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Serotonin Transporter Promoter Polymorphism and Monoamine Oxidase Type A VNTR Allelic Variants Together Influence Alcohol Binge Drinking Risk in Young Women

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The short allelic variant of the serotonin transporter protein promoter polymorphism (5HTTLPR) appears to influence binge drinking in college students. Both monoamine oxidase type A (MAOA) and the serotonin transporter protein are involved in the processing of serotonin, and allelic variants are both associated with differences in the efficiency of expression. We hypothesized that a significant gene × gene interaction would further stratify the risk of binge drinking in this population. Participants were college students (n = 412) who completed the College Alcohol Study, used to measure binge drinking behaviors. Genomic DNA was extracted from saliva for PCR based genotyping. The risk function for binge drinking was modeled using logistic regression, with final model fit $P < 0.0005$. This model was valid only for Caucasian females (n = 223), but the power to detect sex and ethnic effects was small. Young Caucasian women carrying higher expression MAOA VNTR alleles homozygous for the short allelic variant of the 5HTTLPR demonstrated the highest rate of binge drinking by self-report, odds ratio (genotype odds: population odds) and 95% confidence intervals, 3.11 (1.14–18.10). Individuals carrying higher expression MAOA VNTR alleles carrying at least one long 5HTTLPR allelic variant had the lowest risk of binge drinking 0.46 (0.28–0.71). These results support the hypothesis that binge drinking behavior in young adulthood may be influenced by neurobiological differences in serotonergic function conferred by functional polymorphisms in genes involved in serotonin processing.

KEY WORDS: pharmacogenetics; polymorphism (genetics); alcohol drinking

INTRODUCTION

Differences in serotonergic neurotransmission conferred by functional polymorphisms in the promoter region of the serotonin transporter (5HTTLPR) influence the risk for binge drinking behavior [Herman et al., 2003]. Decreased subjective measures of alcohol intoxication were found in homozygotes for the short allelic variant (S) of the 5HTTLPR [Türker et al., 1998; Fromme et al., 2004]. Monoamine oxidase type A (MAOA;E.C. 1.4.3.4) is an X-linked gene product located in mitochondria that preferentially degrades serotonin and norepinephrine. A functional variation in the promoter region consisting of a variable number of 30 base pair repeats (VNTR) [Hinds et al., 1992] alters the transcriptional efficiency for the product; alleles having 2, 3, or 5 repeats being less efficiently transcribed than alleles with 3.5 or 4 repeats [Sabol et al., 1998; Deckert et al., 1999]. In mice lacking MAOA, brain serotonin levels increased nine-fold, indicating that the enzyme participates in the regulation of serotonergic function [Cases et al., 1995]. Taken together, these observations suggested that gene-gene interactions between the functional allelic variations of the 5HTTLPR and the MAOA VNTR together would modulate serotonergic function and therefore binge drinking behavior. We hypothesized that individuals carrying the more efficiently expressed variants of the MAOA VNTR and the less efficiently expressed variant of the 5HTTLPR would be at the highest risk for binge drinking.

METHODS

Research Participants

The study was approved by the respective Institutional Review Boards of George Washington University and the National Institutes on Alcohol Abuse and Alcoholism. All data were anonymously collected from participants (n = 397) enrolled in psychology courses at the university. A demographic description of the study population is shown in Table I. All participants provided written informed consent and completed the College Alcohol Survey (CAS) instrument allowing us to assess alcohol consumption [Wechsler et al., 2000]. A binge drinking episode was defined as five drinks consumed per occasion for a male and four drinks consumed per occasion for a female. This definition of an alcohol binge was empirically derived from observations that alcohol consumption at or above these levels per episode over the previous 2 weeks was strongly associated with increasing risks of alcohol-related problems [Wechsler et al., 1998]. The severity and frequency of alcohol-related problems was also positively correlated with the number of episodes over the 2-week period. The questionnaire therefore addresses binge drinking events that occurred in the 2 weeks prior to completing the survey [Wechsler et al., 2000].

Molecular Genetics

We genotyped for the 5HTTLPR as previously described [Herman et al., 2003]. The MAOA VNTR polymorphisms were determined via PCR-based genotyping. Primers were 5′ Texas

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TABLE I. Population Demographics

Ethnicity	Sex	N(binge)/ N(no binge)	Age (years ± SD)
Caucasian-American	Female	144/79	19.1 ± 2.0
	Male	48/34	19.2 ± 1.2
Asian-American	Female	3/8	19.5 ± 1.7
	Male	26/22	18.5 ± 0.7
African-American	Female	7/9	18.8 ± 1.3
	Male	11/21	18.9 ± 1.4

Red labeled for fluorescent detection (Sigma Genosys, The Woodlands, TX), sense 5′ → 3′ CAGAAACATGAGCACAAACGCCTCAGC; MAOAH.FOR; antisense 5′ → 3′ GACCGCCACTCAGAACGGACGC; MAOAH.REV. The PCR reactions were carried out in 50 μl buffer (GC-Rich Roche; Indianapolis, IN) containing genomic DNA (2.5–10 ng in 0.25 μl) 0.375 μM forward and reverse primers, 0.4 mM of DNTP, 3.0 mM $MgCl_2$, 0.4 mM Tris-HCl, pH 8.0, 2 mM KCl, and 1M GC-rich resolution solution with 2 U enzyme; 3 min at 95°C followed by 40 cycles (30 sec at 95°C; 20 sec at 64°C; and 25 sec at 72°C) in a Perkin-Elmer GeneAmp 9600 PCR cycler (Wellesley, MA). A volume of 1 μl of PCR product, 6 μl of water, and 7 μl DNA loading buffer (Invitrogen, Carlsbad, CA) were electrophoretically separated using a 12 well 6%–12% TBE nondenaturing polyacrylamide matrix (Invitrogen) at 200 V for approximately 60 min at room temperature. The fluorescent products were visualized with an FMBIO II fluorescent gel imager (Hitachi, Tokyo) using FMBIO II ReadImage 1.1 program. Parameters for reading the gel were set at 0.5 mm focusing point, 300 dpi resolution, 256× sampling rate and 80% sensitivity. The size of the amplicons were determined by comparing their migration distances to the migration distances of Texas Red fluorescent labeled molecular weight ladders (Bio-Rad, Hercules, CA), 100–1,000 bp in increments of 100 bp, run in the outer two lanes of the gel. The expected base pair product sizes for the MAOA VNTR polymorphisms were 245, 275, 287, 305, 335 for alleles with the following number of repeats: 2, 3, 3.5, 4, and 5 respectively.

Statistical Analysis

Logistic regressions were performed with JMP 5.0.1a (SAS, Cary, NC). The logistic regression was computed using a maximum likelihood procedure, where $P(y)$ is the probability of binge drinking in the past 2 weeks:

$$P(y) = \frac{1}{1 + e^{-x}} \text{ with } x = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4$$

We did not impose an a priori genotype effect structure on the model by assuming recessive or recessive-additive effects; we used an operator independent mixed stepwise procedure with $P < 0.10$ for inclusion, and $P > 0.05$ for exclusion to construct the final explanatory variable vector. Allelic variants were coded as follows: [0, 1, 2 = LL, LS, SS] for the 5HTTLPR and [0, 1, 2 = *HH*, *HL*, *LL*] for the MAOA VNTR. Male genotypes were coded as [0, 1 = *H*, *L*]. MAOA VNTR alleles of 3.5 and 4.0 repeats were coded as *H* and alleles with 2.0, 3.0, and 5.0 were coded as *L* [Sabol et al., 1998; Deckert et al., 1999]. The full initial model included racial group (Asian, African-American, and Caucasian), sex and age as explanatory variables, and the following interactive effects: MAOA × 5HTTLPR; Race × MAOA; Race × 5HTTLPR; Sex × MAOA. The final model retained only the 5HTTLPR and MAOA VNTR, and their interaction. The regression was valid only in Caucasian females (n = 223). We therefore present the results confined to this sub- group of individuals.

For Bayesian analysis of model performance, we determined the sensitivity and specificity using the self-report for binge drinking as the "gold standard" for presence or absence of binge drinking and the model prediction based on the genotypes of an individual. Output values obtained from the model were 0 if $P(\text{Binge}) < 0.50$ and 1 if $P(\text{Binge}) > 0.50$. Sensitivity and specificity were calculated as follows: Sensitivity = 107/144 = 0.74 and Specificity = 44/79 = 0.56. We determined predictive likelihood ratios as follows: positive likelihood ratio (PLR) PLR = Sensitivity/(1 − Specificity) and negative likelihood ratio (NLR) NLR = Specificity/(1 − Sensitivity).

Given a population prevalence of binge drinking expressed as a probability P, the prior odds of a randomly sampled individual having that phenotype is PriorOddsYes = $P/(1-P)$ and the prior odds of an individual not having the phenotype are PriorOddsYes = $(1-P)/P$. The posterior odds are calculated as follows: PosteriorOdds = PriorOdds × NLR or PLR depending on whether the model was used to predict the absence or presence of binge drinking. The posterior odds were transformed back into a posterior probability for absence or presence of binge drinking with P = PosteriorOdds/(PosteriorOdds + 1).

The 95% confidence intervals for odds ratios, Bayesian likelihood ratios, sensitivity, specificity, and proportions were computed using a bootstrap method [Efron and Tibshirani, 1993]. Parameters were obtained from 10,000 trials. The bootstrap routines were implemented via MatLab (The Math Works, Natick, MA) OS X, using a package of resampling routines obtained from Resampling Stats (Arlington, VA). The MatLab codes for these routines are available at [http://apgs.org/ajmg/].

RESULTS

The 5HTTLPR gene frequencies for the long (L) and short (S) variant alleles were in Hardy–Weinberg equilibrium ($\chi^2 = 5.034$, df = 2, $P = 0.081$). The population sample was not stratified by 5HTTLPR and MAOA VNTR in females ($\chi^2 = 2.77$, dF = 4, $P = 0.60$) as shown in Table II. There were differences in the proportion of binge drinkers between ethnic group, given as percentage and 95% confidence intervals for Caucasian-American, Asian-Americans, and African-Americans 63.3 (56.7–70.0); 49.2 (32.2–66.1); 37.5 (20.8–56.3) with African-Americans exhibiting a significantly lower proportion of binge drinking compared to Caucasian-Americans.

The P-values for inclusion of parameter estimates and P-values associated with model fit and the probability that the parameter $\neq 0$, are shown in parentheses except for the intercept, for which only the model fit P-value is included: β_0(intercept) = 0.5504 (0.0097); β_1 = 0.3552 or −0.3352 (0.0125; 0.0458) for 5HTTLPR if [LL/LS] or [SS] respectively; β_2 = −0.3041 or 0.3041 (0.0023; 0.1032) for MAOA if [*HH*] or [*HL*/*LL*]; β_3 = 0.3473 or −0.3473 (0.0029; 0.0375) for MAOA if

TABLE II. 5HTTLPR × MAOA VNTR—Caucasian Females

Genotypes	5HTTLPR			
MAOA	LL	LS	SS	Total
2.0, 4.0	1	0	0	1
3.0, 3.0	10	19	8	37
3.0, 4.0	36	43	28	107
3.0, 5.0	1	2	0	3
3.5, 3.5	0	2	0	2
4.0, 4.0	26	26	17	69
4.0, 5.0	1	0	3	4
Total	75	92	56	223

$\chi^2 = 2.77$, dF = 4, $P = 0.60$ (rows with frequencies = 0 not included).

TABLE III. Binge/No Binge Frequencies by Genotype

Genotypes	MAOA VNTR			
5HTTLPR	HH	HL	LL	Total
LL/LS	25/30	63/20	14/15	102/65
SS	17/3	20/8	5/3	42/14
Total	42/33	83/28	19/18	144/79
	N(binge)/N(no binge)			

[*HH*] or [*HL*]; $\beta_4 = -0.2977$, 0.8572, 0.2079, or -0.5984 for [*HH*, LL/LS], [*HH*, SS], [*HL*, LL/LS] or [*HL*, SS] (.0029; 0.0174), overall regression fit $P = 0.0005$. The number of individuals engaging in binge drinking behavior by genotypes is shown in Table III, and Table IV shows the results translated into the odds ratios for binge drinking, *P*(Binge)/*P*(No Binge):population odds.

A similar procedure was used to investigate the separate influences of the 5HTTLPR and MAOA genotypes on the risk of binge drinking. For the 5HTTLPR, model parameters and associated *P*-values are: β_0(intercept) = -0.7706 (0.0001), $\beta_1 = 0.3925$ or -0.3925 (0.0165, 0.0181) if [LL/LS] or [SS] with overall regression fit $P = 0.0142$. For the MAO VNTR polymorphism, model parameters and associated *P*-values are: β_0(intercept) = -0.3729 (0.0100); $\beta_1 = 0.1996$ or -0.1996 (0.0019, 0.1677) if [*HH*] or [*HL*/*LL*]; $\beta_2 = -0.5260$ or 0.5260 (0.0043, 0.0044) if [*HL*] or [*LL*], overall regression fit $P = 0.0015$.

DISCUSSION

Our results support the hypothesis that significant gene–gene interactions occur between the 5HTTLPR and the MAOA VNTR to influence the risk of binge drinking. The highest risk was found in homozygotes for the short variant allele of the 5HTTLPR (SS) in combination with the efficiently expressed forms of the MAOA VNTR (*HH*). The lowest risk was found in individuals carrying at least one long variant of the 5HTTLPR (L) in combination with MAOA VNTR alleles associated with higher expression of the enzyme, (*HH*), as shown in Table IV. As found in previous surveys of college alcohol binge drinking, we found that African-Americans tended to binge significantly less frequently than Caucasian-Americans, though we did not have the power to determine if this was the case for Asian-Americans [Wechsler et al., 1998].

While we had good reasons to believe from previous studies that the influence of the short variant allele of the 5HTTLPR might be expressed in a recessive or recessive-additive fashion on aspects of alcohol consumption patterns and intoxication [Türker et al., 1998; Matsushita et al., 2001; Herman et al., 2003] we did not constrain the statistical analyses to a priori recessive or recessive-additive models since we could not predict if the gene × gene interactions of interest would also follow a recessive pattern. Our results, within the constraints of power imposed by the sample size, strongly support that for the 5HTTLPR, the influence of the short variant allele on binge drinking in this female population of students is expressed recessively.

Previous work has shown that individuals carrying a short variant allele (S) associated with lower expression of the serotonin transporter protein compared to the long variant allele (L) experience less intoxication at similar blood alcohol concentrations [Türker et al., 1998; Fromme et al., 2004]. Greater tolerance to the sedative effects of alcohol is found among binge drinkers when compared to lighter-drinking individuals [Holdstock et al., 2000; King et al., 2002]. Alcohol exposure releases serotonin in the central nervous system at relatively low concentrations [Smith and Weiss, 1999], which is associated with downstream effects such as release of dopamine via activation of 5-HT3 receptors [Rodd-Henricks et al., 2003], contributing to some of the subjective effects of alcohol intake. Taken together with our results, we suggest that the combination of higher catabolism and lower reuptake of serotonin may result in decreased sensitivity to the intoxicating effects of alcohol intake by decreasing neuronal serotonin available for alcohol- mediated release, thereby influencing the risk for binge drinking.

We chose a very conservative bootstrap method to determine the confidence intervals for the odds ratios by allowing both the numerator and denominator of the odds within each cell to vary independently during the resampling procedure. By taking into account both the variance in the genotype distributions as well as the variance in the odds for binge drinking, we minimized the Type I error which would have resulted by fixing the number of individuals in a particular genotype group. This increases the chance that these results generalize to populations that may have different underlying rates of binge drinking. This approach also allowed us to validate the logistic risk model because the interaction effects between the 5HTTLPR and the MAOA VNTR alleles with higher expression efficiency were substantiated as outlined below.

The magnitude of the gene × gene interactions can be appreciated from Table IV. These odds ratios compare the risk conferred by genotype to the overall population risk. Individuals homozygous for the higher expression alleles of the MAOA VNTR (*HH*) express the largest difference in risk for binge drinking based on the presence of at least one L allele for the 5HTTLPR expressed as the odds ratio for binge drinking for [*HH*, SS]: [*HH*, LL/LS] = 6.8 (2.13–44.27). The magnitude of the differences in risk for binge drinking by genotype were much smaller when the 5HTTLPR or MAOA VNTR were considered separately, highlighting the importance of considering the effects of gene interactions which can be mechanistically predicted based on our knowledge of the role of the expressed products in modulating the function a particular neurotransmitter processing network, in this case, the serotonergic system.

Individuals with the *HL* MAOA VNTR genotype pattern, when considered alone, had a higher risk of binge drinking than homozygotes, suggesting a heterozygote overdominance

TABLE IV. Binge Drinking Odds Ratios: MAOA × 5-HTTLPR

Genotypes	MAOA VNTR			
5-HTTLPR	*HH*	*HL*	*LL*	
LL/LS	**0.46 (0.28–0.71)**	**1.73 (1.17–2.78)**	0.51 (0.24–1.04)	**0.86 (0.74–0.99)**
SS	**3.11 (1.14–18.10)**	1.37 (0.66–3.69)	0.91 (0.18–1.83)	**1.65 (1.10–3.04)**
	0.69 (0.48–1.01)	**1.63 (1.20–2.35)**	0.58 (0.31–1.05)	

Genotype:population odds.
OR (95% confidence interval).
Bolded values indicate 95% CI which do not straddle 1.

effect for a binge drinking trait, which may be in part unmasked by bidirectional epistatic effects related to the 5HTTLPR. We expected that females with an *HH* genotype, as a group, to have the highest risk for binge drinking. A strong effect in the predicted direction emerged when the 5HTTLPR was considered, where the combination of [*HH*, SS] resulted in the highest risk for binge drinking. There are many possible explanations for this result. The MAOA gene may not be subject to dosage compensation by inactivation. As many as 15%–20% of genes on the X-chromosome escape inactivation and are most frequently found on the short arm [Carrel and Willard, 1999] where MAOA is also found at location Xp11.4-11.3 (http://bioinfo.weizmann.ac.il/carddisp?MAOA/). Many loci containing functional promoter polymorphisms have been described where heterozygotes exhibited patterns of expression that were higher than corresponding homozygotes [Rockman and Wray, 2002]. There is also evidence that levels of expression of MAOA and the serotonin transporter protein influence each other in a bidirectional fashion [Murphy et al., 2003]. A precedent for these kinds of epistatic interactions in other models of gene expression associated with particular metabolic networks [Rockman and Wray, 2002] exists, and the regulation of gene products involved in the modulation of serotonergic function may represent an example of such a network. Our results add to the evidence that models relating complex behavioral traits simultaneously to different loci should ideally be constructed so as to allow inclusion of interactive effects between alleles at the various loci on dependent measures, rather than considering allelic doses at each particular locus as independent explanatory factors.

Bayesian analysis allowed us to evaluate the results of our risk model using likelihood ratios which are less biased by the prevalence of binge drinking in the population, as shown in Table V. Given a prevalence of binge drinking of 64%, an individual randomly sampled from this population had prior probabilities of $P = 0.64$ for binge drinking and $P = 0.36$ for not binge drinking. Therefore the prior odds for binge drinking or not binge drinking were 1.78 and 0.56, respectively, giving posterior odds of 2.99 and 1.19. For an individual deemed at risk, the posterior probability for binge drinking was $P = 0.75$. For those individuals not at risk, the posterior probability of binge drinking was $P = 0.46$, considerably lower than the population prevalence. The current model is more efficient in negative rather than positive predictions for binge drinking, suggesting that other environmental, genetic, or gene× environment factors may exert proportionately more influence in determining a positive binge outcome. We note that congruent results have been found when examining the association of the MAO VNTR with alcoholism [Parsian et al., 2003] indicating an association of the MAOA 4R repeat with a diagnosis of alcoholism, though the relationship of binge drinking in young adulthood to the development of alcoholism is not well described.

In summary, the results of this study suggest that the risk of engaging in binge drinking behavior in our sample population of young female college students is significantly influenced by differences in serotonergic function conferred by the combined influence of allelic variations at the MAOA VNTR and the 5HTTLPR. A larger study is in progress to partition the risk of binge drinking conferred by these allelic variants in the other racial groups and in males.

TABLE V. Bayesian Statistics

	Binge by self-report		
Binge predicted	Yes	No	Total
Yes	107	35	142
No	37	44	81
Total	144	79	223

Sensitivity = 0.74 (0.66–0.81) (95% CI).
Specificity = 0.56 (0.44–0.66).
Positive likelihood ratio 1.64 (1.29–2.18).
Negative likelihood ratio 2.12 (1.51–3.00).

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