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OPRM1 rs1799971 Genotype Predicts Drinking Behavior in Males, but Not Females

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Introduction

- The prevalence of alcohol disorders costs Americans $223.5 billion yearly due mostly from losses in workplace productivity, as well as health care and criminal justice expenses (CDC, 2016).
- Maximum number of drinks consumed in a 24 hour period is a valid indicator of dangerous drinking behavior and may reflect an increased tolerance for high levels of alcohol (Edenberg, 2016).
- Awareness of factors related to such heavy drinking is important for targeting interventions for dangerous alcohol use.
- Men drink significantly more than women, with about 4.5% of men and 2.5% of women meeting the diagnostic criteria for alcohol dependence in 2013 (Wilsnack, et al., 2000), (Esser et al., 2014).
- Alcoholism is highly heritable and the endogenous opioid system has been shown to play a vital role in alcohol and other drug dependencies (Miranda et al., 2010).
- The mu-opioid receptor gene (*OPRM1*) is involved in a variety of pathological conditions, such as alcohol use disorder (AUD). The polymorphism has been shown to modulate sensitivity to alcohol (Bart, et al., 2005), (Sauriyal et al., 2011), (Mauge and Blendy, 2010).
- Carriers of the G allele for rs1799971, a polymorphism of *OPRM1,* result in an amino acid change at position 40 of the mu opioid receptor, and express receptors with 3 times higher affinity to B-endorphins, and this has been associated with an increased risk for substance and alcohol dependence (Miranda et al., 2010), (Zhang, et al., 2005).
- There is more social pressure on females to abstain from alcohol use, so it is possible that this effect will be weaker for females due to the competing effect of social pressure (Nolen-Hoeksema, 2004).
- We hypothesize that individuals with at least one G allele will have a higher number of maximum drinks consumed within 24 hours than A homozygotes.
- We expect this effect to be stronger in males than in females.
- We also expect that males will drink more than females.

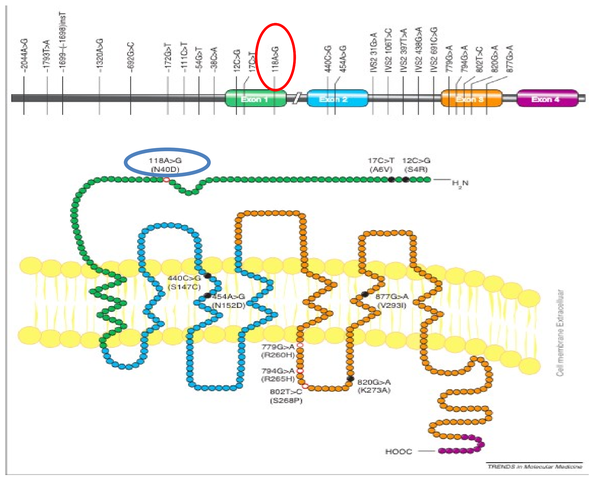

Figure 1. Mutations in the Mu-opioid receptor are related to changes at position 40 of the receptor, and express receptors with higher affinity to endorphins. Circled in red is the location of the polymorphism. Circled in blue is the location of the amino acid change. The SNP being tested produces the changes in the gene and the amino acid sequence in the gene receptor (Lotsch & Geisslinger, 2005), Zhang, et al., 2005).

Methods

Sample. Undergraduates (N=825) were recruited from the psychology department's subject pool at a Midwestern university (70.5% female; 87.4% White; mean age=20.4 [SD=3.15]) and received course credit for one hour of participation, which involved completing self-report questionnaires and donating a buccal cell sample for genotyping. The University's IRB approved the study and all participants gave written informed consent.
Measures. Recommended NIAAA Alcohol Quantity and Frequency Questions concerning the frequency, quantity, maximum number of drinks, and binge drinking were assessed as endorsement of risky drinking behavior, which are correlated with alcohol use disorders (NIAAA), such as "During your lifetime, what is the largest number of drinks containing alcohol that you drank within a 24-hour period?"

Genotyping. DNA was extracted from buccal cells using the Gentra PURGENE Cell Kit (Qiagen, Valencia, CA) following with manufacturer's protocol. The SNP rs1799971 was genotyped using Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA) following manufacturer's protocol in a 5µL volume. Allele frequencies were consistent with a Caucasian population (Sherry et al., 2010) and were in Hardy-Weinberg equilibrium (χ^2=1.43, p>.05) with observed allele frequencies of A=0.86 and G=0.14.
Data Analysis. An ANOVA was performed using SPSS version 22 (IBM, Armonk, NY) using sex and genotype as independent factors, and maximum number of drinks within a 24 hour period consumed as the dependent variable.

Results

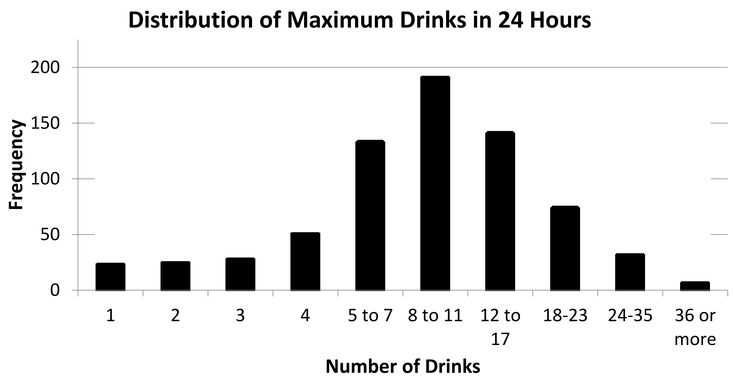

Figure 2. distribution of self-reported maximum drinks within 24 hours (M=5.82 SD= 1.86 N=715). (N= 712 due to incomplete responses from participants).

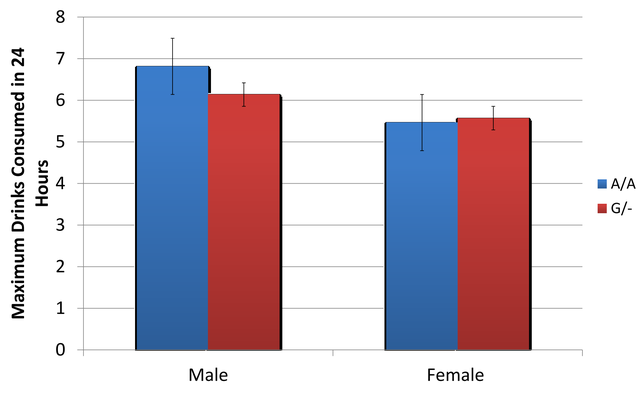

Figure 3. Mean Alcohol Maximum Drink Scores of groups within different rs1799971 genotypes and gender. (Male N=202;Female N=510)

Table 1. Between subjects effects of gender, genotype, and max drinks question.

Source	df	Mean Square	F	Sig.
Sex	1	99.925	31.538	.000
Genotype	1	8.818	2.783	.096
Sex*Genotype	1	16.767	5.292	.022

Conclusions

- In support of our hypothesis, males had a larger number of maximum drinks consumed than females, and the effect of genotype was stronger for males than for females; this is consistent with a large body of research suggesting that men consume more alcohol than females (Esser et al., 2014)
- A homozygous males reported having a higher number of maximum drinks consumed in a 24 hour period when compared to G allele carriers; there is no significant effect for females.
- While the genetic effect we found was opposite of that which we predicted, there is evidence in the literature that supports this finding. In a study that focused on the same parameter of maximum drinks consumed in a 24 hour period, A homozygous males reported significantly higher maximum drinks than those with at least one G allele (Du & Wan, 2009).
- This study differed from some studies that identified the G allele as the risk allele because we did not use a population diagnosed with alcoholism. In studies that focus on populations of alcoholics, G is often identified as the risk allele (Hendershot, Claus & Ramchandani, 2014).
- While there is a large body of evidence suggesting that the G allele is associated with alcoholism, the measure of maximum number of drinks in 24 hours is not necessarily connected to alcoholism, and people who are prone to alcoholism due to their rs1799971 genotype may drink less on a night of a heavy drinking, possibly due to increased sensitivity to alcohol (Mauge and Blendy, 2010)
- Because the sample was a primarily white population (87.4%), risk of differences in allele frequencies between subpopulations may have been reduced. However, the results may not be generalizable for other ethnicities, if differences in drinking behaviors exist.
- The large sample size (N=825) is a strength of this study because it increases accuracy of the results.
- It is important to understand the process by which this genotype influences alcohol use, since both genotypes seem to confer different forms of risky drinking behavior.
- Further research should investigate whether this effect is mediated by alcohol sensitivity.

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Acknowledgements

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