to alcohol abuse and dependence (Chen et al., 2009; Joslyn et al., 2008; Sherva et al., 2010; Wang et al., 2009a). While levels of neuroticism have been shown to influence alcohol use (Larkins & Sher, 2006; McCormick et al., 1998; Read & O'Connor, 2006; Sher & Trull, 1994; Terracciano & Costa, 2004; Terracciano et al., 2008), the relationship among neuroticism, AUDs, and *CHRNA5* and *CHRNA3* SNPs is not well understood.

The present study identified *CHRNA5* and *CHRNA3* polymorphisms associated with neuroticism in young adult Mexican American men and women. Results suggested that two SNPs previously associated with alcohol dependence, rs578776 (*CHRNA3*) and rs588765 (*CHRNA5*) were also associated with neuroticism. The most highly significant association with neuroticism observed in the present study was with the T allele of rs6495307 in *CHRNA3*, which is in strong LD with rs588765. A significant association was also reported for a second set of correlated markers, including rs578776, that showed little LD with the marker set including rs6496307 and rs588765. These results are supported by a previous meta-analysis demonstrating independent association signals for both marker sets with nicotine dependence (Saccone et al., 2010).

In relation to alcohol dependence, previous studies investigating relations between *CHRNA3* and *CHRNA5* polymorphisms and AUDs have shown that the nonsynonymous SNP in *CHRNA5,* rs16969968, and the synonymous SNP in *CHRNA3,* rs1051730, that have shown replicable evidence of association with tobacco phenotypes (Bierut et al., 2008; Saccone et al., 2009, 2010; TAG Consortium, 2010), are also associated with symptoms of alcohol abuse or dependence (Chen et al., 2009). Nonetheless, other studies have reported associations between these genes and alcohol dependence but with different sets of polymorphisms (Wang et al., 2009a). There is evidence to suggest that the relationship between the *CHRNA3* gene and AUDs may be dependent on the population group studied. Sherva et al. (2010) reported an association between the *CHRNA3* SNP rs578776 and alcohol dependence in their African American sample, but not in their European American sample.

The present study suggests that unmeasured variation in neuroticism across participants might also contribute to the lack of consistent findings. In the current sample, rs6495307 was the only SNP to reach nominal association with DSM-IV alcohol dependence, and several SNPs reached nominal associations with DSM-IV nicotine dependence. For both disorders, these associations appeared to be mediated by the presence of neuroticism. The findings from the current study suggest that polymorphisms in the *CHRNA5* and *CHRNA3* genes are involved in the development of neuroticism, and thus indirectly also increase risk for alcohol and nicotine dependence, consistent with previous studies suggesting that high levels of neuroticism predispose individuals to both disorders (e.g., Malouff et al., 2006; Read & O'Connor, 2006; Sher et al., 2005). Future functional studies investigating how these polymorphisms might influence levels of neuroticism and the subsequent development of AUDs will provide important insights into the risk and protective factors for AUDs in Mexican Americans.

The present study also replicated previous reports demonstrating that participants with high neuroticism scores are more likely to have a family history of alcohol dependence and a lifetime history of alcohol and nicotine dependence than those with low neuroticism scores. We have previously demonstrated that neuroticism is associated with an increase in lifetime history of alcohol dependence in Mexican American young adults (Criado & Ehlers, 2007), and this relation has been repeatedly demonstrated in European American samples (e.g., Jackson & Sher, 2003; McCormick et al., 1998; Prescott et al., 1997). It has been suggested that neuroticism may influence risk for psychiatric disorders by increasing susceptibility to the adverse effects of stress (Kendler et al., 2004; Ormel et al., 2001). Building on this hypothesis, studies with Hispanics participants have shown a relationship between neuroticism and stressors associated with acculturation (Finch et al., 2000; Huebner et al., 2005; Mena et al., 1987; Miranda & Matheny, 2000). Neuroticism has also been associated with an increased susceptibility to stressors in US-born Mexican Americans (Finch et al., 2000; Mangold et al., 2007, 2012; Romero & Roberts, 2003), and Mangold et al. (2007) demonstrated that neuroticism may influence the consequences of cultural stressors on risks for mood and anxiety disorders. Consistent with these findings, we have previously shown that lifetime diagnoses of alcohol dependence, substance dependence, and anxiety disorders were associated with elevations in acculturation stress in Mexican American young adults (Ehlers et al., 2009). These data suggest interactions among neuroticism, AUDs and other psychiatric disorders in Mexican American men and women facing unique stressors associated with acculturation. The present study supports the potential influence of polymorphisms in *CHRNA5* and *CHRNA3* on the development of neuroticism, thus suggesting one potential mechanism involved in this acculturation process. Future studies are needed to assess the relationship between acculturation stress, neuroticism and *CHRNA5* and *CHRNA3* polymorphisms in this sample of Mexican American young adults.

In summary, these findings suggest that genetic variations in nicotinic receptor genes may influence the effects of the neuroticism personality trait on the development of AUDs and nicotine dependence in Mexican American young adults. However, whether neuroticism is a consequence rather than a causal or moderating factor involved in the risk of AUDs and other psychiatric disorders remains unknown. Moreover, the relationship between the SNPs in the *CHRNA5* and *CHRNA3* genes with personality traits such as neuroticism is not well understood. Future studies



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are needed to determine the interactions among *CHRNA5* and *CHRNA3* SNPs, neuroticism and neurophysiological endophenotypes associated with increased risk of AUD and nicotine dependence in Mexican American young adults (Ehlers & Phillips, 2007; Ehlers et al., 2011). It is important to consider some of the present study's limitations. First, the findings may not generalize to all Mexican Americans, or all Hispanic young adult Americans. Over half of the participants in the present study were women and thus the findings may not generalize to previous studies that have focused on samples of entirely male participants. Second, the study was limited to young adults between the ages of 18 and 30 years. Because the participants in the study had not passed through the age of risk, the association between the neuroticism personality traits and alcohol use disorders was limited. The limited number of subjects means that we could have missed some associations of smaller effect. Third, information regarding genetic ancestry was not included in the association analyses because genotyping an ancestry informative marker set was cost prohibitive. Attempts were made to collect such data via self-report, but was of limited utility given participants' inability to report estimates of European and Amerindian ancestry. As a result, population substructure cannot be ruled out as a confounding factor in these analyses. Despite these limitations, this report represents an important first step in an ongoing investigation to determine genetic risk and protective factors associated with the development of alcohol and substance use disorders in Mexican Americans.

## Acknowledgments

Funding for this study was provided by grants from the National Institutes of Health (NIH); from the National Institute on Alcoholism and Alcohol Abuse (NIAAA) and the National Center on Minority Health and Health Disparities (NCMHD) 5R37AA010201, (NIAAA) AA006420 (CLE), AA006460 (HJE) and AA007611 (HJE); and from the National Institute of Drug Abuse (NIDA) DA030976 (CLE & IRG). NIAAA, NCMHD, and NIDA had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The authors thank Derek Wills, Greta Berg, Evelyn Phillips, Philip Lau, Susan Lopez, Linda Corey, Dr Xiaoling Xuei, and Rachel Thowe for assistance in data collection and analyses, and Shirley Sanchez for assistance in editing the paper.

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https://doi.org/10.1017/thg.2014.11 Published online by Cambridge University Press