Functional Variants in *TAS2R38* and *TAS2R16* Influence Alcohol Consumption in High-Risk Families of African-American Origin

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Background: A novel family of G protein-coupled receptors, *TAS2Rs*, has recently been characterized and linked to sensitivity to bitter taste compounds. We have previously reported that a missense mutation in the *TAS2R16* gene reduces the sensitivity of the receptor to bitter-taste stimuli and that it is associated with risk for alcohol dependence. Other family-based studies on the genetic transmittance of taste perception have previously demonstrated a correlation between genetic variation in *TAS2R38* and sensitivity to bitter-taste compounds such as phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP). Haplotypes resulting from 3 common nonsynonymous coding single-nucleotide polymorphisms in the *TAS2R38* gene have been shown to alter receptor functions and taste sensitivity to PTC and PROP. The perceived bitterness of PROP has also been associated with oral sensation and drinking behaviors.

Methods: We used family-based association methods to test for association between *TAS2R38* haplotypes and alcohol dependence as well as a measure of alcohol consumption (Maxdrinks) and age of onset of drinking behaviors in a sample of families densely affected with alcoholism. We have also extended our analysis of *TAS2R16* to include the Maxdrinks phenotype.

Results: A positive correlation was observed between *TAS2R38* haplotypes and Maxdrinks in Collaborative Study on the Genetics of Alcoholism (COGA) high-risk women of African-American origin. The common taster haplotype is significantly associated with a lower mean Maxdrinks compared with the other haplotypes. Similarly, the allele of *TAS2R16* that is associated with a lower risk for alcohol dependence is also associated with lower mean Maxdrinks scores in African-American families. In contrast to the previously reported significant association between *TAS2R16* and alcohol dependence, we found no evidence that *TAS2R38* haplotypes influence alcohol dependence in the COGA dataset.

Conclusion: Functional variants in both *TAS2R16* and *TAS2R38* correlate with alcohol consumption in African-American families.

Key Words: *TAS2R38* Haplotype, Alcohol Dependence, Maxdrinks.

HUMANS AND OTHER mammals can detect 5 basic tastes: bitter, sweet, sour, salty, and umami (the taste of monosodium glutamate) (Lindemann, 2001). The sense of taste evokes responses ranging from aversion to the pleasure of food consumption. Bitter-taste perception enables humans and other mammals to avoid the ingestion of potentially harmful substances, a crucial response for survival (Drewnowski and Rock, 1995; Tepper, 1998). In 1931, Fox, reported that the ability to taste the bitterness of phenylthiocarbamide (PTC) varies greatly across individuals. A number of family studies on the genetic transmittance of taste perception have observed a correlation between genetic variation and sensitivity to bitter-taste compounds such as PTC and 6-*n*-propylthiouracil (PROP) (Drayna et al., 2003; Tepper, 1998; reviewed in Drayna, 2005). Evidence from epidemiological studies suggested gender differences in the genetically mediated taste responses to PTC/PROP; females are more responsive than males to the bitterness of PTC/PROP (Bartoshuk et al., 1994; Drewnowski et al., 2001; reviewed in Guo and Reed, 2001). The distributions of PTC/PROP tasters and nontasters also differ among ethnic groups; a higher

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proportion of tasters were observed in Africans and Asians compared with Caucasians (Bartoshuk et al., 1994; Guo et al., 1998; Parr, 1934). Bitter taste (along with sweet and umami taste) transduction is mediated by G protein-coupled receptor (GPCR) signaling pathways (Chaudhari and Roper, 1998; Lindemann, 2001; Scott, 2004; Wong et al., 1996). Recent studies have indicated that a novel family of taste GPCRs, *TAS2Rs*, map to human chromosomes 5p15, 7q31, and 12p13 and play an active role in the perception of bitter compounds (Adler et al., 2000; Bufe et al., 2002; Chandrashekar et al., 2000; Matsunami et al., 2000; Mueller et al., 2005).

The *TAS2R* genes contain an intron-less coding region and exhibit substantial coding sequence diversity, resulting in human populations that differ considerably in allele frequencies for *TAS2R* polymorphisms (Kim et al., 2005). This high level of allelic variation has resulted in many polymorphic amino acid substitutions in human *TAS2R*s (Kim et al., 2003, 2005; Ueda et al., 2001). Among these, we have previously shown that 1 coding single-nucleotide polymorphism (cSNP) in *TAS2R16* alters receptor sensitivity to a class of bitter compounds, known as β-glucopyranosides (Bufe et al., 2002; Hinrichs et al., 2006; Soranzo et al., 2005) and is associated with risk for alcohol dependence particularly in some populations (Hinrichs et al., 2006). Another *TAS2R* gene, the *TAS2R38* gene, has been associated with taster status for PTC and PROP (Duffy et al., 2004a; Kim et al., 2004). Three common nonsynonymous cSNPs in *TAS2R38* give rise to 5 haplotypes. Functional expression studies demonstrate that these 5 haplotypes code for operatively distinct receptors, providing a direct molecular link between heritable variation in bitter-taste perception and functional variation within this gene (Bufe et al., 2005). The common PAV variant is associated with the Taster phenotype because it is the most sensitive to PTC or PROP (Bufe et al., 2005). Another common variant AVI is associated with the Nontaster phenotype; it is not sensitive to PTC or PROP concentrations as high as 1 mM. Three less common variants, PVI, AAI, and AAV, convey intermediate PTC/PROP sensitivities. When stimulated with the same concentrations of PTC or PROP, they exhibit response levels only 40% of that observed with the PAV variant (Bufe et al., 2005).

Individual differences in bitterness sensitivity to PROP may predict alcohol intake. Studies have shown that individuals who taste less PROP bitterness perceive all alcoholic beverages as less bitter and drink more, suggesting that genotype at the *TAS2R38* locus may be a significant predictor of alcohol intake, although PROP bitterness explained more variance in alcohol intake than did the *TAS2R38* genotype (Duffy et al., 2004a; Lanier et al., 2005). A cluster of 9 bitter-taste receptor genes including the *TAS2R38* gene maps to the long arm of chromosome 7, a region in which we have previously observed linkage with both alcohol dependence and Maxdrinks (Hinrichs et al., 2006; Saccone et al., 2005). Given the relationship between taste perception and alcohol consumption and our previous findings of an association between *TAS2R16* and alcohol dependence, we have begun to extend our examination of the relationship between alcohol consumption and alcohol dependence to other bitter-taste receptors with functional changes in this cluster. Of the 8 remaining genes (*TAS2R3*, *TAS2R4*, *TAS2R5*, *TAS2R38*, *TAS2R39*, *TAS2R40*, *TAS2R41*, and *TAS2R60*), only *TAS2R38* is well characterized and has previously been examined in the context of alcohol consumption. For this reason, we focus our study on the examination of the 3 common cSNPs in the *TAS2R38* gene in 2,309 individuals from the Collaborative Study on the Genetics of Alcoholism (COGA) families and test whether variation in this gene alters susceptibility to alcohol dependence or influences alcohol intake in a high-risk population. We also examine whether alleles of *TAS2R16* are associated with alcohol consumption in the COGA families.

MATERIAL AND METHODS

Study Subjects

Alcohol-dependent probands, defined by meeting lifetime criteria for both DSM-IIIR alcohol dependence (American Psychiatric Association, 1987) and Feighner-criteria for definite alcoholism (Feighner et al., 1972), were systematically recruited from alcohol-treatment units. Families where 2 additional first-degree relatives also met lifetime criteria for alcohol dependence were invited to participate in the genetic protocol. A total of 262 families including 2,309 individuals with an average of 4.6 alcohol-dependent individuals per pedigree were selected for the genetic studies. Two hundred nineteen of the families were classified as of European ancestry and 35 families were of African-American ancestry. The remaining families were either of mixed ancestry or were derived from other ethnic and racial groups. Detailed protocols regarding the ascertainment of probands and relatives are described in previous reports (Nurnberger et al., 2004; Reich et al., 1998) and are available on the COGA website (http://zork.wustl.edu/niaaa/coga_instruments/resources.html).

All subjects were assessed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999), a semistructured interview designed as a polydiagnostic instrument that generates current and lifetime Feighner, DSM-IIIR, DSM-IV (American Psychiatric Association, 1994), and ICD-10 (World Health Organization, 1993) diagnoses of alcohol dependence. In addition to generating an alcohol dependence diagnosis, the SSAGA enables collection of information about several drinking behaviors including Maxdrinks, age at first intoxication, and age of onset of regular drinking. The measure Maxdrinks (Saccone et al., 2000) was recorded via the question, "What is the largest number of drinks you have ever had in a 24-hour period?" Twin studies have shown the heritability of Maxdrinks (Slutske et al., 1999) and our own work has demonstrated a correlation with alcohol dependence (Saccone et al., 2000). The SSAGA also asks individuals to report on the age at which they first began drinking regularly, as defined by drinking at least once a month for 6 months or more.

SNP Assays

Genotyping of the 4 cSNPs, Pro49Ala, Leu73Met, Ala262Val, and Val296Ile, in the *TAS2R38* gene reported in dbSNP (http://

www.ncbi.nlm.nih.gov/SNP/) was performed using Pyrosequencing (http://www.pyrosequencing.com) and Sequenom mass-array technology (http://www.sequenom.com/) as described in our previous paper (Hinrichs et al., 2006).

Association Analysis

The program PDTPHASE within the UNPHASED suite of programs (http://www.hgmp.mrc.ac.uk/~fdudbrid/software/unphased/) was used to test for evidence of association with the 2 SNP haplotype that defines Taster status for PTC and PROP. The pedigree disequilibrium test (PDT) is a family-based association test and thus avoids problems of false positives arising from population stratification (Martin et al., 2000). The PDT uses all available trios (2 parents plus child) in a family as well as discordant siblings. We classified as unaffected only individuals without a diagnosis of alcohol dependence (by any of the diagnostic systems used), DSM-III-R illicit drug dependence, or DSM-III-R antisocial personality disorder because evidence from several twin studies suggests that there are genes in common that underlie the risk for these correlated phenotypes (Kendler et al., 2003; Krueger et al., 2002; Young et al., 2000). In addition, a small number of individuals ($N = 73$) were removed from the unaffected group (and coded as unknown) because they endorsed more than 3 symptoms of alcohol dependence, but did not meet criteria for a diagnosis due to the criterion requiring a clustering of symptoms within a specified period of time. While 2 statistics SUM and AVE were used with PDT, we only list the results generated by the SUM statistic to simplify the tables. The 3 closely correlated alcohol-dependence phenotypes, DSM-IIIR and Feighner definite alcoholism, DSM-IV alcohol dependence, and ICD-10 alcohol dependence, were tested to examine the consistency of results.

For the quantitative traits age of initiation of regular drinking, age of first intoxication, and Maxdrinks, we used the program QPDT implemented in the program UNPHASED (http://www.hgmp.mrc.ac.uk/~fdudbrid/software/unphased/) to test for association with *TAS2R38* haplotypes. A log transform of the Maxdrinks raw data was used to correct for skewness of distribution and a linear regression was used to perform age and gender adjustments.

RESULTS

Four nonsynonymous cSNPs in *TAS2R38*, rs713598 (P49A), rs4613903 (L73M), rs1726866 (A262V), and rs10246939 (V296l) were genotyped in the entire COGA genetic sample. Single-nucleotide polymorphism rs4613903 is not polymorphic in our sample. Each of the 3 polymorphic SNPs was in Hardy–Weinberg equilibrium in the founders. While the allele frequency of the SNP rs10246939 is similar in our European American and African-American subsets, allele frequencies of SNPs rs713598 and rs1726866 differ significantly (Table 1a). Variation in the frequency of taster and nontaster haplotypes was observed in different ethnic groups. In the European American subset of families, 2 common haplotypes and 1 rare haplotype were detected using PDTPHASE. The taster haplotype PAV and the nontaster haplotype AVI represent 42 and 53% of all haplotypes, respectively. The intermediate-taster haplotype AAV accounted for just 4% of all haplotypes observed (Table 1b). In contrast, 3 major haplotypes were observed in our African-American subset of families. The taster-haplotype PAV represents 44% of haplotypes, the nontaster haplotype AVI represents 37% of haplotypes, and an intermediate taster haplotype (AAI) represents 16% of observed haplotypes (Table 1b). We also observed 1 rare taster haplotype, PAI, and 1 rare intermediate taster haplotype, AAV, in the African-American subset of families.

In vitro mutational analyses have demonstrated that amino acid positions 49 and 262 carry a greater impact on stimulus binding and cellular activation than does amino acid position 296 (Bufe et al., 2005); therefore, we used a haplotype derived from 2 cSNPs, P49A, and A262V, to test for an association between the *TAS2R38* variants (taster status) and alcohol dependence and related quantitative traits. No consistent association was observed between alcohol dependence and the *TAS2R38* variants. In European Americans, the 2 common haplotypes, PA_ (taster) and AV_ (nontaster), did not show any association with DSM-IV (Table 2) and ICD-10 alcohol dependence (data not shown). A marginal association was detected with DSM-IIIR and Feighner definite alcohol dependence ($p = 0.051$) in individuals with the rare intermediate-taste haplotype (AA_) (data not shown). The intermediate taster with the AA_ haplotype is more common among African Americans; however, no evidence of an association between *TAS2R38* haplotypes and alcohol dependence was observed in this subset of families.

We also used the QPDT to examine the association between *TAS2R38* variants and several quantitative measures of drinking behavior. The common taster haplotype, PA_, is associated with lower mean Maxdrinks scores in African-American families but not in European American

Table 1a. Allele Frequency of 3 Polymorphic cSNPs in *TAS2R38* in the COGA Genetic Sample

SNP	Amino acid	European American	African American
rs713598 (C/G)	P49A	0.42/0.58	0.55/0.45
rs1726866 (C/T)	A262V	0.47/0.53	0.72/0.28
rs10246939 (C/T)	V296I	0.48/0.52	0.48/0.52

cSNPs, coding single-nucleotide polymorphism; COGA, Collaborative Study on the Genetics of Alcoholism.

Table 1b. Distribution of 3-cSNPs Haplotypes in *TAS2R38* in the COGA Genetic Sample

Haplotype	Taste status[a]	European American	African American
PAV	Taster	0.42	0.44
PAI	Taster	—	0.01
AAV	Intermediate	0.04	0.01
AAI	Intermediate	—	0.16
AVI	Nontaster	0.53	0.37

[a]Phenotypic status of specific genotypes as determined in Kim et al. (2004) and Bufe et al. (2005).

cSNPs, coding single-nucleotide polymorphism; COGA, Collaborative Study on the Genetics of Alcoholism.

Table 2. *TAS2R38* Haplotypes and DSM-IV Alcohol Dependence

Haplotype	Sum Z	Sum p	Trio-T[a]	Trio-NT[a]	Affected sib-pair[a]	Unaffected sib-pair[a]	Frequency	Taste status[b]
*Families of European American origin (number of individuals = 1,965)**								
PA_	− 0.468	0.640	528.8	559.4	423.9	409.9	0.414	Taster
AA_	0.938	0.349	62.2	54.5	53.2	48.1	0.045	Intermediate
AV_	0.106	0.916	698.9	677.2	528.7	546.9	0.539	Nontaster
*Families of African American origin (number of individuals = 298)***								
PA_	− 1.396	0.163	80.7	89.9	84.7	90.0	0.455	Taster
AA_	− 0.087	0.931	33.9	36.7	23.9	22.0	0.175	Intermediate
AV_	1.628	0.104	69.1	55.7	61.1	58.0	0.369	Nontaster

*Global test: $\chi^2 = 0.74$, $p = 0.69$.
**Global test: $\chi^2 = 3.07$, $p = 0.22$.
[a]As haplotypes are not observed directly, these figures are based on the probabilities.
[b]Taste status is inferred based on the literature, rather than measured.

families (Table 3a). To test whether there is gender effect on the association, we stratified our African-American families by gender and found that the association between the *TAS2R38* haplotype and Maxdrinks only exists in women (Table 3b). The common taster haplotype, PA_, is under-transmitted to female alcoholic subjects and is significantly associated with a lower mean Maxdrinks. The intermediate-taster haplotype and nontaster haplotype are overtransmitted to female alcoholic subjects. The correlation between the *TAS2R38* gene and other measures of drinking behavior, such as age of first regular drinking and age at first intoxication were also tested but no evidence of association was observed in either European American or African-American families (data not shown). In our previous studies, we reported a functional SNP in the *TAS2R16* gene (rs846664), which is common in families of African-American origin, and is associated with increased risk for alcohol dependence (Hinrichs et al., 2006). The alcohol dependence risk allele of this SNP is also associated with higher mean Maxdrinks scores in African-American families (Table 4). No gender effect was observed for this correlation.

DISCUSSION

Bitter-taste sensitivity to PTC has long been recognized as an inherited trait in humans (Fox, 1932); however, the literature is inconsistent on the mode of inheritance. It is now generally believed that the genetics of PTC perception is not simply Mendelian in its transmission pattern, but involves multiple alleles, or multiple genes with incomplete dominance (reviewed in Kim and Drayna, 2005 and in Drayna, 2005). Several studies have reported a correlation between the perceived bitterness of PTC and PROP with alcohol intake, alcohol preference, nicotine abuse, and the susceptibility to diet-related disease (Duffy et al., 2004b; Enoch et al., 2001; Tepper, 1998). Molecular studies indicate that taste sensitivity is conferred by several nonsynonymous coding SNPs that form several haplotypes in most populations. Recently, functional expression studies have demonstrated that different haplotypes from the *TAS2R38* gene code for operatively distinct receptors (Bufe et al., 2005).

While genetic analyses support the association between variation in the *TAS2R38* gene and bitter-taste sensitivity to PTC or PROP (Drayna et al., 2003; Duffy et al., 2004a; Kim et al., 2003), the association between *TAS2R38* haplotypes and alcohol dependence remains unclear. Some earlier studies reported significantly higher numbers of nontasters among children of alcoholic individuals than among children of nonalcoholic individuals (Pelchat and Danowski, 1992) and subjects who had alcoholism in their family were more likely to be nontasters of PROP than the control group (DiCarlo and Powers, 1998). However, other studies observed no reliable association between taste sensitivity to PROP and either a diagnosis of alcohol dependence or a parental history of alcohol dependence (Kranzler et al., 1996, 1998). The present study sought to use family-based association methods to test for a direct correlation between *TAS2R38* haplotypes (rather than taste perception) and alcohol dependence as well as a measure of alcohol consumption (Maxdrinks) and age of onset of drinking behaviors. We found no evidence indicating that variation in *TAS2R38* is a risk factor for alcohol dependence or the alcohol consumption behaviors

Table 3a. Association Between *TAS2R38* Haplotypes and the Quantitative Trait, Maxdrinks

Haplotype	Sum Z	Sum p	Frequency	Taste status[a]
*European American families (number of individuals = 1,452)**				
PA_	− 0.782	0.434	0.411	Taster
AA_	− 0.045	0.964	0.045	Intermediate
AV_	0.796	0.426	0.543	Nontaster
*African American families (number of individuals = 219)***				
PA_	− 2.068	0.039	0.456	Taster
AA_	1.702	0.089	0.191	Intermediate
AV_	1.121	0.262	0.345	Nontaster

*Global Sum test: $\chi^2 = 0.83$, $p = 0.66$.
**Global Sum test: $\chi^2 = 5.62$, $p = 0.06$.
[a]Taste status is inferred based on the literature, rather than measured.

Table 3b. Gender Effect on the Association Between *TAS2R38* Haplotypes and the Quantitative Trait, Maxdrinks in Families of African-American Origin

	Female ($N = 105$)			Male ($N = 114$)			
Haplotype	*Z*	*p*	Frequency	*Z*	*p*	Frequency	Taste status[a]
African-American families (number of individuals = 219)							
PA_	− 2.108	0.035	0.43	− 0.303	0.762	0.48	Taster
AA_	1.974	0.048	0.20	0.507	0.612	0.18	Intermediate
AV_	1.187	0.235	0.37	− 0.015	0.988	0.33	Nontaster

Global Sum test: $\chi^2 = 6.5$, $p = 0.038$; Global Sum test: $\chi^2 = 0.23$, $p = 0.89$.
[a]Taste status is inferred based on the literature, rather than measured.

Maxdrinks in high-risk families of European American origin.

In women of African-American origin, we observed that the common taster haplotype PA_ is significantly associated with a lower mean Maxdrinks compared with the other haplotypes (Tables 3a, 3b). Similarly, the *TAS2R16* variant, which causes increased bitter-taste sensitivity, was previously reported to decrease risk for DSM-IV alcohol dependence (Hinrichs et al., 2006). The protective allele of *TAS2R16* is also associated with lower mean Maxdrinks scores in both men and women of African-American origin (Table 4). Thus, these 2 genes, which influence bitter-taste sensitivity, appear to have a similar effect: that increased bitter-taste sensitivity lowers maximum drinks consumed in a 24-hour period and the risk for alcohol dependence.

Our analyses indicate that there are differences in the frequency of functional SNPs within the bitter-taste receptors. These differences would be predicted to lead to population differences in human taste sensitivity. In *TAS2R16*, the risk allele for alcohol dependence is very rare in European Americans but is fairly common in African Americans (Hinrichs et. al, 2006). In this study, we observed a lower frequency of nontaster and a higher frequency of intermediate-taster haplotypes in African Americans compared with European Americans. Functional expression studies suggest that different haplotypes convey different PROP/PTC response magnitudes. Heterozygous individuals can express very different ratios of PAV and AVI alleles, with some heterozygotes having PAV-like taste sensitivities while others have AVI-like sensitivities (Bufe et al., 2005). This suggests that other factors, either in *cis* or in *trans*, are involved in PROP/PTC sensitivity among people with intermediate-taster genotypes for *TAS2R38*. The ethnic differences could result from selection pressure. A study of selective effects on the *TAS2R38* gene using analyses of molecular genetic data suggested that balancing natural selection has acted to maintain taster and nontaster alleles at the PTC locus in human populations (Wooding et al., 2004). The high frequency of PTC heterozygotes in African Americans could have resulted from a fitness advantage through the perception and avoidance of bitter toxins in African populations. The high frequency of PTC taster alleles in European Americans could result from positive selection with local adaptation. An investigation on the functional role for K172 of the *TAS2R16* gene as a malaria-resistance allele has demonstrated a clear signal of positive selection in the *TAS2R16* gene (Soranzo et al., 2005). The low-sensitivity ancestral K172 allele was retained at moderately high frequencies throughout central Africa, which appeared remarkably similar to those of some malaria-resistance alleles. A modest selective advantage in malaria-infected areas was postulated by chronic low-level ingestion of cyanogenic foods resulting in high frequencies of the nontaster allele of *TAS2R16* in central Africa. Given these results and that many cSNPs have been reported in the other *TAS2Rs* within the gene cluster on chromosome 7, a detailed analysis of the effect of these genes on alcohol consumption and alcohol dependence, particularly in populations of African origin, seems worthwhile.

In summary, taste perception is a complex trait influenced by numerous genes. Further, there are European American and African-American population differences in the frequency of these variants. We have observed modest findings with 2 genes, which contribute to bitter-taste sensitivity and influence alcohol consumption. As alcohol consumption is a necessary precursor leading to alcohol dependence, taste perception may represent one of the many pathways that contribute to the development of or protection against alcohol dependence.

Table 4. *TAS2R16* Is Associated with Maxdrinks in African Americans

Allele	*Z*	*p*	Gametes	Frequency
N	− 2.057	0.040	205.8	0.735
K	2.057	0.040	74.2	0.265

Global test: $\chi^2 = 4.23$, $p = 0.04$.

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