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Testing multiple levels of influence in the intergenerational transmission of alcohol disorders from a developmental perspective: The example of alcohol use promoting peers and μ-opioid receptor M1 variation

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Abstract

This study examined the interplay between the influence of peers who promote alcohol use and μ-opioid receptor M1 (*OPRM1*) genetic variation in the intergenerational transmission of alcohol use disorder (AUD) symptoms while separating the "traitlike" components of AUD symptoms from their age-specific manifestations at three ages from emerging adulthood (17–23 years) to adulthood (29–40 years). The results for males were consistent with genetically influenced peer selection mechanisms as mediators of parent alcoholism effects. Male children of alcoholics were less likely to be carriers of the G allele in single nucleotide polymorphism A118G (*rs1799971*), and those who were homozygous for the A allele were more likely to affiliate with alcohol use promoting peers who increased the risk for AUD symptoms at all ages. There was evidence for women of an interaction between *OPRM1* variation and peer affiliations but only at the earliest age band. Peer influences had stronger effects among women who were G-carriers. These results illustrate the complex ways in which the interplay between influences at multiple levels of analysis can underlie the intergenerational transmission of alcohol disorders as well as the importance of considering age and gender differences in these pathways.

Alcohol use disorders (AUDs) show considerable intergenerational transmission (Beirut et al., 1998; Merikangas et al., 1998), which is thought to reflect the operation of multiple underlying mechanisms in gene–environment interplay. For example, Sher (1991) identified three mechanisms, each of which reflects factors that operate on multiple levels of influence and each of which is biopsychosocial in nature. The *enhanced reinforcement* pathway posits that heritable individual differences in alcohol use effects in combination with socially transmitted information about alcohol effects lead children of alcoholics (COAs) to expect and to experience either greater positive reinforcement from alcohol use (e.g., Soderpalm & Soderpalm, 2011) or less negative effects of alcohol use (Schuckit & Smith, 1997; for a review on subjective responses to alcohol, see Morean & Corbin, 2010). The *stress and negative affect* pathway suggests that a combination of heritable temperamental characteristics and poor parenting causes COAs to have poor emotion regulation and coping (Zucker, Donovan, Masten, Mattson, & Moss, 2008), and it hypothesizes that COAs are likely to be exposed to higher levels of early adversity and ongoing environmental stress (e.g., King, Molina, & Chassin, 2008). This combination of poor emotion regulation, coping skills, and high levels of stress, along with the possibility that COAs experience elevations in the stress response dampening effects of alcohol (Sher & Levenson, 1982; Zimmerman et al., 2009), in turn makes it more likely that COAs will turn to alcohol use as a way to cope with environmental stress. Finally, the *deviance proneness* pathway suggests that a combination of heritable individual differences in temperamental behavioral undercontrol and poor parenting may lead COAs to be impulsive, sensation seeking, and "deviance prone" (Iacono, Malone, & McGue, 2003; King & Chassin, 2004; King et al., 2009; Ohannessian & Hesselbrock, 2008; Sher, Wallitzer, Wood, & Brent, 1991; Zucker et al., 2008). This "deviance proneness mechanism" suggests that the intergenerational transmission of substance use disorders is part of a broader intergenerational transmission of externalizing problems (Iacono, Malone, & McGue, 2008; Krueger et al., 2002).

Most relevant for the current study, within the deviance proneness pathway, individuals who are impulsive and sensation seeking may be motivated not only to engage in alcohol use but also to seek out affiliations with alcohol using peers

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who provide opportunities, models, and encouragement for drinking behavior. Thus, although peer influences on substance use are often studied as competitors to parental influences (e.g., Duncan, Duncan, & Hops, 1994; Reifman, Barnes, Dinrcheff, Farrell, & Uhteg, 1998), the deviance proneness mechanism suggests that affiliation with a peer group who promotes alcohol use is actually a proximal mediator in the intergenerational transmission of alcohol disorders. Accordingly, the current study examines the role of peer influences and their interplay with genetic risk in the intergenerational transmission of alcohol problems.

There is a strong and robust correlation between membership in a substance use promoting peer social network and substance use (Kandel, 1985; Rosenquist, Murabito, Fowler, & Christakis, 2010). In adolescence, when substance use initiation typically occurs, peer influences have been considered to be particularly important because, for adolescents, the presence of peers is particularly rewarding. Chein, Albert, O'Brien, Uckert, and Steinberg (2010) found that situations in which peers were present activated adolescent brain regions that are associated with reward. Middle adolescence has been thought to be particularly important for peer influences, with increasing ability to resist peer influence observed after adolescence (Gardner & Steinberg, 2005; Monahan, Steinberg, & Cauffman, 2009; Steinberg & Monahan, 2007; Sumter, Bokhorst, Steinberg, & Westenberg, 2009). However, whether the magnitude of peer influence declines after middle adolescence, social network analyses in adulthood have also shown significant relations between alcohol use and membership in an alcohol-using social network (Bullers, Cooper, & Russell, 2001; Rosenquist et al., 2010).

Given previously reported age differences in the magnitude of peer influence effects, it is important to examine these effects within a developmental perspective. Moreover, the effects of peer influences on alcohol problems are likely to be time specific rather than having persistent, long-term effects. For example, over time, individuals may change peer groups and thus their drinking problems should be more influenced by their current peer affiliations than long-past peer affiliations.

In order to test these time-specific effects at different ages, the current study examines the effects of alcohol use promoting peers on alcohol problems at three age periods from emerging adulthood to adulthood. These ages capture periods of considerable change in drinking behaviors, from escalation and peaks in emerging adulthood to later declines in adulthood (Chen & Kandel, 1995; Harford, Grant, Yi, & Chen, 2005; Johnston, O'Malley, Bachman, & Schulenberg, 2007). These age-related changes in drinking may be accompanied by changes in the magnitude of peer influences. For example, peer influences may be stronger in emerging adulthood because the developmentally limited drinking that occurs during this age period may be particularly peer driven. We use a state–trait model to separate stable "traitlike" aspects of alcohol problems from their age-specific manifestations at the three age periods and then examine peer influences on each of the age "states."

The magnitude of peer influence may also vary as a function of gender, although the data are somewhat conflicting. For example, Sumter et al. (2009) found that girls were more resistant to peer influence than boys, although this difference was largest during middle adolescence. In contrast, Dick et al. (2007) found that friends' substance use was more strongly related to adolescent drinking for girls than for boys, and friends' drinking showed genetic influences for girls but not for boys (see also Loehlin, 2010). However, Flannery, Vazsonyi, Torquati, and Fridich (1994) found that peer drinking and susceptibility to peer influences were the strongest predictors of early adolescent substance use for both boys and girls. Given these conflicting findings, we tested whether the peer effects varied for men and women.

Although there are robust correlations between one's own drinking and peer drinking in both adolescence and adulthood, these correlations are likely the result of two different processes: peer selection and peer influence (as well as the results of shared social environments such as neighborhoods or workplaces). That is, individuals who use alcohol are likely to select similar alcohol-using friends (i.e., peer selection) and individuals whose friends either use alcohol or approve of alcohol use are likely to increase their alcohol use (i.e., peer influence). Numerous studies have tested whether peer selection or peer influence better explains the resemblance between an individual's substance use and that of his/her friends (Bauman & Ennett, 1996; Dishion & Owen, 2002; Kandel, 1985; Simons-Morton & Farhat, 2010). Longitudinal studies have reported both significant peer selection and peer influence effects (Bullers et al., 2001; Dishion & Owen, 2002; Poulin, Denault, & Pedersen, 2011; Rosenquist et al., 2010), even after including covariates such as rebelliousness (Curran, Stice, & Chassin, 1997).

Nevertheless, peer selection effects are often stronger than peer influence effects (Bullers et al., 2001; Parra, Krull, Sher, & Jackson, 2007; Simons-Morton & Farhat, 2010). This has led researchers to speculate about the possibility of an active gene–environment correlation, such that genetic influences lead to the selection of similar peers (Loehlin, 2010). Behavior genetic findings suggest that there are significant genetic influences on affiliations with deviant or substance-using peers (Cleveland, Wiebe, & Rowe, 2005; Fowler et al., 2007; Hill, Emery, Harden, Mendle, & Turkheimer, 2008) and that the magnitude of genetic influence on the association with deviant peers increases with age (Kendler, Jacobson, et al., 2007). Increasing genetic influences with age may reflect greater control over social environments as people age (i.e., greater "niche picking").

Most of these studies have used behavioral genetic methods to examine whether peer influences are genetically influenced and whether their effects on substance use outcomes are potentially spurious, because of a similar underlying genetic diathesis for both substance use and affiliation with deviant peers. However, if there are genetic influences on peer selection, this does not necessarily mean that peer influences are spurious. Rather, peer influences may act as

mediators of genetic effects on substance use. That is, individuals of particular genotypes may select alcohol-using friends, and those friends in turn may influence them to drink (Reiss, 2010). We test this possibility in the current study. Moreover, peer selection effects have recently been tested with measured genes. For example, Fowler, Settle, and Christakis (2011) found that networks of peers were more likely to share the same dopamine receptor D2 genotype. Although this may reflect dispositional factors (e.g. personality) that lead to peer homophily, it is some of the earliest evidence for a biological substrate for peer selection. For reasons discussed below, the current study tested the influence of the variation in the functional A118G (*rs1799971*) single nucleotide polymorphism (SNP) of the μ-opioid receptor M1 (*OPRM1*) gene as an influence on affiliation with alcohol use promoting peers.

In addition to mediating the effects of genetic risk, it is possible that peer influences moderate the effects of genetic risk. Guo, Elder, Cai, and Hamilton (2009) found that the effects of genetic risk on adolescent drinking were larger for those with heavier drinking peers. Similarly, Agrawal et al. (2010) found heritable effects on peer substance use among a sample of young women, but they also found that regular substance use was more heritable for women who reported more peer substance use. Peer environments that support alcohol use may act to expose genetic vulnerability and thus show larger genetic effects on drinking, whereas peer environments that constrain drinking may suppress the effects of genetic risk. Moreover, this pattern of gene–environment interaction may also vary with age. Kendler (2011) found that the interaction between peer group deviance and genetic risk on drinking was strong in early adolescence, weaker in middle adolescence, and no longer significant in early adulthood. Few studies of gene–peer environment interaction have been conducted with measured genes, but van der Zwaluw, Larsen, and Engels (2011) did not find significant interactions with best friends' drinking and dopamine receptor D4 in predicting adolescent drinking. In contrast, Johnson et al. (2010) found a significant interaction between peer smoking and the neuronal acetylcholine receptor subunit α-5 gene in predicting nicotine dependence. The current study tested the interactions between peer influence and the functional A118G (*rs1799971*) SNP of the *OPRM1* gene, a gene likely to be important in drug reinforcement.

OPRM1

The μ-opioid receptor, which is encoded by the *OPRM1* gene, plays an important role in substance dependence (Dackis & O'Brien, 2005), serving as a primary site of action for many of the most frequently abused opioids, such as morphine, heroin, fentanyl, and methadone (Basbaum & Fields, 1984; Zadina, Hackler, Ge, & Kastin, 1997). Moreover, some of the rewarding effects of alcohol are caused by their interaction with the μ-opioid receptor (Herz, 1997; Kreek, 1996). Given its potential role in alcohol and drug disorders, the *OPRM1* gene has been the focus of many genetic studies of substance use problems.

One of the most commonly studied SNPs on the *OPRM1* gene is the A118G (*rs1799971*) SNP. The G allele of *rs1799971* causes a substitution of asparagine for aspartate at amino acid position 40 in the receptor protein (Kreek et al., 2005; Miranda, Nielsen, Butelman, & LaForge, 2010). Although several reports indicate that this variant is functional, there is less agreement regarding how this variant alters functionality. For example, it has been suggested that the G allele variant affects receptor activity, resulting in a significantly higher affinity for endogenous ligand β-endorphin (Bond et al., 1998), although others failed to corroborate this finding (Befort et al., 2001; Beyer, Koch, Schröder, Schulz, & Höllt, 2004). Conversely, another study linked the G allele to lower mRNA and OPRM1 protein levels, indicating that this variant may result in a loss of μ-opioid receptor function (Zhang, Wang, Johnson, Papp, & Sadée, 2005).

Studies relating the A118G SNP to alcohol dependence have produced mixed findings, including a positive association between the G allele and alcohol dependence in Korean, Japanese, and primarily European American samples (Bart et al., 2005; Kim, Kim, Kang, et al., 2004; Miranda et al., 2010; Nishizawa et al., 2006). Some have found no association with alcohol dependence (Bergen et al., 1997; Gscheidel et al., 2000; Kim, Kim, Song, et al., 2004; Loh, Fann, Chang, Chang, & Cheng, 2004; Sander et al., 1998), and still others reported that the G allele had a protective effect against alcohol dependence in Mexican Americans and in a primarily Caucasian sample (Du & Wan, 2009; Town et al., 1999).

There is more consistent support for an association between the A118G SNP and intermediate phenotypes for alcoholism. For example, in a sample of moderate and heavy drinkers with no history of alcohol problems or attempts to quit, those carrying at least one copy of the G allele reported higher subjective feelings of intoxication, stimulation, sedation, and happiness than those who were homozygous for the A allele across increasing levels of breath alcohol concentration (Ray & Hutchison, 2004). Similarly, in a sample of heavy drinkers, those with the G allele reported greater feelings of vigor and less negative mood compared to A homozygotes during drinking episodes in the natural environment (Ray et al., 2010). In a sample of male heavy drinkers, those with the G118 allele reported more craving for alcohol in a cue-reactivity task (van den Wildenberg et al., 2007) and demonstrated relatively strong automatic approach biases for alcohol and other appetitive stimuli, but not for general negative or positive stimuli (Wiers, Rinck, Dietus, & van den Wildenberg, 2009). Finally, those carrying the G allele reported drinking to enhance positive affect more than those homozygous for the A allele, and the association between the *OPRM1* genotype and alcohol-related problems was mediated by drinking to enhance positive affect (Miranda et al., 2010). These studies suggest that those with the G allele may be more sensitive to the reinforcing effects of alcohol, which in turn influences their vulnerability to develop alcohol use

problems. It is of clinical importance that naltrexone, an opiate receptor antagonist and FDA-approved treatment for alcohol dependence, appears to be differentially effective as a function of variability in the *OPRM1* gene (Kranzler & Edenberg, 2010).

Of relevance to peer influences, recent work has revealed that μ-opioid receptor mediated signaling and the *OPRM1* A118G SNP may affect social functioning and behavior in humans and nonhuman animals. For example, μ-opioid receptor knockout mice pups have reduced distress during mother–infant separation (Moles, Kieffer, & D'Amato, 2004) and the functional μ-opioid receptor gene polymorphism in rhesus macaques (*OPRM* C77G) was associated with higher levels of infant and maternal attachment behaviors (Barr et al., 2008; Higham et al., 2011). In humans, the G allele of the A118G SNP has been associated with dispositional and neural sensitivity to social rejection (Way, Taylor, & Eisenberger, 2009); lower scores on a self-report of avoidant attachment and social anhedonia (Troisi et al., 2011); and children's greater enjoyment of parent–child interactions for children whose parents had a history of problems, such as mental health problems, substance use, or criminality (Copeland et al., 2011). To the extent that carriers of the G allele show greater sensitivity to social rejection and greater enjoyment of social interactions, they may also be more influenced by alcohol-using peers. Thus, the current study tested the role of the A118G SNP in predicting affiliation with alcohol-using peers and in interaction with peer affiliations to predict alcohol problems.

In summary, the current study tested the interplay between genetic risk and peer influence in the intergenerational transmission of alcohol problems. Specifically, we asked whether genetic risk mediated parent alcoholism effects on traitlike alcohol problems in offspring and whether it predicted the selection of alcohol use promoting peers. We also tested whether the relation between peer influence and alcohol problems varied as a function of genetic risk. We used a state–trait framework to test these questions in a developmental framework, asking if the effects varied across three age periods from emerging adulthood to adulthood. Finally, we tested whether these effects varied for men and women.

Method

Participants

Participants were from a larger ongoing longitudinal study of familial alcoholism (Chassin, Flora, & King, 2004; Chassin, Rogosch, & Barrera, 1991). At Wave 1, the total sample ($N = 454$; $M_{age} = 12.7$, $SD_{age} = 1.45$) consisted of 246 COAs and 208 demographically matched non-COAs. Data were collected annually for Waves 1 through 3, and then at 5-year intervals for Waves 4 through 6. Full-biological siblings were added at Waves 4 ($n = 327$), 5 ($n = 389$), and 6 ($n = 410$). Sample retention was excellent with 90% of original participants retained at Wave 4 ($N = 407$), 91% of original participants and previously recruited siblings retained at Wave 5 ($N = 708$), and 89% ($N = 773$) at Wave 6. Retention was unbiased by gender or ethnicity and slightly poorer for COAs than for non-COAs at Waves 4 and 5, but not 6.

Of all those who were interviewed at Waves 4, 5, or 6 ($N = 914$), participants were excluded if they had not yet provided or refused to provide genomic data ($N = 454$), were outside of the study's age range ($n = 64$; see below), were lifetime alcohol abstainers throughout the study ($n = 29$), or if they reported an ethnicity that was anything other than non-Hispanic Caucasian ($n = 129$), thus leaving a final sample of $N = 238$. The large amount of missing genomic data is because this data collection is still in progress. The reason for the exclusion of lifetime abstainers is because some exposure to alcohol is required to unmask genetic risk and to have a possibility of developing alcohol-related symptoms. In addition, a genetic effect for alcohol dependence among drinkers has been well established in twin studies, whereas a genetic effect on lifetime abstention has not (Heath, Meyer, Hardine, & Martin, 1991). We focused on a racially homogeneous sample to minimize problems of population stratification. Compared to excluded participants, the final sample ($N = 238$) was unbiased by gender, parental alcoholism, and alcohol symptoms at Waves 4, 5, and 6, although the final sample reported a slightly higher mean affiliation with alcohol use promoting peers at Waves 5 and 6 but not 4. The final sample's mean age was 21.0 ($SD = 2.4$) at Wave 4, 26.3 ($SD = 2.6$) at Wave 5, and 32.6 ($SD = 2.8$) at Wave 6. By design, the study was composed of roughly equal numbers of COAs and non-COAs; in the current sample 52.5% were COAs, 52.1% were male, and 38.2% had completed at least an associate's degree by Wave 6.

For analyses the participants were classified into three age bands based on previous research on alcohol involvement (Chen & Kandel, 1995; Harford et al., 2005; Johnston et al., 2007). Age band 1 (ages 17 to less than 23) reflected emerging adulthood, a period in which alcohol involvement tends to escalate and peak. Age band 2 (ages 23 to <29) reflected young adulthood, a period associated with "maturing out" when alcohol involvement tends to decline. Finally, age band 3 (ages 29 to 40) reflected adulthood, a period where alcohol involvement tends to either decline further or stabilize.[1] Through the use of missing data techniques, the analyses included all participants ($N = 238$).[2]

However, because there was a large amount of missing genomic data, in order to confirm the findings of our final model, we also estimated the same model with the larger

1. A variety of other ages were evaluated as alternative cutoffs for our age bands. However, when compared to our original cutoffs, these modifications had little effect on changes in rates of various drinking behaviors across the age bands.
2. Of the current sample ($N = 238$), 73.5% had data for age band 1 ($n = 175$), 91.6% had data for age band 2 ($n = 218$), and 92.9% had data for age band 3 ($n = 221$). In addition, 61.3% had complete data across the age bands ($n = 146$), 35.3% had data for two age bands ($n = 84$), and 3.4% had data for one age band ($n = 8$).

sample of non-Hispanic Caucasians (again eliminating abstainers and those outside of the age range) but using missing data techniques and including those who were missing genetic data ($N = 529$).

Original sample recruitment

COA families were recruited using court records of DUI arrests, health-maintenance organization wellness questionnaires, and community telephone screenings (for details, see Chassin et al., 1992). Computerized structured interviews were used to confirm parental lifetime alcohol abuse or dependence. Reverse directories were used to locate potential non-COA families in the same neighborhoods as COA families; and telephone screening was used to match non-COA families to COA families on ethnicity, family structure, adolescent's age, and socioeconomic status. For non-COA families, computerized structured interviews were used to confirm that neither parent met lifetime criteria for alcohol abuse or dependence (see the Measures Section).[3]

Details concerning sample representativeness are reported elsewhere (Chassin et al., 1992). Recruited and nonrecruited participants did not differ on alcoholism indicators from archival records. Further, the alcoholic parents had rates of other psychopathology similar to those of a community-dwelling alcoholic sample (Helzer & Pryzbeck, 1988). However, recruited participants were less likely than nonrecruited potential participants to be Hispanic and to be married (Chassin et al., 1992).

Procedure

At each wave, data were collected via in-person computer-assisted interviews. Family members were typically interviewed simultaneously and in separate rooms to avoid contamination and to increase privacy. Telephone interviews were used for participants who relocated out of state. Confidentiality was reinforced with a Department of Health and Human Services Certificate of Confidentiality. Interviews typically lasted 1–3 hr, and participants were paid up to $70 for each interview.

Measures

AUD symptoms. Using items from Waves 4, 5, and 6 that assessed past-year alcohol-related consequences and dependence symptoms, we were able to assess 9 of the 11 alcohol disorder symptoms that have been proposed for *DSM-V* (American Psychiatric Association, 2010). These were the following:

1. failures in major role obligations;
2. use in physically hazardous situations;
3. social or interpersonal problems;
4. tolerance;
5. withdrawal;
6. use in larger amounts or over longer periods of time than intended;
7. persistent desire or unsuccessful efforts to control use;
8. much time spent obtaining, using, or recovering from use; and
9. craving.

However, Symptoms 5, 7, 8, and 9 were dropped from all analyses because of extremely low endorsement within specific subgroups of interest (e.g., among females). See Table 1 for symptom endorsement rates and mean symptom counts for the overall sample and subgroups of interest.

In assessing the measurement structure of the five dichotomous AUD symptoms, we found that single-factor confirmatory factor analysis (CFA) models showed excellent fit to the data at each of the three age bands (e.g., all comparative fit indexes [CFIs] ≥ 0.99, all standardized factor loadings ≥ 0.71). Given this evidence for unidimensionality, we then estimated a state–trait model to represent a general latent trait factor indicated by all symptoms across age bands and three residual latent state factors, each indicated by all symptoms within a given age band. In this model, we constrained residual state factors to be uncorrelated with the trait factor and with each other, and we constrained indicator factor loadings, thresholds, and error variances to be equal over time (i.e., strict measurement invariance). This model showed excellent fit to the data, $\Delta\chi^2\ (103) = 114.16$, $p = .21$; CFI = 0.99, root mean square error of approximation (RMSEA) = 0.02, and did not fit the data significantly worse than a fully unconstrained model, $\Delta\chi^2\ (28) = 35.76$, $p = .15$, so its constraints were retained in subsequent analyses. Finally, to assess measurement invariance between males and females, we estimated a multiple-group state–trait model that imposed the same measurement invariance constraints between groups that were imposed over time in the single-group model. This model (see Figure 1) showed excellent fit to the data, $\Delta\chi^2\ (225) = 233.55$, $p = .33$; CFI = 0.99, RMSEA = 0.02, so its constraints were retained in subsequent analyses.

Affiliations with alcohol use promoting peers. Participants reported their affiliations with alcohol use promoting peers using five items that assessed both descriptive and injunctive peer norms (see Cialdini, Reno, & Kallgren, 1990; items adapted from the Monitoring the Future study, Johnston, O'Malley, & Bachman, 1988). Descriptive norm items asked the number of friends who used alcohol occasionally and regularly, with response options ranging from (0) *none* to (6) *all*. Injunctive norm items asked how their friends would feel about them using alcohol occasionally, regularly, and heavily each weekend, with response options ranging from 0 (*strongly disapprove*) to 5 (*strongly approve*).

3. At the time of initial recruitment, 17 potential non-COA families were dropped from the study because a parent reported drinking problems close to the diagnostic threshold. This was done to reduce the danger of later "crossover" into the COA group (Chassin et al., 1991).

Table 1. *Descriptive data for subgroups and the full sample with genetic data (N = 238) at age bands 1, 2, and 3*

	Symptom Endorsement (%)							
Subgroup & AB	S1	S2	S3	S4	S6	Mean Symptom Count	Mean Peer Affiliation	Children of Alcoholics (%)
Females								
AB 1 ($n = 82$)	11.0	13.4	9.8	7.3	11.0	0.524	2.866	47.6
AB 2 ($n = 104$)	8.7	9.6	4.8	4.8	20.2	0.447	3.254	53.8
AB 3 ($n = 107$)	5.6	7.5	3.7	2.8	13.1	0.302	3.303	53.3
Males								
AB 1 ($n = 93$)	19.4	29.0	22.6	15.1	21.5	1.075	3.426	48.4
AB 2 ($n = 114$)	11.4	21.1	13.2	9.6	22.8	0.809	3.633	50.0
AB 3 ($n = 114$)	7.9	18.4	13.2	8.8	27.2	0.774	3.582	48.2
OPRM1-A								
AB 1 ($n = 132$)	15.9	24.2	18.9	11.4	16.7	0.871	3.237	49.2
AB 2 ($n = 162$)	9.3	15.4	8.6	5.6	19.1	0.580	3.481	53.1
AB 3 ($n = 167$)	5.4	12.0	7.8	5.4	19.8	0.503	3.468	51.5
OPRM1-G								
AB 1 ($n = 43$)	14.0	14.0	9.3	11.6	16.3	0.651	2.944	44.2
AB 2 ($n = 56$)	12.5	16.1	10.7	12.5	28.6	0.804	3.384	48.2
AB 3 ($n = 54$)	11.1	16.7	11.1	7.4	22.2	0.685	3.383	48.1
Total								
AB 1 ($n = 175$)	15.4	21.7	16.6	11.4	16.6	0.817	3.164	48.0
AB 2 ($n = 218$)	10.1	15.6	9.2	7.3	21.6	0.638	3.454	51.8
AB 3 ($n = 221$)	6.8	13.1	8.6	5.9	20.4	0.548	3.447	50.7

Note: Symptoms are numbered in the order in which they are listed in the Measures Section. Peer affiliation scores are raw scores. AB, age band.

A series of CFAs suggested that these items formed separate descriptive and injunctive factors as well as separate "occasional" and "regular" method factors. A one-factor model showed poorer fit than a two-factor model with separate descriptive and injunctive factors, $\Delta\chi^2$ (14) = 177.83, $p < .001$, which in turn showed poorer fit than a four-factor model with two additional occasional and regular factors, $\Delta\chi^2$ (5) = 32.11, $p < .001$. The four-factor model showed good fit to the observed data, $\Delta\chi^2$ (76) = 131.14, $p < .001$; CFI = 0.959, RMSEA = 0.056. However, there were high correlations between the descriptive and injunctive norm factors in the four-factor CFA models (i.e., standardized covariances were .72, .76, and .70 at age bands 1, 2, and 3, respectively, all ps $< .001$), thus precluding their inclusion as separate predictors in the same model. Therefore, an additional hierarchical CFA was estimated in order to model a higher-order peer affiliation factor that was indicated by the lower-order descriptive and injunctive factors (and was independent of method variance from the occasional and regular factors). In these models, the two method factors were assumed to be uncorrelated with each other and with the two descriptive and injunctive factors, and equality constraints were imposed on factor loadings for the descriptive and injunctive factors across the three age bands to reduce model complexity. This model fit the data well, χ^2 (84) = 111.92, $p < .001$; CFI = 0.949, RMSEA = 0.059, so factor scores for the higher-order peer affiliation factor were saved from this model, providing a unidimensional peer affiliation variable that was used in subsequent analyses.

Genomic data. Genetic data were collected with cheek brushing or saliva samples using Oragene collection kits. Extraction of DNA, standardization, and plating were completed in the Department of Psychiatry at Washington University School of Medicine and genotyping was done through the Washington University Genome Sequencing Center. A set of 1,536 SNPs were designed for genotyping using the Illumina Golden Gate technology. After genotyping was complete, the following quality control analyses were conducted: (a) cluster plots were examined to rule out ambiguous genotype calls; (b) checks for Mendelian inconsistencies, incorrect gender assignments and sample swaps, and cryptic relatedness were conducted and appropriate corrections were made; and (c) SNPs with low call rates (<95%) and deviations from Hardy–Weinberg equilibrium ($p < 10^{-6}$) were flagged. The A118G SNP (*rs1799971*) was in Hardy–Weinberg equilibrium ($p = .726$) and had excellent call rates (99.9978%). As in prior work, the A118G SNP was scored such that carriers of the G (minor) allele comprised one group (AG or GG), and A allele homozygotes comprised another (AA). Among self-identified non-Hispanic Caucasians, 24.4% ($N = 58$) possessed at least one copy of the G allele and the minor allele frequency (MAF) was 16%. For males, the MAF was 15% and for females the MAF was 16%.

Parental alcoholism. Lifetime alcoholism diagnoses (*DSM-III* abuse or dependence) were obtained from both parents at Wave 1 using the Diagnostic Interview Schedule, Computerized Version III (Robins, Helzer, Croughan, & Ratcliff, 1981). For noninterviewed parents (18%), alcoholism diagnoses were established using Family History Research Diagnostic Criteria (Endicott, Andreasen, & Spitzer, 1975) on the basis of spousal reports. Participants were classified as COAs

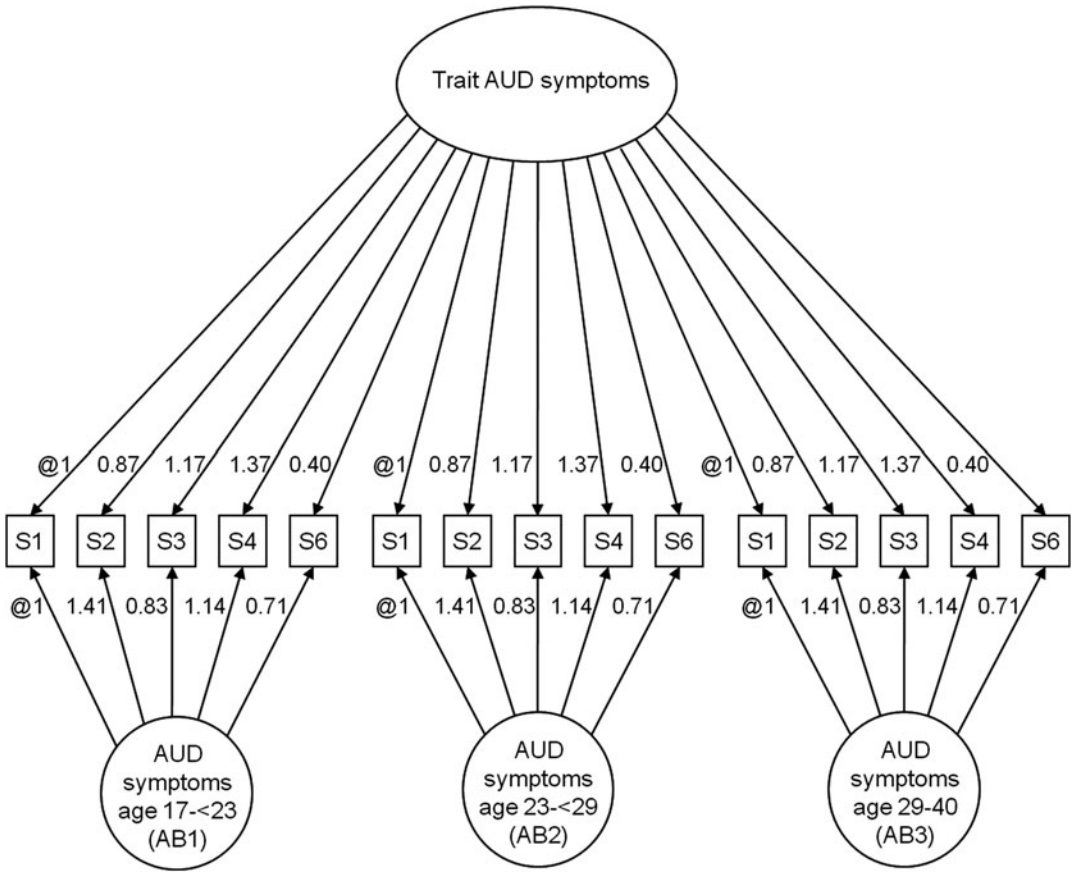

Figure 1. Unstandardized factor loadings from the multiple-group state–trait measurement model with estimates constrained to be equal between genders. Factor loadings labeled @1 were constrained to 1 for the purpose of model identification. All factor loadings were significant at $p <$ .001. Standardized factor loadings ranged from .318 to .771 for the trait factor and from .450 to .873 across the three state factors. Symptoms are numbered in the order in which they are listed in the Measures Section. AUD, alcohol use disorder; AB, age band.

if they had at least one biological, custodial parent who was alcoholic at Wave 1 and all others were classified as non-COAs (see Table 1 for rates).

Analyses and Results

All models were estimated using Mplus Version 6.11 (Muthén & Muthén, 1998–2010) and used full information maximum likelihood estimation in order to handle missing data. As described earlier, because there were large amounts of missing genetic data, we estimated our model both for those who provided genetic data ($N = 238$) and among the full non-Hispanic Caucasian alcohol-using sample ($N = 529$). We used a robust sandwich estimator (i.e., Mplus option TYPE = COMPLEX) in order to adjust standard errors and chi-square statistics for the clustering of participants within families. To test our hypotheses, we estimated a model that built upon the multiple group (i.e. gender groups) state–trait model of AUD symptoms that was described in the Measures Section. Rather than freely estimating measurement model parameters in this model, we constrained indicator factor loadings, thresholds, and error variances to be equal to those from the final multiple-group state–trait measurement model in order to maintain an acceptable number of free model parameters relative to our sample size.

Thus, our model tested the effects of parental alcoholism on *OPRM1* and on the trait AUD factor, as well as the effect of *OPRM1* on the trait AUD factor. In addition, the model tested the effects of *OPRM1* on the three peer affiliation variables, the effects of *OPRM1* on the three residual state AUD factors, and the effects of the three peer affiliation variables on the three corresponding residual state AUD factors.[4] Finally, by including orthogonalized interaction terms,[5] this

4. Initially, to account for age heterogeneity at age band 1, all models included age as a covariate predictor of state AUD symptoms and affiliation with alcohol use promoting peers at this age band. However, age effects were consistently nonsignificant across models and thus were dropped from analyses.
5. Our models used orthogonalized interaction terms in order to avoid multicollinearity of the peer affiliation variables and *OPRM1* with their interactions (Draper & Smith, 1966, 1981). Orthogonalized interaction terms were computed by regressing a given interaction term on both its corresponding peer affiliation variable and *OPRM1* (simultaneously) and saving the residuals as a new variable. The resulting orthogonalized

model tested whether *OPRM1* interacted with the three peer affiliation variables in predicting the three corresponding residual state AUD factors.

We initially allowed all of the effects described above to vary between genders. We then tested gender invariance of each individual effect using Wald chi-square tests of parameter constraints. Our final model constrained effects to be gender invariant if they did not initially differ with at least marginal significance ($p < .10$). The resulting final model showed excellent fit to the data, $\Delta\chi^2$ (497) = 493.33, $p = .54$; CFI = 1.00, RMSEA = 0.00 (see Figure 2).

Below we describe the results of interest from this final model (for coefficients, see Figure 2). First, we describe the results pertaining to the hypothesized mediational pathway from parental alcoholism to trait AUD symptoms through *OPRM1*. Second, we describe the results pertaining to the hypothesized genetically influenced peer selection mediational pathways whereby parental alcoholism predicts *OPRM1*, which in turn predicts affiliation with alcohol use promoting peers, which in turn predicts age-specific AUD symptoms. In this section we also report Wald chi-square tests of parameter constraints assessing differences across the age bands in the effects of *OPRM1* on peer affiliations and the effects of peer affiliations on AUD symptom states. Third and finally, we describe the results pertaining to the hypothesized interaction effects between *OPRM1* and affiliations with alcohol use promoting peers on AUD symptom states, and we report Wald chi-square tests of differences in these interaction effects across the age bands. When reporting on mediated effects, we rely upon the joint significance test (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) in which a mediational chain is considered to be significant if each path involved in the chain is significant. The joint significance test has good statistical power and controls Type 1 error at or below its nominal level (MacKinnon et al., 2002). When reporting on estimates that varied at least marginally significantly between genders (and thus were allowed to vary between genders in the final models), we describe male and female results separately and report the Wald chi-square tests indicating gender differences.

Effects of parental alcoholism on trait AUD symptoms through OPRM1

For both males and females, those with alcoholic parents were significantly less likely to carry the G allele (see Table 1 and Figure 2). In terms of the direct effect of parental alcoholism on trait AUD symptoms, there was a significant gender difference, $\Delta\chi^2$ (1) = 19.72, $p < .001$, such that parental alcoholism predicted increased trait AUD symptoms significantly for females (see Figure 2) and marginally significantly for males ($p = .089$). *OPRM1* did not significantly predict trait AUD symptoms. Given the lack of significant *OPRM1* effects on trait AUD, the results failed to support the hypothesized mediational pathway from parental alcoholism to trait AUD symptoms through *OPRM1* according to the joint significance test of mediation.

Effects on AUD symptom states

As mentioned above, for both men and women, those with an alcoholic parent were significantly less likely to carry the G allele. The effects of *OPRM1* on affiliation with alcohol use promoting peers varied for men and women, significantly at age band 1, χ^2 (1) = 9.52, $p = .001$, and with marginal significance at age bands 2 and 3, χ^2 (1) = 2.82, $p = .09$, and χ^2 (1) = 3.78, $p = .05$, respectively. For males, those who possessed the *OPRM1*-G allele reported significantly less affiliation with alcohol use promoting peers at all three age bands (see Figure 2). For females, there were no significant relations between *OPRM1* and peer affiliations. Finally, for both genders, affiliations with alcohol use promoting peers predicted increased state AUD symptoms at all three age bands (see Figure 2). These effects did not differ between genders at any of the three age bands, but the age band 1 effect was freed to vary between genders to facilitate probing of the significant age band 1 interaction (see below). Thus, the hypothesized mediational pathway whereby parental alcoholism predicts *OPRM1*, which in turn predicts affiliation with alcohol use promoting peers, which in turn predicts the three corresponding AUD symptom states, was supported for males but not for females.

The results also showed direct effects of lacking the *OPRM1*-G allele on decreased state AUD symptoms for males at age bands 2 and 3 (see Figure 2). These effects differed significantly by gender at age bands 2 and 3, $\Delta\chi^2$ (1) = 4.62, $p = .03$, and χ^2 (1) = 4.22, $p = .04$, respectively, although this effect was also freed to vary between genders at age band 1 in order to facilitate probing of the significant age band 1 interaction (see below).

We next tested age differences in these effects. For both males and females, omnibus tests showed that there were no significant age differences in the effects of affiliation with alcohol use promoting peers on state AUD symptoms, $\Delta\chi^2$ (2) = 0.22, $p = .89$, and χ^2 (2) = 3.61, $p = .16$; the effects of *OPRM1* on affiliation with alcohol use promoting peers, $\Delta\chi^2$ (2) = 0.22, $p = .90$, and χ^2 (2) = 4.44, $p = .11$; or the effects of the *OPRM1*-G allele on state AUD symptoms, $\Delta\chi^2$ (2) = 3.84, $p = .15$, and χ^2 (2) = 1.44, $p = .49$, respectively.

Interactions between OPRM1 and peer affiliations in predicting AUD symptom states

The only interaction between genetic risk and peer affiliation was found for females at age band 1 (see Figure 2). For males, there were no significant interactions at any age band

interaction terms were correlated with corresponding peer affiliation variables and with *OPRM1* at exactly 0.00 (all *p*s = 1.00), and they were correlated with corresponding nonorthogonalized interaction terms from .86 to .89 (all *p*s < .001).

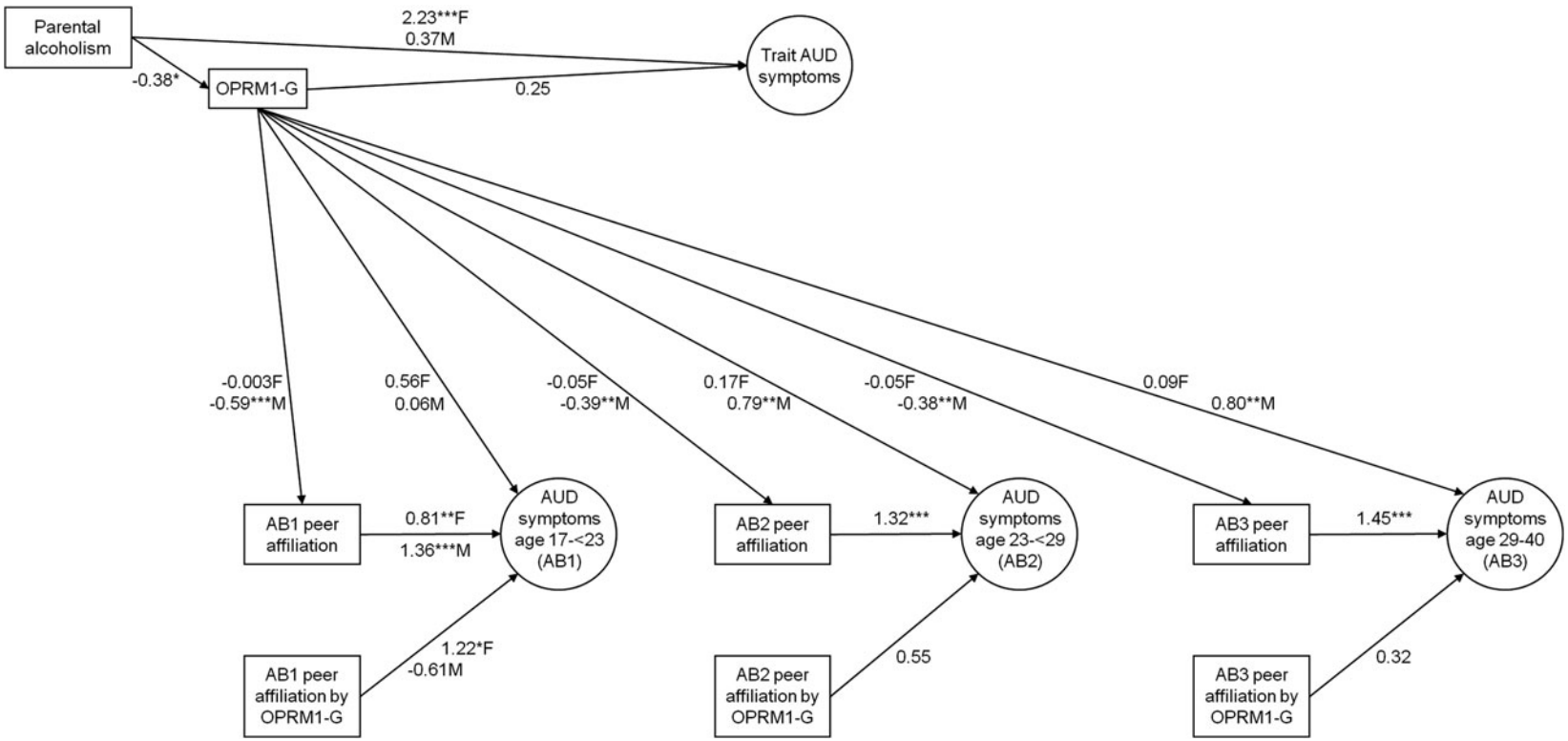

Figure 2. Unstandardized results from the final multiple group model for men and women. Effects are given separately for females (F) and males (M) only when they differed significantly (other effects were constrained to be equal between the genders). Although not depicted here, correlations were allowed among the three peer affiliation variables and among the three orthogonalized interaction terms. These correlations were constrained to be equal between genders. μ-Opiod receptor M1 (*OPRM1*) was coded *OPRM1*-A = 0 and *OPRM1*-G = 1. AB, age band. *$p < .05$. **$p < .01$. ***$p < .001$.

(see Figure 2) and males and females differed in this interaction term only at age band 1, χ^2 (2) = 7.72, $p = .01$.

We probed this interaction by reestimating the model after rescaling both the *OPRM1* variable and the peer affiliation variable in order to obtain the effects of both variables on state AUD symptoms at different levels of the other (see Figure 3).[6] The effects of peer affiliations on state AUD symptoms were larger when the effects were conditional on possessing the *OPRM1*-G allele ($b = 2.44$, $p < .001$) than when effects were conditional on lacking the *OPRM1*-G allele ($b = 0.81$, $p = .002$).

The effects of the *OPRM1*-G allele on state AUD symptoms increased in magnitude with increases in affiliations with alcohol use promoting peers and were nonsignificant at low levels of these peer affiliations. Specifically, estimates for the effects of *OPRM1* on state AUD were $b = 2.45$ ($p < .001$) at 0.5 *SD* above the mean of alcohol use promoting peer affiliations, $b = 1.63$ ($p < .001$) at the mean of peer affiliations, and $b = 0.82$ ($p < .001$) at 0.5 *SD* below the mean of affiliation with alcohol use promoting peers.[7]

Supplemental analysis of the full sample of alcohol-using non-Hispanic Caucasians

Because there was a large amount of missing genomic data, in order to confirm the findings of our final model, we estimated the same model with the larger sample of non-Hispanic Caucasian nonalcohol abstainers including those who were missing genomic data ($N = 529$). The model with the larger sample showed excellent fit to the data, $\Delta\chi^2$ (498) = 578.27, $p = .01$; CFI = 0.96, RMSEA = 0.03. All effects observed in the smaller sample were maintained in the larger sample except that the effect of the *OPRM1*-G allele on increased age band 3 state symptoms for males went from significant in the smaller sample to marginally significant in the larger sample ($b = 0.803$, $p = .002$, and $b = 0.377$, $p = .074$; respectively). New effects observed in the larger sample were an effect of the *OPRM1*-G allele on increased trait AUD symptoms ($b = 0.39$, $p = .045$; in the smaller sample, $b = 0.25$, $p = .19$); an effect of the *OPRM1*-G allele on increased age band 2 state symptoms among females ($b = 0.557$, $p = .010$; in the smaller sample, $b = 0.166$, $p = .616$); and an effect of parental alcoholism on increased trait AUD symptoms among males ($b = 1.118$, $p < .001$), which was marginally significant in the smaller sample ($b = 0.366$, $p = .089$).[8]

Discussion

The current study tested influences on the intergenerational transmission of alcohol problems that operate on multiple levels of analysis, namely, genetic risk (as indexed by the G allele in the A118G SNP of *OPRM1*) in interplay with the influence of alcohol use promoting peers. We tested whether genetic risk mediated the effects of parent alcoholism on alcohol problem traits. We also tested whether genetic risk mediated the effects of parent alcoholism on age-related alcohol problem states through a peer selection mechanism in which G carriers in the A11G SNP would be differentially likely to affiliate with alcohol use promoting peers who in turn would influence age-specific manifestations of alcohol problems. We also tested whether the effects of affiliation with alcohol use promoting peers would be magnified for G-carriers (who are thought to be sensitive to peer rejection). Finally, we examined age and gender differences in these mechanisms.

In terms of familial alcoholism, our data replicated the well-established finding (including previous analyses from the current longitudinal project) that those with an alcoholic parent are more likely to experience alcohol-related problems (Beirut et al., 1998; Chassin et al., 2004; Heath et al., 1997; Merikangas et al., 1998; Sher et al., 1991). This was seen in a significant unique effect of parent alcoholism on trait alcohol problems for women. Although the unique effect of parent alcoholism on trait alcohol problems was significant for men only in the full sample (marginal in the small sample), there were mediated effects of parental alcoholism for men on state alcohol problems in both samples. Thus, there was clear evidence of the intergenerational transmission of alcohol disorder. We also replicated the widely reported effects of affiliations with alcohol use promoting peers on alcohol problems. Although it has been suggested that peer influence effects are strongest at younger ages, and we expected that peer influences would be strongest at emerging adulthood when developmentally limited drinking is at its peak, we

6. As recommended by Young-Wolff, Enoch, and Prescott (2011), we assessed whether this interaction effect was spurious because of scaling by retesting it following monotone transformations of the main effect variables. The interaction remained significant after a log transformation of the *OPRM1* variable (after adding a constant of 1) and after a log transformation of the age band 1 peer affiliation variable with the exception of a marginally significant effect for the larger sample model with a log transformed peer variable ($p = .068$).

7. In order to explore the potential differences between the effects of descriptive and injunctive norms, those factor scores were computed and saved from the four factor nonhierarchical model with two additional "occasional" and "regular" factors (see Measures Section). Results were similar to those of our original models. The only differences were that (a) the significant effect of parental alcoholism on a decreased likelihood of possessing the *OPRM1*-G allele became marginally significant in the injunctive norms model ($b = –0.33$, $p = .06$) and (b) the marginally significant interaction at age band 2 ($b = 0.55$, $p = .07$) became significant in the descriptive norms model ($b = 0.56$, $p = .03$).

8. For the large sample, we again tested models for descriptive and injunctive norms separately and again found similar results. The only differences were that (a) the significant effect of the *OPRM1*-G allele on increased trait AUD symptoms became nonsignificant in both the descriptive norms and injunctive norms models ($b = 0.24$, $p = .22$, and $b = 0.30$, $p = .11$; respectively), (b) the marginally significant effect of the *OPRM1*-G allele on increased age band 3 state AUD symptoms ($b = 0.38$, $p = .07$) became significant in both the descriptive norms and injunctive norms models ($b = 0.51$, $p = .01$, and $b = 0.46$, $p = .04$; respectively), and (c) the marginally significant interaction at age band 2 ($b = 0.71$, $p = .08$) became significant in the descriptive norms model ($b = 0.78$, $p = .004$).

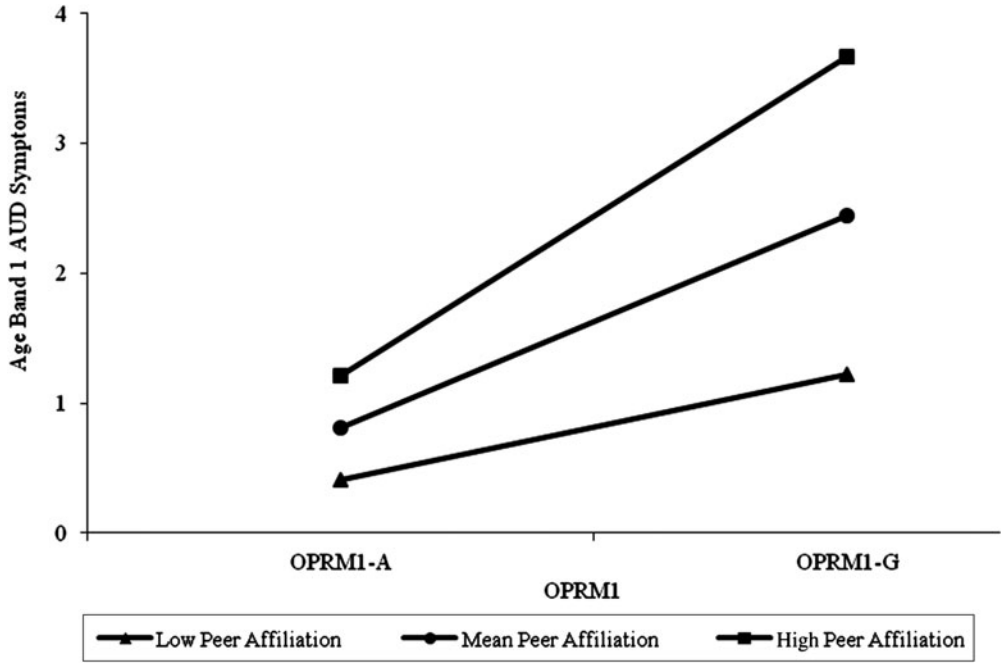

Figure 3. Predicted age band 1 state alcohol use disorder symptoms among females at different levels of μ-opiod receptor M1 (*OPRM1*) and affiliation with alcohol use promoting peers.

found significant peer effects on all age-specific manifestations of alcohol problems that did not significantly vary with age. This may be because our youngest age band reflected emerging adulthood whereas peaks in peer influence effects have been suggested to occur at younger ages (i.e., during middle adolescence; Gardner & Steinberg, 2005; Monahan et al., 2009; Steinberg & Monahan, 2007; Sumter et al., 2009). Thus, assessments at younger ages might have found a pattern of stronger peer effects and later declines compared to the stability of significant peer effects that we found from emerging adulthood into adulthood.

A major goal of the current study was to test the role of *OPRM1* genetic variation and affiliations with alcohol use promoting peers in explaining the intergenerational transmission of alcoholism. We found that those (male and female) with an alcoholic parent were less likely to carry the G allele in the A118G SNP of *OPRM1*. We found significant effects of *OPRM1* on trait alcohol problems in the large sample model but not the small sample model. Thus, there was no consistent evidence of a simple role for this SNP in the intergenerational transmission of alcohol disorders. As noted earlier, there is mixed evidence concerning the simple association of this SNP with alcohol dependence, including findings that the G allele elevates risk for alcohol dependence (Bart et al., 2005; Miranda et al., 2010) and reduces risk for alcohol dependence (Town et al., 1999), as well as several findings of no association (Bergen et al., 1997; Gscheidel et al., 2000; Kim, Kim, Song, et al., 2004; Loh et al., 2004; Sander et al., 1998).

However, the lack of a consistent unique relation with trait alcohol problems does not mean that μ-opioid receptor variation plays no role in the intergenerational transmission of alcoholism. Rather, our findings showed that (for men) carriers of the G allele were less likely to affiliate with alcohol use promoting peers and this reduced level of deviant peer association rendered them less likely to develop state alcohol problems. The finding that G-carriers were less likely to affiliate with alcohol use promoting peers may reflect that they have been reported to enjoy social interactions with parents and be sensitive to peer rejection (Copeland et al., 2011; Way et al., 2009). Juvonen (1991) found that the more peers perceived a classmate to be deviant (rule breaking, socially withdrawn etc), the more likely they were to reject that classmate; this rejection by "normal" peers is posited to lead to affiliation with other deviant and rejected classmates. Thus, perhaps carriers of the G allele are more motivated to maintain relations with mainstream peers rather than be rejected from these peer groups and affiliate with more deviant peers.

Whatever mechanism underlies the relation between the variation in *OPRM1* and affiliation with alcohol use promoting peers, this relation is consistent with those found in previous studies using latent rather than measured genes, which also suggest significant genetic influence on deviant peer affiliation (e.g., Cleveland et al., 2005). However, the current results further suggest that peer influences may in turn partially mediate the effect of genetic risk on alcohol problems. As Reiss (2010) notes, an active gene– environment correlation in which individuals with particular genotypes "select" their own environments, does not eliminate the possibility that these environments can still influence behavior. If G-carriers select peers who are relatively less likely to promote alcohol use, then this peer environment can also reduce risk for

the development of alcohol problems and this peer environment can partially explain why G-carriers are less likely to develop alcohol problems. Moreover, given that G-carriers are less likely to have an alcoholic parent, this peer selection mechanism represents one etiological pathway that operates on multiple levels and underlies the intergenerational transmission of alcohol disorders.

In addition, for men, there was some evidence of unique direct effects (above and beyond the effects of alcohol use promoting peers) on state alcohol problems in which G-carriers were at *higher* risk for "alcohol" problems. As reviewed earlier, there is evidence that G-carriers of the A118G SNP in *OPRM1* are more sensitive to the reinforcing effects of alcohol, and our findings might thus suggest that sensitivity to the reinforcing effects of alcohol explains the effects of *OPRM1* that are *not* mediated by peer social influence. However, this explanation must be viewed with caution because the significant direct effects of *OPRM1* on state AUD symptoms were less consistently found in our larger sample, including those who had not yet provided genetic data. Thus, replication is needed before substantive interpretations of this finding can be offered with confidence.

Although genetically influenced peer selection mechanisms were found for men, women showed a different pattern in which there was a significant gene–environment interaction at the youngest age band. Agrawal et al. (2010) similarly found an interaction between peer substance use and genetic vulnerability for an individual's own substance use in a female sample. Moreover, Kendler (2011) also found an interaction between peer group deviance and genetic risk for drinking that weakened with age, albeit at younger ages than the current study. This interaction showed that the effects of affiliations with alcohol use promoting peers were stronger for G-carriers and weaker for those who lacked the G allele. Given that G-carriers are reported to be sensitive to social rejection, the stronger effects of peer influences might reflect a greater desire to conform to peer influence and thus avoid peer rejection. Moreover, the effects of *OPRM1* on state AUD symptoms were stronger at higher levels of affiliation with alcohol use promoting peers, replicating previous findings that genetic risk is expressed more strongly in environments that are more permissive toward alcohol use.

That men showed evidence of genetically influenced peer selection mechanisms whereas females showed evidence of interactions between peer affiliations and genetic risk effects may help to explain conflicting findings concerning whether there are gender differences in peer influence. That is, the results of studies might differ, depending on whether they examine peers as mediators or moderators of the effects of genetic risk (or intrapersonal characteristics more broadly). Loehlin (2010) also reported differences in gene–environment correlations for men and women but found that women (rather than men as in the current data) showed gene–environment correlations.

Although the current study contributes to the literature by testing models of the intergenerational transmission of alcohol problems at multiple levels of influence within a developmental framework, and considering gender differences in the pathways, there are also limitations that must be considered and that point to important directions for future research. First, the current study provides an illustrative example of these processes using a SNP that has both theoretical and empirical relevance to alcohol disorders. However, there are few studies of gene–environment interplay using measured genes (particularly *OPRM1*), and much more replication is needed before stronger inferences can be made. Moreover, our data concerning the effects of one SNP are in no way capable of capturing the enormous complexity of multiple genetic influences on alcohol disorder. It is also important to remember that different results are seen for different alcohol phenotypes (e.g., alcohol consumption vs. alcohol problems as in the current study). Thus, future research would benefit from testing additional genetic risk factors and testing whether the obtained effects are similar across different alcohol phenotypes, particularly contrasting the effects on alcohol use with the effects on clinically significant alcohol problems. Second, our state–trait model allowed for tests of the influences of genetic variation and peer affiliation at different developmental periods, but it does not provide a prospective test of the effects of peer influences on age-specific manifestations of alcohol problems. These prospective effects of alcohol use promoting peers would theoretically operate over a much shorter time interval than the one captured in our age bands. Future studies with multiple measurements over brief time intervals would better clarify the nature of the interplay between genetic risk and peer influences. Third, we relied on participants' reports of their peer affiliations, and different methods of measuring peer deviance have been reported to produce different effects (Bullock, Deater-Deckard, & Leve, 2006). In this regard, it would be particularly useful to test models with peer reporters. Fourth, our data examined the intergenerational transmission of alcohol problems, but we did not consider co-occurring drug problems. Because alcohol problems with and without co-occurring drug problems may have different determinants (Kendler, Myers, & Prescott, 2007), future research should test whether the current findings were produced by co-occurring drug problems or would be found for alcohol problems in the absence of drug problems. Fifth and finally, because of concern with population stratification, we focused only on non-Hispanic Caucasian participants and further studies are required to test these mechanisms with other racial/ethnic groups.

Despite these limitations, the current study contributes to the literature by demonstrating that genetically influenced peer selection mechanisms in part underlie the intergenerational transmission of alcohol problems for males and that gene–environment interaction is predictive for young women. Thus, our findings underscore the importance of considering both age and gender differences in these pathways. The current study provides an illustrative example of how influences at multiple levels can be studied within a developmental framework to better understand the intergenerational transmission of alcohol disorder.

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