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## The Influence of Gene-Environment Interactions on Alcohol Consumption and Alcohol Use Disorders: A Comprehensive Review

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### Abstract

Since 2005, a rapidly expanding literature has evaluated whether environmental factors such as socio-cultural context and environmental adversity interact with genetic influences on drinking behaviors. This article critically reviews empirical research on alcohol-related genotype-environment interactions (GxE) and provides a contextual framework for understanding how genetic factors combine with (or are shaped by) environmental influences to influence the development of drinking behaviors and alcohol use disorders. Collectively, evidence from twin, adoption, and molecular genetic studies indicates that the degree of importance of genetic influences on risk for drinking outcomes can vary in different populations and under different environmental circumstances. However, methodological limitations and lack of consistent replications in this literature make it difficult to draw firm conclusions regarding the nature and effect size of alcohol-related GxE. On the basis of this review, we describe several methodological challenges as they relate to current research on GxE in drinking behaviors and provide recommendations to aid future research.

### Keywords

Gene-environment interactions; alcohol; drinking; adoption; twin; genotype

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Alcohol dependence (AD) and alcohol abuse (AA) are chronic disorders comprising a wide range of clinical symptoms. In the United States (U.S.), approximately 12.5% of males and 5% of females meet criteria for an alcohol use disorder (AUD, abuse or dependence) occurring in the past year, and an estimated 42% of males and 20% of females will experience an AUD during their lifetimes (Hasin, Stinson, Ogburn, & Grant, 2007). Furthermore, excessive alcohol consumption is associated with marked functional impairment and morbidity, ranking as the third leading cause of preventable death in the U.S. (Hasin et al., 2007; Mokdad, Marks, Stroup, & Gerberding, 2004).

Given that drinking behaviors are jointly determined by genetic *and* environmental risk factors, alcohol consumption and AUDs are appropriate phenotypes for investigating gene-

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environment interactions (GxE) (Heath & Nelson, 2002). GxE are defined as when the expression of a gene or genotype differs across environments or equivalently, the effect of the environment on the observed phenotype varies by genotype (Gunzerath & Goldman, 2003). Although twin studies consistently find moderate to high heritability of drinking behaviors (Agrawal & Lynskey, 2008; Dick, Prescott, & McGue, 2009c) and there is a growing list of replicated genes that influence alcohol consumption and convey risk for AUDs (Dick & Foroud, 2003; Kalsi, Prescott, Kendler, & Riley, 2009; Köhnke, 2008; Spanagel, 2009), these genes individually account for only a small percentage of the variance in drinking outcomes in a particular sample. If genetic effects are contingent on exposure to environmental risk factors, the “missing variance” between the genetic influence implied by twin studies and that explained by measured genes may be partially attributable to GxE.

There are two principal processes whereby environmental circumstances have been theorized to interact with genetic influences with respect to drinking behaviors. First, environmental restrictions, including social norms promoting abstinence and restricted availability of alcohol, are hypothesized to dampen the expression of genetic influences on drinking behaviors (Shanahan & Hofer, 2005). In environments characterized by high levels of social control, a large proportion of individuals, irrespective of genotype, are expected to exhibit low levels of drinking. Conversely, in more permissive settings, people’s alcohol consumption will reflect the full range of their genotypes. A second mechanism is that the social context can act as a stressor that potentiates the behavioral expression of genetic liability on risk for alcohol consumption and AUDs. In effect, this renders individuals with genetic risk even more sensitive to the pathogenic effects of environmental stressors (Rende & Plomin, 1992).

## Current Objectives

This review integrates twin, adoption, and molecular genetic studies of GxE to provide a contextual framework for understanding how genetic factors combine with (or are shaped by) environmental influences in the etiology of drinking behaviors and AUDs. The specific purposes of this article are to: 1) review and synthesize the evidence concerning GxE in alcohol consumption and AUD risk in humans, 2) discuss methodological limitations in current research on alcohol-related GxE, and 3) present recommendations for future research. A large, overarching challenge to the current review pertains to the provision of a coherent model of GxE in alcohol consumption and AUDs. By unifying diverse theoretical and methodological approaches, we provide a comprehensive review that can be used to guide future research in both etiology and treatments.

The studies we reviewed were identified by searching PubMed for adoption, twin, and molecular genetic English language articles published through May 2010. Search terms included combinations of ‘alcohol,’ ‘gene,’ ‘environment,’ ‘twin,’ ‘adoption,’ ‘interaction,’ and ‘GxE.’ This search strategy was supplemented by reviewing the reference sections of all identified studies.

## GxE Studies Using Inferred Measures of Genotypic Variation

We first review studies of alcohol-related GxE based on twin and adoption designs. The goal of these approaches is to estimate whether the impact of genotype varies for people in

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<sup>1</sup>We use the term alcohol-related to refer to all drinking behaviors, including normal range alcohol consumption. We do this because studies we review have used a wide variety of definitions of drinking outcomes. When we use the terms alcohol abuse (AA) and alcohol dependence (AD) this refers to DSM-defined alcohol use disorders (AUDs). When relevant, we further indicate in Tables 1 and 3 the specific alcohol-related outcome measures utilized in the identified studies.

different measured or implied environments. In these designs “genotype” refers to an individual’s entire genetic makeup.

Adoption studies are particularly well-suited to the study of GxE because they unambiguously separate genetic and environmental sources of variation in an outcome. Given certain assumptions<sup>2</sup>, adoptees resemble their adoptive relatives only due to shared family environmental influences, and resemble their biological relatives only due to genetic influences. For the purposes of studying GxE for alcoholism, adoption studies compare the drinking outcomes of individuals who have high versus low genetic risk, inferred from history of alcoholism in the biological parents, adopted into a range of environmental risks.

Twin studies use the fact that monozygotic (MZ) pairs share 100% of their genetic variation, whereas dizygotic (DZ) twins share on average 50% of their genetic variation, to partition sources of variation in a phenotype into main effects from three latent components: additive genetic (A) variance shared by twins due to genetic alleles that combine additively, common environmental (C) variance that comes from experiences that make members of a twin pair similar to each other, and individual-specific (non-shared) environmental (E) variance that makes members of a twin pair different from each other. Estimation of each source’s (i.e., A, C, E) contribution to individual differences in a phenotype is made by comparing the similarity of samples of MZ and DZ twin pairs<sup>3</sup>. In a traditional twin design, interactions between genetic and common environmental factors are confounded with estimates of genetic main effects, and interactions between genetic and individual-specific environmental factors are confounded with estimates of individual-specific environmental effects (Eaves, Last, Martin, & Jinks, 1977; Heath & Nelson, 2002). If the twin model is expanded by including explicit measures of the environment or additional types of relatives, variance due to GxE can be separated from the variance due to latent genetic and environmental main effects (Purcell, 2002). GxE is indicated if the variation in a behavior attributable to genotype differs across environmental conditions. Sometimes, depending on the study methodology, this is indicated by differences in heritability (*proportion* of total variance due to genetic influences) across environmental conditions, although later we note some methodological concerns about this practice.

We identified 16 published studies that investigated how inferred genotype interacts with environmental constraints and adversity to influence variation in alcohol-related phenotypes (Table 1). In order to provide a clear view of the longitudinal and cumulative nature of risk-resilience factors for AUDs, we start with articles describing moderating factors in adolescence such as peer pressure, parental influences, and age at first drink and move to moderators in adulthood. It is important to note that many of the “environmental” measures used in alcohol-related studies of GxE are genetically influenced (e.g., age at drinking onset; Prescott & Kendler, 1999). We consider the implications of this important methodological issue in a later section.

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<sup>2</sup>Adoption studies assume that adoptees are placed randomly into adoptive homes and that risk is not transmitted from biological parents to offspring via environmental pathways such as the intra-uterine or early environment. To the extent that these assumptions are inaccurate, estimates of genetic and environmental influences will be biased. Adoptees also tend to be over-sampled from high risk biological families and placed in above-average environments (Stoolmiller, 1999; Tsuang et al., 2001), potentially creating a restricted range of environmental and genetic influences and reducing statistical power to detect GxE (McGue & Bouchard, 1998).

<sup>3</sup>A fourth component, dominance, is inferred from twin data when MZ pairs are more than twice as similar as DZ pairs. However, dominance is rarely implicated in twin studies of alcohol-related behaviors so we do not consider it further. Twin studies also make several defensible assumptions including: random mating, equal shared environments between MZ and DZ pairs, and independence of genetic and environmental latent components. To the extent these assumptions are not true, estimates of genetic and environmental influences will be biased.

## Environmental Moderators of Inferred Genotype

**Parental and peer influences**—There is strong evidence that parental and peer factors are associated with adolescent alcohol consumption and the development of AUDs. In addition to genetic influences, possible environmental mechanisms include reduced supervision, more permissive views on drinking, and social learning (Sher, Grekin, & Williams, 2005). Parents and peers have also been proposed to moderate genetic risk for alcohol consumption via their influence on the restrictiveness of the social environment and exposure to adversity.

To date, four published adoption studies have investigated whether AUD risk is higher among adoptees with presumed genetic liability who are also exposed to risky adoptive-family environments. In two independent samples of Swedish male adoptees (Cloninger, Bohman, & Sigvardsson, 1981; Sigvardsson, Bohman, & Cloninger, 1996), environmental risk (indicated by adoptive father occupational status) moderated genetic risk for a severe form of alcoholism with later onset and lower heritability (Type I), but not for a form characterized by earlier onset and externalizing comorbidity (Type II). Rates of severe Type I alcoholism among males with both high genetic and environmental risk were (11.4–11.5%), substantially higher than those with low environmental risk and those with low genetic risk (regardless of environment) whose rates ranged from 2.3% to 6.7%. In contrast, Bohman, Sigvardsson, and Cloninger (1981) found no evidence for GxE on lifetime alcoholism in a parallel study of Swedish female adoptees.

Based on the Iowa adoption study, Cutrona et al. (1994) reported that women adoptees with a biological alcoholic background who experienced high levels of early adoptive family conflict were more likely to have had an AUD (38%) than those who experienced low levels of early adoptive family conflict (4%). Early-life family conflict was unrelated to AUD probability among women without a biological alcoholic parent, indicative of genetic influences on sensitivity to environmental risk. In contrast, no evidence of GxE was found for four other indices of adoptive family environment studied in these women, nor for any indices of adoptive family environment studied in the men in this sample (Table 1).

Five twin studies have examined whether parental and peer factors moderate genetic risk for drinking. Miles, Silberg, Pickens, and Eaves (2005) found that genetic influences accounted for more of the standardized variance in the initiation of alcohol consumption among adolescent female twins from Virginia raised in families categorized into lower versus higher levels of parental closeness. However, the difference between groups was relatively small (heritability of 96% vs. 74%) and tests of alcohol-related GxE were not significant for four other measures of family environment (Table 1). Using data from Finnish adolescent same-sex twin pairs (Finn Twin study) assessed at ages 14 and 17, Dick et al. (2007a) reported drinking frequency heritability was significantly higher among teens with the greatest number of alcohol-using peers (60%) compared to those with the fewest alcohol-using peers (22%). In contrast, parental monitoring and time spent with parents did not moderate genetic influences on adolescent drinking at ages 14 or 17, though there were significant moderation effects observed for adolescent smoking, with genetic influences assuming greater importance with reduced parental monitoring.

Two studies used reports of substance use by sibling pairs and their friends who participated in the National Longitudinal Study of Adolescent Health (Add Health) to investigate the moderating influence of peer substance use on genetic risk on drinking frequency among adolescents. Harden, Hill, Turkheimer, and Emery (2008) found that teens with higher genetic liability had significantly greater frequencies of drinking and smoking if their best friends did as well, indicative of GxE. This held true even after adjusting for the tendency of teens with higher liability to have friends with greater substance use (i.e., a gene-

environment correlation). Subsequently, Guo, Elder, Cai, and Hamilton (2009) report that genetic influences on drinking frequency were moderated by peer drinking: heritability of drinking frequency was highest for sibling pairs with high exposure to drinking friends (range 0.87–1.0) and lowest for pairs with low exposure to drinking friends (range 0.0–0.33).

Kendler, Gardner, and Dick (in press) found additional evidence for significant GxE on alcohol consumption among adult male twins from Virginia based on retrospective reports of adolescent environmental exposures. Alcohol availability, peer group deviance, and low prosocial behaviors (e.g., low levels of participation in organized sports and community activities) moderated genetic risk for AUDs and non-specific externalizing disorders during early and mid-adolescence, such that genetic influences were greater in less restrictive environments with easier access to alcohol. There was little evidence for GxE for three other measures of environmental exposure or during later adolescence (after age 17).

**Age at first drink**—Cross-sectional and longitudinal studies have found that age at first drink is strongly associated with alcohol-related problem behavior and AUDs (Grant & Dawson, 1997; Pitkanen, Kokko, Lyyra, & Pulkkinen, 2008). The association may be partially accounted for by non-familial factors (Buchmann et al., 2009; Grant et al., 2006) as well as due to overlapping risk for early alcohol consumption and AUDs (McGue, Iacono, Legrand & Elkins, 2001; Prescott & Kendler, 1999). Early alcohol consumption could also interact with genetic liability, potentiating AUD risk among individuals exposed to alcohol at an early age. Using data from a sample of Australian adult twins, Agrawal and colleagues (2009) found that self-reported age at first drink moderated estimates of genetic influences on number of lifetime AD symptoms. Among early drinkers, variation in AD symptoms was predominantly attributable to genetic influences (e.g., approximately 70% for onset by age 14), whereas for those with later drinking onset, variation in AD symptoms was decreasingly attributable to genetic influences (e.g., approximately 45% and 15%, respectively, for onset ages of 16 and 19).

**Region of residence**—Neighborhood-level risk factors, including low socioeconomic status, residential instability, and decreased community-resident and parent-child supervision are associated with adverse youth outcomes (Leventhal & Brooks-Gunn, 2000; Winstanley et al., 2008). There is some evidence that urban environments have greater residential mobility and fewer social constraints than rural environments, potentially creating a more tolerant (or oblivious) environment with easy access to alcohol that could allow for a greater range of expression of genetic liability to deviant behaviors.

A series of three reports using data from the Finn Twin study has examined the role of region of residence as a moderator of genetic influences on drinking among adolescents. Heritability of drinking frequency was found to be greater in urban than rural environments, at ages 16 (34% vs. 18%), 17 (62% vs. 49%) and 18.5 (59% vs. 53%), consistent with GxE (Rose, Dick, Viken, & Kaprio, 2001). This pattern of results was replicated among 18-year-olds using more specific neighborhood characteristics, such that drinking frequency heritability was higher in municipalities with a greater percentage of young adults and more migration (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001). Neighborhood characteristics were not found to moderate genetic influences on drinking among 14-year-olds (Dick et al., 2009a), but only 34% of this younger sample had initiated drinking, limiting power to test GxE.

In an independent study of twins from Minnesota, the heritability of alcohol problems was greater in urban (49%) than rural (3%) environments among adolescent males (Legrand, Keyes, McGue, Iacono, & Krueger, 2008), replicating the effect observed in the Finnish

sample. There was a similar, albeit non-significant, GxE pattern among adolescent females. Parallel patterns of significant GxE were also reported for other types of rule breaking behaviors among males.

**Religious involvement**—Abstinence from alcohol and protection from AUDs has also been associated with religious involvement (Miller, Davies, & Greenwald, 2000; Moreira-Almeida, Neto, & Koenig, 2006). Protective effects of religion may be mediated by the degree to which religion fosters restrictive social norms that differentiate from the more liberal attitudes regarding alcohol consumption in the general culture (Haber & Jacob, 2007; 2009). Because religious proscriptions, rather than personal choice, may determine drinking behaviors among religious individuals, religious upbringing has been proposed as a moderator of genetic influences on alcohol initiation and alcohol consumption among adolescents.

Koopmans, Slutske, van Baal, and Boomsma (1999) found that religious upbringing moderated genetic influences on alcohol initiation in a sample of adolescent and young adult twins from the Netherlands, such that heritability of alcohol initiation was higher among females without than those with a religious upbringing (39% vs. 0%). There was a similar (but statistically non-significant) pattern of GxE among males. Conversely, adolescent church attendance was not a moderator of genetic influences on adolescent alcohol consumption among adult male twins from Virginia (Kendler et al., in press).

**Marital Status**—Married individuals typically drink less heavily than those who are divorced, separated, or who have never been married (Chilcoat & Breslau, 1996; Temple et al., 1991). Being part of a stable couple often leads to new social constraints, including fewer social activities and greater disapproval of heavy drinking, that may partially mediate marriage-related reductions in alcohol consumption (Leonard & Eiden, 2007). Consequently, marriage may reduce the expression of genetic risk for AUDs by fostering new social and financial (e.g., children, home ownership) responsibilities that discourage heavy drinking.

One twin study has investigated this issue using a GxE approach. Heath, Jardine, & Martin (1989) found that marital status moderated the manifestation of genetic influences on alcohol consumption among female twins from Australia. Genetic influences explained a greater proportion of the variance in weekly alcohol consumption among unmarried females (younger cohort, 60%; older cohort, 76%) compared to married females (younger cohort, 31%; older cohort, 46–59%). There was no evidence for shared environmental influences, and the remainder of variance was attributable to individual-specific environment.

### Summary of GxE Findings based on Inferred Measures of Genotypic Variance

Collectively, these studies provide provocative evidence that the importance of genetic influences on drinking behaviors varies under different environmental circumstances, highlighting the importance of socio-cultural factors in the expression of genetic propensities for drinking outcomes. Positive GxE findings from twin studies were all in the predicted direction of effect, such that the relative importance of genetic influences on variance in drinking behaviors was greater in more permissive socio-cultural environments with easier access to alcohol and substance using peers, and lower in more restrictive social environments (cf. Turkheimer, Haley, Waldron, D’Onofrio, & Gottesman (2003) for a similar outcome regarding cognitive abilities). Results from adoption studies provided somewhat more limited support for a diathesis-stress model of GxE in which individuals’ genotypes influenced how likely they were to use or misuse alcohol in response to environmental adversity or stressors. In particular, sensitivity to the pathogenic effects of

stressors on drinking was important for a less genetically influenced form of alcoholism with a later onset (Type I) among males.

Overall, 14 of the 16 studies reviewed reported at least one significant GxE, whereas 11 studies reported one or more non-significant GxE (Table 2), and there were no clear patterns of gender differences in GxE (Table 1). Limited evidence for GxE in adoption studies may be due in part to the lower power of these specific studies to address GxE questions of this nature. Measurement of environmental risk was limited in the Swedish adoption studies, and the Iowa study was restricted by its small sample size. Additionally, the large number of non-significant findings and high probability of type I error suggest that studies of aggregate genetic influences may currently overstate the true effect size of alcohol-related GxE.

## GxE Studies Using Measured Genotypes

Studies of inferred genetic risk described in the previous section examined how the environment can potentiate or limit variation in drinking behaviors for the aggregate effects of genotypes. However, these studies offer no knowledge about which genes contribute to these interactions and were not designed to do so. In this next section, we review studies examining interactions between specific genetic loci and measured environmental factors. First, we provide a definition of a single nucleotide polymorphism (SNP) for clarification. A SNP is a DNA sequence variation occurring when a single nucleotide (A, T, C, or G) differs between paired chromosomes in an individual. For example, for a CT SNP, we say that there are two alleles: C and T and that this individual has the CT genotype. Other possible genotypes for individuals in a population are CC and TT. Readers interested in more detailed information are referred to Carey (2002) and the International HapMap Project website.

Similar to studies of aggregate genetic influence, molecular genetic GxE studies have typically evaluated whether environmental adversity and socio-cultural factors differentially influence drinking outcomes among individuals with different genotypes. There were 20 published studies investigating GxE in alcohol-related phenotypes using measured genotypes for 9 different genes (Tables 3 and 4) in the literature.

## Genotypic Moderation of Environmental Risk

**Serotonin Transporter Gene**—A functional polymorphism (*5-HTTLPR*) in the promoter (regulatory) region of the serotonin transporter gene (*SLC6A4*) has been widely studied as a potential predictor of depression liability and stress response (Caspi et al., 2003; Clark, Flint, Attwood, & Munafó, 2010). There is a long (L) and short (S) version (or variant) of the *5-HTTLPR* polymorphism. Furthermore, it has been found that the L variant comes in two forms:  $L_A$  and  $L_G$  (Hu et al., 2005; Nakamura, Ueno, Sano, & Tanabe, 2000). The frequencies of the S and  $L_G$  variants range from 0.40 – 0.09 respectively in Caucasians to 0.25 – 0.24 respectively in African Americans. The S and  $L_G$  variants alter expression of the gene. The S variant is associated with an approximately 50% reduction in transporter availability compared with the L variant; likewise, the same reduction in transporter availability is found when the  $L_G$  and  $L_A$  variants are compared (Lesch et al., 1996). There appears to be a weak positive association between the *5-HTTLPR* S variant and increased AD risk (Feinn, Nellissery, & Kranzler, 2005). Unfortunately, earlier studies included in this meta-analysis and described later did not distinguish the two forms of the L variant and this may have diluted the significance of the results, particularly in studies that included African Americans, in whom the  $L_G$  variant is at a high frequency.

Six studies have examined whether the *5-HTTLPR* polymorphism (L and S variants, LL, LS and SS genotypes) interacts with environmental risk factors to predict drinking outcomes.

These studies are reviewed in chronological order starting with positive GxE findings. In the first study, young Swedish adults who had the LS genotype and neutral or poor family relationships were more likely to drink until they were intoxicated (89–90%) than those with other combinations of genotypes and family relationship quality (range 39–67%) (Nilsson et al., 2005). A similar pattern of GxE was found for quantity of alcohol consumption. In a study of maltreated children and matched community controls aged 8 to 16 (Kaufman et al., 2007), individuals with the LS and SS genotypes with exposure to maltreatment were at a greater risk for alcohol initiation (33%) compared to those not exposed to maltreatment (8%), and those with the LL genotype with or without a history of maltreatment (24% and 0%, respectively). It is noteworthy that none of the children with the SS genotype had initiated alcohol consumption, and similar to findings reported by Nilsson et al. (2005), the GxE associated with the S variant was attributable to the LS genotype.

A longitudinal study of U.S. college students found a small but significant interaction between *5-HTTLPR* genotype and past-year stressful life events (SLEs) that accounted for 1.1–3.1% of the variance in frequency of drinking outcomes assessed at two time-points (Covault et al., 2007). Individuals with the SS genotype who experienced multiple past-year SLEs drank more frequently and heavily compared to those with any other combination of genotype and past-year SLEs. There was a similar pattern of GxE for non-prescription drug use. In contrast, among German young adults, those individuals with the LL genotype who experienced early psychosocial adversity had approximately twice as many binge drinking days compared to the LL individuals not exposed to significant early adversity and compared to individuals with LS and SS genotypes regardless of adversity (Laucht et al., 2009). Additionally, current SLEs were associated with greater drinking only among LL and LS individuals.

Two studies with more limited measures of stressors did not find evidence consistent with GxE. There was no evidence for an interaction between *5-HTTLPR* genotype and past year SLEs on AD risk in a sample of Caucasian probands from the Collaborative Study on the Genetics of Alcoholism (COGA) (Dick et al., 2007b). In a sample of Mexican-Americans with AUDs, education and marital status did not interact with variation in *5-HTTLPR* genotype or in the dopamine receptor D2 gene to predict AUD severity (Du & Wan, 2009). However, there was evidence for an interaction between a polymorphism in the opioid receptor mu1 (*OPRM1*) and education in relation to AUD severity (Table 3).

Clearly, results are conflicting across the six studies of *5-HTTLPR* genotype and cannot be considered replications, even in a very broad sense. Research on life stress and *5-HTTLPR* genotype interactions in alcohol-related outcomes is marked by wide variation in the conceptualization of stressors and drinking outcomes, so the variable-defined space they cover is fairly non-overlapping. Researchers inconsistently used a variant-based linear model (i.e., coding 0, 1 or 2 risk variants) versus a genotypic model (i.e., coding genotypes into 2 or 3 nominal categories), and the “risk” genotype varied across studies. To our knowledge, only one of the studies reviewed here (Laucht et al., 2009) distinguished between the two forms of the L allele, potentially reducing power of the others to detect GxE.

**Corticotropin-Releasing Hormone Receptor 1 Gene**—Alcohol consumption stimulates the release of corticotropin-releasing hormone (CRH) and activates the HPA axis (Clarke & Schumann, 2009). There is mixed evidence for an association between the corticotropin-releasing hormone receptor 1 gene (*CRHR1*) and alcohol-related phenotypes (Dahl et al., 2005; Treutlein et al., 2006).



Three studies have examined whether variation in the *CRHR1* gene moderates environmental risk for alcohol-related outcomes. In a German sample of 15-year-olds, Blomeyer and colleagues (2008) found that variation at one *CRHR1* SNP (rs1876831, C or T alleles) interacted with severe SLEs experienced during the past three years: adolescents with the CC genotype who experienced high rates of SLEs were approximately twice as likely to report lifetime heavy drinking and had twice the number of maximum drinks per drinking occasion compared to those with TT or CT genotypes and those with low SLEs regardless of genotype. There was no GxE with respect to current monthly drinking or average drinks per month. A similar pattern of GxE was observed four years later when participants were aged 19 (Schmid et al, 2010). The final study found that a *CRHR1* haplotype (chromosomal region) (including rs1876831) interacted with childhood sexual abuse (CSA), such that CSA was associated with greater alcohol consumption and AD only among adults who had two copies (i.e., were homozygous) of the haplotype that included the rs1876831 C allele (Nelson et al., 2010).

**Monoamine Oxidase A Gene**—The monoamine oxidase A gene (*MAOA*), located on the X-chromosome, encodes an enzyme that metabolizes monoamine neurotransmitters, including dopamine, norepinephrine, and serotonin (Shih & Thompson, 1999). The *MAOA* gene has a polymorphism in the promoter (regulatory) region (*MAOA-LPR*) that affects gene activity (Sabol, Hu, & Hamer, 1998). The low-activity variant has been implicated in increased sensitivity to environmental stressors (Meyer-Lindenberg et al., 2006).

Three studies have examined *MAOA*-related GxE with respect to drinking behaviors. Nilsson and colleagues studied two small samples of young adults from Sweden to investigate interactions among *MAOA* and psychosocial adversity (quality of family relations and childhood maltreatment) on alcohol-related problem behavior. Males with childhood maltreatment and the low-activity *MAOA* variant had more alcohol-related problems (median = 19.0) than males with the high-activity variant (median = 6.5), and males with no history of childhood maltreatment regardless of *MAOA* (low-activity, median = 3.0; high-activity, median = 1.5). There was no GxE associated with family relations (Nilsson et al., 2007). A different pattern of findings was observed for females, for whom psychosocial adversity was associated with a greater number of alcohol-related problems among females homozygous for the high-activity *MAOA* variant (median = 3.0), compared to carriers of the low-activity variant (median = 2.0) and those without exposure to psychosocial adversity (median = 2.0 and 0.0, respectively, among those homozygous for the high-activity variant and carriers of the low-activity variant) (Nilsson, Wargelius, Sjöberg, Leppert, & Orelund, 2008). In a sample of American Indian adult women, Ducci et al. (2008) found that CSA was associated with greater risk for AUDs (particularly antisocial AUDs) among women with two copies of the low-activity *MAOA* variant compared to those with one or two copies of the high-activity variant.

**Ankyrin Repeat and Kinase Domain Containing gene**—The Taq1 polymorphism of the Ankyrin Repeat and Kinase Domain Containing (*ANKK1*) gene (formally thought to be a polymorphism within the dopamine receptor D2 gene) has been widely investigated as a candidate gene for AUDs, but with conflicting and controversial results (Köhnke, 2008; Neville, Johnstone, & Walton, 2004).

Three studies have investigated whether the Taq1A polymorphism interacts with environmental factors to influence drinking outcomes. In a longitudinal study of adolescent drinking in the Netherlands, van der Zwaluw et al. (2010) found that parental permissiveness toward drinking interacted with Taq1 A1 genotype. For example, adolescents who reported high parental rule setting at one assessment had relatively low levels of alcohol use (< 1 drink in the prior week) one year later regardless of genotype. However, adolescents who

reported low levels of parental rule setting consumed significantly more alcohol at follow-up only if they had the A1 allele (5.5 drinks); those with the A2A2 genotype were similar to the high parental rule setting groups (1.5 drinks in past week).

In a Brazilian sample of alcoholic men (Bau, Almeida, & Hutz, 2000), there was significant GxE (explaining 6.6% of the variance in physiologic dependence symptoms), such that SLEs were associated with a greater number of physiological AD symptoms (but not other AD symptoms or antisocial personality symptoms) among those with the Taq A1 allele compared to those without an A1 allele. Lastly, in a sample of adult males of Mayan descent in Honduras, Madrid, MacMurray, Lee, Anderson, and Comings (2001) found an interaction between Taq1 genotype and level of occupational and economic stress on AA symptoms. Carriers of the A1 allele had a greater number of AA symptoms when exposed to increasing amounts of life stress (low stress = 0.6 – 2.5, moderate stress = 1.8 – 2.2, high stress = 4.8 – 7.0). There was little influence of level of stress on AA symptoms among A2 allele homozygotes (symptom range 2.9–3.7).

**GABA<sub>A</sub> Receptor Genes**—GABA, the body's major inhibitory neurotransmitter, is associated with the sedating effects of alcohol consumption and the development of alcohol tolerance (Hiller-Sturmhöfel & Swartzwelder, 2004). *GABRA2*, the gene that encodes one of the subunits of GABA<sub>A</sub> receptors, has been widely studied as a candidate gene for AUDs although there is inconsistency across studies as to which allele confers increased risk (Enoch, 2008).

Two studies have investigated whether environmental factors moderate the risk for AD associated with *GABRA2*. Using probands and control families from the COGA study, Dick, Agrawal, et al. (2006) found that proband carriers of the *GABRA2* SNP rs279871 T allele who also had a single stable marriage had substantially lower rates of AD (28%) than those with any other combination of genotype and marital status (41% to 56%). There was a similar non-significant GxE trend among COGA controls. It is noteworthy that a similar pattern of GxE was found in a subsequent study, in which the association between variation in *GABRA2* based on 10 SNPs (including rs279871) and trajectories of externalizing behavior from adolescence into young adulthood decreased with higher levels of parental monitoring (Dick et al., 2009b).

In a case-control study of 832 African American males, *GABRA2* haplotype and SNP variation was not found to interact with childhood trauma to predict AD (Enoch et al., 2010b). However, there was an interaction between childhood trauma and a potentially functional SNP rs11503014 associated with addiction vulnerability, particularly to cocaine.

**Alcohol Dehydrogenase and Aldehyde Dehydrogenase Genes**—Functional polymorphisms in the genes that code for the enzymes responsible for metabolizing alcohol and acetaldehyde (alcohol dehydrogenase (*ADH1B*) and aldehyde dehydrogenase (*ALDH2*)) are consistently associated with protection from AUDs (Li, 2000; Luczak, Glatt, & Wall, 2006). Alcohol consumed by individuals with *ALDH2*\*2 genotypes is metabolized to acetaldehyde, which accumulates in the body due to absent *ALDH2* enzyme activity and results in the very unpleasant flushing syndrome (Harada, Agrawal, & Goedde, 1981).

Three studies have investigated the moderating role of social context on the protective effects of the higher activity *ADH1B* allele (*ADH1B*\*2) and the inactive *ALDH2* allele (*ALDH2*\*2). Higuchi et al. (1994) assessed the role of *ALDH2*\*2 on AD risk based on clinical admissions data obtained between 1979 and 1992, a time period when socio-cultural shifts led to increases in per capita alcohol consumption in Japan. Results indicated that individuals with two copies of the inactive *ALDH2*\*2 allele were completely protected from

AD in all cohorts. However, individuals with one inactive and one active *ALDH2\*2* allele followed the cultural norm and increased their drinking dramatically over time, some even to the point of developing AD. The proportions of alcohol dependent individuals with one copy of the *ALDH2\*2* allele were: 2.5%, 8.0%, and 13.1%, respectively, in 1979, 1986, and 1992. Likewise, in a small sample of East Asian adolescents adopted into western homes, those with an *ALDH2\*2* allele were more likely to have consumed alcohol and gotten drunk if they had a sibling that did the same (Irons, McGue, Iacono, & Oetting, 2007), indicative of an environmental interaction with this genotype. There was no effect of adopted parent AUD; however, there was likely insufficient power to detect this effect given the small sample size. The final study investigated the interaction between *ADH1B\*2* and cultural factors on drinking in Israel among recent Russian Jewish immigrants, Ashkenazi Jews, and Sephardic Jews (Hasin et al., 2002). Overall, individuals with *ADH1B\*2* allele were less likely to drink heavily. However, the suppressive effects of *ADH1B\*2* on heavy drinking appeared to be qualitatively weakest among recent Russian immigrants, presumably due to their greater exposure to a heavy drinking culture.

### Summary of Molecular Genetic GxE Findings

Collectively, molecular genetic studies (Tables 3 and 4) provide some evidence for the two forms of alcohol-related GxE implicated in studies using aggregate measures of genotypic variation. First, consistent with a diathesis-stressor model, both distal and proximal stressors were more strongly associated with drinking among individuals with certain gene variants. Second, results indicated that more permissive socio-cultural factors may dampen the protection afforded by variation in alcohol metabolism genes that buffer against heavy drinking. For example, the decreasing protective effect of the *ALDH2\*2* allele over time in Japan co-occurred with socio-cultural changes associated with post-industrial urbanization, including more liberal attitudes toward drinking and decreasing alcohol prices (Higuchi, Matsushita, Maesato, & Osaki, 2007; Takano, Nakamura, & Watanabe, 1996). Such results highlight the possibility that macro changes in alcohol-related economic and public policies (e.g., availability, advertising, and social norms) may protect against AUDs among individuals with genetic liability *and* among those with genotypes that provide protection from heavy drinking.

Overall, 17 of the 20 published GxE reports we located in the molecular genetics literature found at least one significant GxE, whereas 15 reported one or more non-significant GxE (Table 4). The substantial heterogeneity among samples, ascertainment strategies, environmental factors and drinking outcomes and the inconsistent patterns of results leave many questions about the neurobiological and behavioral consequences of GxE unanswered. Of studies that identified GxE, there were consistent findings regarding which genotype is associated with alcohol-related outcomes in response to environmental factors for *CRHR1*, *ANKK1*, and alcohol metabolizing genes, but conflicting findings for *5-HTTLPR* and *MAOA*. While it is reasonable that GxE varies with development or stressor severity, there are too few studies on the same genes (aside from *5-HTTLPR*) to assess whether sample characteristics and methodological factors are systematically related to GxE findings. When considering results in light of these wide-ranging inconsistencies, findings generally do not constitute replication and may overstate the true GxE effect size.

We evaluated whether variation in sample characteristics (age, gender, nationality), and methodological features (study design, variation in predictors and outcomes) covaried systematically with *5-HTTLPR* genotype GxE findings. Negative findings appeared to loosely correspond to sample size, participant age, quality of stress assessment and severity of drinking outcomes. While the four studies that used younger subjects, smaller samples, and broader measures of drinking behaviors found significant GxE (Covault et al., 2007; Kaufman et al., 2007; Nilsson et al., 2005; Laucht et al., 2009) two studies with older

subjects, larger samples, limited measures of SLEs, and more severe alcohol-related outcomes did not find evidence for GxE (Dick et al., 2007b; Du & Wan, 2009). While this may indicate that GxE decreases over the course of development or across stages of alcohol consumption, inconsistency in evidence for GxE may simply result from poorer measurement quality of stressors in studies with larger samples sizes. Few researchers tested whether males and females differed in alcohol-related GxE, and results were inconsistent across studies (Table 3).

Given high rates of co-occurring major depression and AUDs (Swendsen & Merikangas, 2000) and evidence that *5-HTTLPR* genotype predicts vulnerability to the development of depression following stress exposure (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), it is noteworthy that only one study considered participants' neuroticism and depression symptoms in the alcohol-related GxE analyses (Covault et al., 2007). If positive GxE results are mediated by an interaction between *5-HTTLPR* genotype and stress on depression risk, inconsistent findings may result from differing levels of comorbid depression across samples. Interestingly, of the two studies that found no evidence for GxE, one excluded participants who met the criteria for major depression (Du & Wan, 2009) and the other found GxE associated with major depression and not AD (Dick et al., 2007b).

It is provocative that several studies found that groups with genetic risk alleles who drank more than others in response to stressors actually drank less than others in the absence of stressors (e.g., Ducci et al., 2008; Kaufman et al., 2007; Madrid et al., 2001; Schmid et al., 2010). Such results suggest that certain genetic "risk" alleles may also buffer against risk for drinking when stress is not present, potentially contributing to the lack of evidence for genotype-drinking associations. Future studies that incorporate the full range of the environmental spectrum are needed to investigate whether the effects of alleles that have been implicated in alcohol-related GxE studies are directional or increase variability in response to the environment (Belsky & Pleuss, 2009).

### **Integrating aggregate genotype studies with molecular genetic approaches**

This article unifies diverse theoretical and empirical approaches, providing a comprehensive review of published research on alcohol-related GxE. There are two main differences in how GxE have been investigated and conceptualized across the twin, adoption and molecular genetic literature. First, efforts to identify alcohol-related GxE have been relatively more recent for measured gene studies. Second, twin researchers utilized measures of the permissiveness or restrictiveness of socio-cultural environmental factors and described GxE as environmental moderation of genetic influences, whereas molecular genetic studies typically utilized environmental measures of adversity and framed GxE as genetic moderation of environmental influences. Though these interpretations are statistically identical, they may be indicative of the differing ways in which twin and molecular genetics researchers have ascertained their samples and conceptualized models of GxE. Compared to molecular genetic studies, twin studies are typically more epidemiologically based with larger samples and a broader range of general environments. To the degree that molecular genetics studies have used clinical populations, this may shape the use of environmental adversity versus measures of environmental constraints. Given that classical genotype studies can be used to guide the selection of environmental factors in molecular genetic studies, future molecular genetic investigations of GxE should be informed by the measures of environmental constraints implicated in older studies (Moffitt et al., 2005).

There are also several important similarities across inferred and measured genotype studies of alcohol-related GxE. Consistent with GxE findings for antisocial behaviors (Moffitt, 2005), it is noteworthy that both the aggregate genotype *and* molecular genetic studies we

reviewed frequently found positive GxE findings in the absence of main effects. There are a number of potential explanations for the lack of main effects. First, greater heritability or genotypic effects on drinking problems are not necessarily equivalent to higher mean levels of drinking problems, only more variability: certain environments may provide more diverse options and opportunities for individuals to show their genetic predispositions. For example, some adolescents may respond to the greater diversity of social opportunities in urban settings by consuming *less* alcohol. Second, the estimated main effect of genes on drinking behaviors may be weak if the genetic effect is manifest only among individuals exposed to a particular type of environmental risk. Similarly, environmental influences may not be detected if the environmental factor only confers risk among individuals with genetic liability. Third, because there is often greater power to detect GxE in the absence of main effects (Kraft & Hunter, 2005), studies with environmental main effects may have been underpowered to detect GxE, and therefore have been less likely to appear in the published literature.

Both molecular and inferred genotype studies provide preliminary evidence that GxE differentially influence drinking over the course of development. Although the timing of age at first drink is largely influenced by environmental influences shared by siblings (Hopfer, Crowley, & Hewitt, 2003), genetic factors explain an increasingly greater proportion of individual differences in drinking as adolescents age (Bergen, Gardner, & Kendler, 2007; Rose & Dick, 2004). Some evidence using retrospective reports of adolescent environmental exposures indicates that alcohol-related GxE show stronger effects on drinking between ages 12–17, and more limited effects after age 17 (Kendler et al., in press). Likewise, studies of *5-HTTLPR* genotype indicated that GxE effects were limited to adolescents and young adults, consistent with greater plasticity of genetic influences on drinking at earlier developmental stages (Table 4). Given evidence that early life stress can modulate the capacity to cope with later stress (e.g., by altering genetically influenced components of the HPA axis) and cause changes in the expression of genes that modulate the pleasurable effects of alcohol (Clarke et al., 2008; Enoch, 2011; Spanagel, 2009), it is possible that alcohol-related GxE at later ages are mediated through genetically influenced vulnerability to the pathogenic effects of early life stressors (i.e., GxE<sub>E</sub>). Detailed longitudinal analyses of clearly operationalized distal and proximal environmental risk factors associated with both the onset and course of drinking and AUDs are needed for a more thorough understanding of cumulative and persistent nature of alcohol-related GxE across development (Caspi et al., 2010; Sher et al., 2010).

Additionally, emerging evidence from inferred genotype and molecular genetic studies indicate that with a few exceptions (e.g., genes influencing alcohol metabolism), environmental moderation of genetic risk among adolescents may occur via impact on broadly defined risk rather than genetic influences specific to drinking behaviors. For example, neighborhood factors were found to moderate genetic and environmental risk for behavior problems among 14-year-olds in a manner paralleling the GxE reported for alcohol consumption among young adults (Dick et al., 2009a). Likewise, similar patterns of GxE were found across alcohol-related phenotypes and rule-breaking/externalizing behaviors (e.g., Dick et al., 2009b; Legrand et al., 2008) and other substance use disorders (e.g., Covault et al., 2007; Harden et al., 2008) among adolescent samples. Finally, a recent report suggested more pronounced alcohol-related GxE associated with genetic risk for non-specific externalizing disorders than genetic risk specific to AUDs in early and mid-adolescence (Kendler et al., in press). These results are consistent with the notion that AUDs develop as the result of a genetically influenced, externalizing pathway (Krueger et al., 2002; McGue, Iacono, Legrand, Malone, & Elkins, 2001), and indicate that susceptibility to environmental influences in adolescence may be more of a trait-like characteristic that affects risk for a range of psychopathology (GxE pleiotropy) (Belsky & Pluess, 2009; Uher

& McGuffin, 2008). Continued investigation of alcohol-related GxE has the potential to both clarify the specificity of alcohol-related GxE and inform nosological classifications.

## Limitations of the current literature and directions for future research

The judicious addition of GxE research to the behavior genetics armamentarium has the potential to improve understanding of the etiology of problematic alcohol consumption and AUDs. However, this area of research is relatively new and constrained by various methodological and conceptual limitations. A number of researchers have elegantly reviewed these limitations as they relate to the study of GxE across a broad range of phenotypes (Eaves, 2006; Uher, 2008; Wong, Day, Chan, & Wareman, 2003). We focus our discussion on conceptual and methodological limitations as they relate to GxE on alcohol consumption and AUDs and provide recommendations to aid future research.

## Selection and Measurement of Environmental Risk Factors and Drinking Outcomes

Selection of environmental risk factors and alcohol-related outcomes is challenging and marked by methodological limitations. Inconsistent and ad hoc approaches for measuring environmental risk decreased the sensitivity of alcohol-related GxE studies to detect interaction effects and complicated efforts to synthesize results. Additionally, measurement of alcohol-related outcomes was quite varied (e.g., alcohol initiation, drinking quantity/frequency, intoxication frequency, AUDs), and may have contributed to inconsistent evidence for GxE. Many alcohol-related GxE studies collected information on environmental exposures and drinking outcomes at the same measurement occasion, raising concerns about the causal nature of environmental risk factors and drinking outcomes. Several of the “environmental” measures in the reviewed studies, such as SLEs or parental rules about drinking, are arguably the *consequence* of an individual’s (or his or her parents’) drinking, rather than a contributing factor, limiting the interpretation of GxE.

Environmental risk factors and drinking outcomes were typically examined using the same type of assessment instrument (e.g., self-report questionnaire or interview), and some of the observed covariance may be attributable to method variance rather than covariance of the underlying constructs. This is particularly problematic given the evidence that heritability estimates can vary with assessment method (MacGregor, Cornes, Martin, & Visscher, 2006). Researchers can increase validity and statistical power by more accurately measuring the timing of environmental exposures and drinking behaviors using multiple assessment methods or multiple informants, mindful of the direction of effects.

## Selection of Genetic Risk Factors

A large number of genes have been studied as candidates for AD risk and the list is rapidly expanding with results from high-density marker arrays (e.g., genome-wide association studies). However, in the studies we reviewed, researchers typically utilized genes that were available in their existing datasets (e.g., the serotonin transporter gene) rather than selecting genes based on hypotheses of biological plausibility (e.g., genes influencing metabolism). The effects of a particular gene may be contingent on other genes (i.e., epistasis) (Enoch et al., 2010a; Huang et al., 2007; Lee et al., 2009; Skowronek et al., 2006), and it is interesting to consider whether unmeasured genes moderate the GxE processes that have been identified with respect to drinking behaviors (i.e., GxGxE). Unfortunately, most studies were underpowered to test for three-way interactions as evidence for epistasis.

Perhaps especially worthy of consideration is the need to conduct alcohol-related GxE studies using endophenotypes (Gottesman & Gould, 2003) or intermediate phenotypes,

measures that are closer to the pathophysiology of alcohol dependence than clinical diagnoses or consumption measures (e.g., alcohol-metabolizing enzymes, electroencephalographic markers, and event-related potentials) (Gunzerath & Goldman, 2003; Schuckit, 2000; Sher et al., 2010). Inclusion of such measures in alcohol-related GxE studies will supplement the use self-report measures of drinking behaviors and connect genetic variation to behavioral variation (e.g., Hutchison et al., 2008; Filbey et al., 2008), allowing for better selection of genes and environments based on biological plausibility.

### Type I Error

Approximately three-quarters of the alcohol-related GxE studies did not detect one or more GxE effects that they reported testing, and it is likely that some unknown proportion of published results represent false positives (Type I error). In many published reports it is unclear how many different combinations of genotypes, environmental risk factors, and outcomes have been analyzed without correcting for multiple testing. Additionally, statistical interactions are sensitive to scaling: different measurement scales can give different answers and non-linear transformations can eliminate (or create) evidence for GxE (Eaves, 2006). This is particularly problematic for alcohol-related GxE studies given the large number of potential interactions tested, lack of sufficient information on why variables were scaled certain ways, and the ensuing high probability of false positives.

A related concern is that studies that produce negative evidence of GxE are less likely to be submitted and published, resulting in the well-known publication bias of larger effect sizes and overestimation of evidence for alcohol-related GxE (Flint & Munafó, 2008). The likelihood of spurious GxE can be reduced by: i) investigating whether a monotone transformation (i.e., taking the logarithm or square root of G or E) removes the interaction (Dempfle et al., 2008; Moffitt, Caspi & Rutter, 2005), ii) differentiating between a priori and exploratory hypotheses and accurately reporting the number of statistical tests conducted and the effect sizes of all GxE tested (including non-significant tests for all environments, genotypes, and alcohol-related outcomes) (Dempfle et al., 2008; Sullivan, 2007), iii) reporting descriptive statistics separately by genotype (Moffitt, Caspi & Rutter, 2005; Uher & McGuffin, 2008), iv) replicating studies with different samples and in other settings (Moffitt, Caspi, & Rutter, 2005), and v) including nonreplications in meta-analyses.

### Statistical Power

Studies attempting to identify main effects of measured genes are limited by low statistical power, and this is even more of a concern in studies of GxE (Kraft & Hunter, 2005). In twin models, there is significantly less power to detect moderation of genetic or common environmental influences than moderation of individual specific environmental effects, and studies are likely underpowered to detect moderation of raw genetic variance when GxE effect sizes are small (Neale, Eaves, & Kendler, 1994). Power to detect GxE in a molecular genetic study depends on a variety of factors, including genotype frequencies, frequency of exposure to the environmental factor, magnitude of the interaction effect, whether the dependent variable is categorical or continuous, and the amount of measurement error (Wong et al., 2003). An adequately powered molecular genetic GxE study with a binary outcome (e.g., AUD diagnosis) might require several thousand cases and controls. Measurement error is particularly noteworthy, as many studies of alcohol-related GxE relied on retrospective self-reports of environmental factors and drinking outcomes. Ways to reduce measurement error in GxE models include using repeated measures, longitudinal measurement, and latent variable models (McArdle & Prescott, 2010).

Issues of statistical power are even more limiting when considering GxE effects separately by subgroups. For example, molecular genetic GxE studies typically included gender as a

covariate to adjust for differences in prevalence of risk factors or outcomes, but did not have power to test whether genders varied in GxE. If males and females differ in their exposure to environments that promote AUD risk, or in their genotypic sensitivity to environmental factors, GxE will contribute to gender differences in AUD risk. Given the large literatures on sex differences in cultural influences (Nolen-Hoeksema & Hilt, 2006) and physiological consequences of drinking (Mancinelli, Vitali, & Ceccanti, 2009) there are good reasons to think genetic factors may work differently in women, underscoring the importance of having sufficient sample sizes to study GxE separately by gender as well as race (Prescott et al., 2005). On the other hand, it is important to also note that post hoc exploratory analyses, including dividing samples into subgroups (e.g., gender), greatly increase the likelihood of false positives and non-replications (Flint & Munafó, 2008).

### Presentation of Twin Model Results

Another issue concerns interpretation of results from twin models that found evidence for alcohol-related GxE on the basis of a reduction in standardized variance proportions. The heritability estimate (proportion of total variance due to genetic influences) can differ across environments even when the genetic estimate (actual variance in raw units) is constant (see Visscher, Hill, & Wray, 2008). Accordingly, an interaction may incorrectly be concluded when results are presented in standardized form. Consider, for example, a twin study of drinking quantity that stratifies participants on levels of presumed stressful life event (SLE) exposure and finds the MZ:DZ ratio is similar but the groups have increasing variability across level of SLE. If the results are standardized, this will appear as a decrease in heritability across increasing levels of SLE exposure (i.e., genetic variance accounts for a smaller proportion of the variation for the higher SLE groups). Thus this ExE effect (latent E x SLE) would be erroneously interpreted as GxE (heritability x SLE). Only four of the 12 twin studies reviewed provided estimates in both standardized and unstandardized formats (Table 1). Studies of GxE using inferred measures of genotypic variance should report unstandardized moderated twin results and explicitly differentiate whether GxE is due to differences in the actual variance versus the proportion of total variance attributable to genetic influences.

### Gene-Environment Correlation

As is true of all statistical interactions, GxE are most easily detected under circumstances where the interaction term and genetic and environmental main effects are not correlated (Cohen, Cohen, West, & Aiken, 2003). When genetic factors influence exposure to risk or protective environments, a gene-environment correlation (rGE) is created (Plomin, DeFries, & Loehlin, 1977). This is particularly relevant for alcohol research because parents who are heavy drinkers often create environments that increase risk for problematic alcohol consumption by their children (e.g., due to poor parenting style, marital dissolution, or economic hardship). Although results from extended pedigree studies suggest that rGE contributes a minimal amount of variance to drinking (Eaves et al., 1989), even a small rGE has the potential to influence conclusions about GxE (Albert, Ratnasinghe, Tangrea, & Wacholder, 2001; Liu, Fallin, & Kao, 2004).

Confounding of GxE with rGE is of greatest concern in studies using inferred measures of genotypic variance, although certain twin models allow for the measurement and adjustment of rGE (Purcell, 2002). When genotypes and environments are both measured, as in molecular genetic GxE studies, estimates of rGE can be incorporated directly into analyses of GxE. Unfortunately, studies we reviewed inconsistently tested for rGE, and rarely considered the possible implications of interpreting GxE in the context of rGE. Studies that found significant GxE after directly adjusting for rGE provide greater confidence that the genetic factors that influence environmental exposure do not *entirely* account for the



observed GxE findings (Tables 1 and 3), although it is still possible that unmeasured third variables account for covariation between genotypic and environmental risk.

## Conclusion

Drinking behaviors develop within a complex matrix of social, behavioral, epigenetic, and genetic influences. Contemporary GxE studies have moved alcohol research beyond a focus on *direct* genetic and environmental effects to address *variability* in drinking among individuals with the same genetic or environmental risk factors. Since 2005, a rapidly expanding literature has tested whether socio-cultural context and environmental adversity moderate genetic risk for drinking behaviors. However, at present, our understanding of the specific mechanisms by which genetic and environmental moderators promote risk and resilience in development and course of drinking behaviors remains limited. There are many issues regarding the development of drinking behaviors and AUDs – they are heterogeneous between persons and over time, and there are important clinical features such as age at drinking onset, co-occurring psychopathology, and use of other substances that are related to symptom course, but have rarely been examined within a GxE framework. Perhaps this is because statistical power is challenged in typical circumstances, and power may be untenable if these complexities are modeled. Further, it is often unclear how to conceptualize such features – do they reflect genetic vulnerability, environmental risk or a mixture? While it seems unlikely that genetic effects on drinking behaviors are independent of environmental context, or likewise that environmental causes of drinking are unaffected by genotype, the presence of significant methodological limitations and lack of unambiguous replications in this literature make it difficult to draw definitive conclusions regarding the nature and effect size of alcohol-related GxE. Continued rigorous study and replication of alcohol-related GxE is needed to clarify inconsistent genotype-AUD association studies and to identify the mechanisms by which genes and environmental factors combine to influence the development of drinking behaviors.

### Research Highlights

- This review synthesizes evidence from adoption, twin and molecular genetic studies of gene-environment interactions.
- Some studies reviewed provide evidence that socio-cultural context and adversity moderate genetic influences on drinking behaviors.
- Methodological limitations limit knowledge of the nature and effect size of these interactions.
- Recommendations to aid future investigations of alcohol-related gene-environment interactions are provided.

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Table 1

Gene-Environment Interactions Using Measures of Inferred Genotypic Variance (N=16)

First Author Year	Population	Subjects <sup>a</sup>	Mean age (SD) R	Alcohol-Related Outcome	Environment Main Effect	Covariates	rGE	GxE
<i>Twin Studies</i>								
Heath et al., 1989	Australia	1047 MZF 643 DZF	35.7 (14.3)	Past week # drinks	Marital status nr	Twin social contact; Stratified by age cohort	No	A ↑ E ↓ for unmarried <sup>b</sup>
Agrawal et al., 2009	Australia	698 MZF 513 DZF 494 MZM 395 DZM 661 DZO 736 single twins	30 (2.5) R: 24–36	Lifetime DSM-IV AD sx	Age at first drink –	Gender dif tested	Yes; Adjusted	A ↑ E ↓ w/ younger first drink <sup>b,c</sup> ; moderation A (M=F) moderation E (M≠F)
Dick et al., 2001	Finland <i>Finn Twin Study</i>	462 MZF 392 DZF 327 MZM 399 DZM	18.5	Past month drinking freq	% Young adults + Migration ns Alc sales +	Gender dif tested	nr	A ↑ C ↓ w/ ↑ young adults & ↑ migration (M = F) <sup>b</sup> ; C ↓ w/ ↑ alc sales (M≠F) <sup>b</sup>
Rose et al., 2001	Finland <i>Finn Twin Study</i>	357 MZF 298 DZF 194 MZM 252 DZM	T1=16 T2=17 T3=18.5	Current drinking freq	Rural/urban residency ns	None	nr	A ↑ C ↓ in urban settings across time points <sup>b</sup>
Dick et al., 2007a	Finland <i>Finn Twin Study</i>	749 DZM 700 DZF 692 MZM 777 DZM	T1=14.1 T2=17.6	Current: (1) T1 drinking freq (2) T2 drinking freq	T1: Parental monitoring & time spent w/ parents – for (1) & (2) T2: # of alc-using peers + for (2)	None	Adjusted	(1) Parental monitoring & time w/ parents ns; (2) A ↑ E ↓ C ↓ w/ ↑ alc-using peers <sup>b</sup> ; parental monitoring & time w/ parents ns
Dick et al., 2009a	Finland <i>Finn Twin Study</i>	373 MZF 341 DZF 340 MZM 378 DZM	14.1 (0.1)	Current drinking freq	F: Urban residency + % Young adults + % Migration + M: All ns	Gender dif tested	Adjusted	All GxE ns <sup>b,c</sup> ; E ↓ w/ ↑ % young adults (F only)
Koopmans et al., 1999	Netherlands	457 MZF 356 DZF 327 MZM 238 DZM 543 DZO	17.8 (3.1) R: 12–26	Drinking initiation	Religious upbringing (yes/no) ns	Gender dif tested	nr	F: A ↑ C ↓ E ↓ w/ religious upbringing <sup>b,c</sup> M: all ns
Harden et al., 2008	United States <i>Add Health</i>	833 F <sup>d</sup> 803 M <sup>d</sup>	16.1 (1.7) R: 11–21	Past yr SU freq (drinking, smoking, intoxication)	Same-sex best friend past yr SU freq (drinking, smoking, intoxication) +	Age; Gender dif tested	Yes; Adjusted	SU freq ↑ among those w/ ↑ G liability and ↑ best friend SU <sup>c</sup>
Guo et al., 2009	United States <i>Add Health</i>	127 MZF/M 101 DZF/M 372 sib pairs	16	Past yr drinking freq	Sib concordance (high, low, discordant) for friend past yr drinking freq +	None	nr	Drinking freq only heritable among pairs concordant for friends w/ high drinking freq <sup>c</sup>

First Author Year	Population	Subjects <sup>a</sup>	Mean age (SD) R	Alcohol-Related Outcome	Environment Main Effect	Covariates	rGE	GxE
Legrand et al., 2008	United States <i>Minnesota Twin &amp; Family Study</i>	213 MZF 114 DZF 184 MZM 97 DZM	17.5 R: 16–18	Alc problems <sup>e</sup>	Rural/urban residency ns	Gender dif tested	nr	F: all ns M: A ↑ C ↓ in urban settings <sup>b,c</sup>
Miles et al., 2005	United States <i>VTSABD</i>	386 MZF 185 DZF	14.5 (2.3) R: 8–16	Drinking initiation	Family envf: (1) Parent closeness ns (2) Leadership nr (3) Discipline nr (4) Dependence nr (5) Decision-making nr	Age: (1) to (5) & all GxE in initial model	nr	A ↑ E ↓ w/ ↓ parental closeness <sup>b</sup> , ns for (2) to (5)
Kendler et al., in press	United States <i>VATSPSUD</i>	469 MZM 287 DZM 290 single twins	40.3 (9.0) R: 24–62	Average monthly alc consumption	Retrospective report of adolescent env exposures: (1) Alc availability + (2) ↓ Attend church + (3) ↑ Peer deviance + (4) ↓ Prosocial activity + (5) ↓ Parental bonding + (6) ↓ Parent monitor +	Analyses stratified by age cohort	Not tested	Age 12–14 <sup>b</sup> : (1)(3)(4) + ↑ G risk for AUD, (1)(3)(4)(6) + ↑ G risk for ext disorder; Other moderators ns; Age 15–17 <sup>b</sup> : (1)(3) + ↑ G risk for AUD, (1)(3)(4) + ↑ G risk for ext disorder; Other moderators ns Age 18–21 & 22–25 <sup>b</sup> : all ns
<b>Adoption Studies</b>								
Bohman et al., 1981	Sweden <i>Stockholm Adoption Study</i>	913 F	R: 23–43	Lifetime alcoholism	Postnatal env risk <sup>g</sup> +	None	Yes	G risk x env ns
Cloninger et al., 1981	Sweden <i>Stockholm Adoption Study</i>	862 M	R: 23–43	Lifetime alcoholism (1) Type I mild (2) Type I medium (3) Type I severe (4) Type II	Postnatal env risk <sup>g</sup> +	None	Yes	G risk x env + for (1) & (3) G risk x env ns for (2) & (4)
Sigvardsson et al., 1996	Sweden Gothenburg	577 M	R: 28–47	Lifetime alcoholism (1) Type I mild (2) Type I severe (3) Type II alc	Postnatal env risk <sup>g</sup> +	None	Yes	G risk x env ns for (1) & (3) G risk x env + for (2)
Cutrona et al., 1994	United States Iowa	140 F 160 M	R: 18–40	Lifetime DSM-III AUD	Adoptive Family (1) AUD: ns (2) Conflict: ns (3) Cohesion: ns M, – F (4) Psychopathology: ns (5) Parent loss: ns	Gender dif tested; (1) to (5) & all GxE in model	Yes	M: (1) to (5) all ns F: (2) associated w/ ↑ AUD among those w/ G risk, (1)(3)(4)(5) all ns

Notes. Results are listed separately for twin and adoption studies and organized chronologically in alphabetical order by study population; SD = standard deviation; R = range; rGE = gene-environment correlation; GxE = gene-environment interaction; MZF = monozygotic female twin pairs; DZF = dizygotic female twin pairs; MZM = monozygotic male twin pairs; DZM = dizygotic male twin pairs; DZO = opposite sex twin pairs; + = significant positive association with alcohol-related outcome (p<0.05); – = significant negative association with alcohol-related outcome (p<0.05); nr = not reported; ns = not significant; A = additive genetic, C = common environment, E = individual-specific environment; ↑ = greater; ↓ = lower; M = male; F = female; Alc = alcohol; w/ = with; G = genetic; env = environmental; dif = differences; AUD = alcohol use disorder; = alcohol dependence; SU = substance use; Ext. = externalizing; freq = frequency; T1 = time one, T2 = time two, T3 = time three; yt = year; sib = sibling; Add Health = National Longitudinal Study of Adolescent Health; VTSABD = Virginia Twin Study of Adolescent Behavioral Development; VATSPSUD = Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.

- <sup>a</sup>Twin study subject numbers refer to complete twin pairs.
- <sup>b</sup>Standardized estimates reported.
- <sup>c</sup>Unstandardized estimates reported.
- <sup>d</sup>Number includes pairs of MZ and DZ twins, full siblings, half siblings, cousins.
- <sup>e</sup>DSM-III-R alcohol dependence symptoms and nine items assessing non-criterion behaviors (Krueger et al, 2004).
- <sup>f</sup>Assessed using the Family Adaptability and Cohesion Evaluation Scale (Olson et al., 1979).
- <sup>g</sup>Including placement experience, adoptive home environment, adoptive father occupation.

**Table 2**  
 Summary of Findings from Alcohol-Related GxE Studies Using Inferred Measures of Genotypic Variance.

<u>Alcohol-Related Outcomes</u>	<u>Environmental Factors</u>				
	<u>Region of residence/Alcohol availability</u>	<u>Family factors</u>	<u>Prosocial activities<sup>a</sup></u>	<u>Peers</u>	<u>Early first drink</u>
Alcohol initiation	<u>Significant Result</u>				
	Koopmans et al., 1999				
	<u>Non-Significant Result</u>				
	Koopmans et al., 1999				
Adolescent and young adult alcohol consumption	<u>Significant Result</u>	<u>Significant Result</u>	<u>Significant Result</u>	<u>Significant Result</u>	<u>Significant Result</u>
	Rose et al., 2001	Miles et al., 2005	Kendler et al., in press	Dick et al., 2007a	Dick et al., 2007a
	Dick et al., 2001	Kendler et al., in press		Harden et al., 2008	Harden et al., 2008
	Legrand et al., 2008			Guo et al., 2009	Guo et al., 2009
	Kendler et al., in press			Kendler et al., in press	Kendler et al., in press
		<u>Non-Significant Result</u>			
		Miles et al., 2005			
	<u>Non-Significant Result</u>	Dick et al., 2001			
	Legrand et al., 2008	Kendler et al., in press			
	Dick et al., 2009a				
Adult alcohol consumption	<u>Non-Significant Result</u>	<u>Significant Result</u>		<u>Non-Significant Result</u>	<u>Significant Result</u>
	Kendler et al., in press	Heath et al., 1989		Kendler et al., in press	Agrawal et al., 2009
Adult alcohol use disorder		<u>Significant Result</u>			
		Cloninger et al., 1981			
		Cutrona et al., 1994			
		Sigvardsson et al., 1996			
		<u>Non-Significant Result</u>			
		Bohman et al., 1981			
		Cloninger et al., 1981			
	Cutrona et al., 1994				

Alcohol-Related Outcomes	Environmental Factors			
	Region of residence/ Alcohol availability	Family factors	Prosocial activities <sup>a</sup>	Peers
				Early first drink

Sigvardsson et al., 1996

Notes. Significant result refers to  $\geq 1$  significant GxG ( $p < 0.05$ ); Non-Significant Result refers to  $\geq 1$  non-significant GxG.

<sup>a</sup>Includes religious involvement, organized sports, community & school activities.

Table 3

Studies of Gene-Environment Interactions Using Measured Genotypes (N=20)

First Author (Year)	Population	Subjects	Mean age (SD) R	Alcohol-Related Outcome	Environment Main Effect	Genetic Main Effect	Covariates	rGE	GxE
Covault et al., 2007	United States	136 M 159 F	T1: 18.7 (0.8)	30-day survey of daily: (1) Drinking freq (2) Binge freq Measured at T1 & T2 <sup>a</sup>	Past yr SLEs <sup>b</sup> T1: ns T2: ns	5-HTTLPR SS (vs. LL) T1: ns for (1) & (2) T2: + for (1) & (2)	Gender dif tested; depression; excitement seeking, neuroticism	T1: No T2: SS – SLEs	T1: SLEs x SS (vs. LL) + for (1) (F only), ns for (2) T2: SLEs x SS (vs. LL) + for (1) & (2) 5-HTTLPR x SLEs ns
Diek et al., 2007 <sup>b</sup>	United States COGA Study	882 AD 1031 non-AD; M & F	Nr	Lifetime AD <sup>c</sup>	≥ 1 past-year SLEs <sup>d</sup> (versus none) nr	5-HTTLPR ns	None	nr	5-HTTLPR x SLEs ns
Du & Wan, 2009	United States Mexican-American	69 F AUD 296 M AUD 338 control	Median: 37	AUD severity <sup>e</sup>	Current marital status ns; Ed –	5-HTTLPR ns; OPRM1 118 AA genotype +; DRD2 -141 C Ins/Ins genotype +	Age, gender, smoking status	nr	OPRM1 118 AA x ed +; all other GxE ns
Kaufman et al., 2007	United States SAFE Homes Program	44 F maltx <sup>f</sup> 32 M maltx <sup>f</sup> 51 control	12.5 (2.3) R: 8–16.5	(1) Drinking initiation (2) Intoxication (yes/no)	Childhood maltx + for (1) & (2)	5-HTTLPR LS + for (1), ns for (2)	Age, gender, APS, family hx of SUD	No	5-HTTLPR LS x maltx + for (1), ns for (2)
Laucht et al., 2009	Germany Mannheim Study of Children at Risk	142 M 167 F	19	Past 45-day <sup>g</sup> (1) # Drinks (2) Binge drinking	Early family adversity <sup>h</sup> ns; Current SLEs <sup>i</sup> + for (1) & (2)	5-HTTLPR ns for (1) & (2)	Gender dif tested	No	5-HTTLPR LL x early adversity ns for (1), + for (2); 5-HTTLPR LL x SLEs + for (1) & (2) (M only)
Nilsson et al., 2005	Sweden SALVe	81 M 119 F	16 & 19	(1) Alc consumed/yr (2) High intoxication freq	Poor/neutral family relations (versus good) + for (1) & (2)	5-HTTLPR LS + for (1) & (2)	None	nr	5-HTTLPR LS x poor/neutral family relations + for (1) & (2)
Blomeyer et al., 2008	Germany Mannheim Study of Children at Risk	135 M 145 F	15	(1) Current drinking <sup>j</sup> (2) Lifetime heavy drinking <sup>j</sup> (3) Mean drinks/monthly <sup>j</sup> (4) Max drinks/occasion <sup>j</sup>	Past 3 yr SLEs <sup>j</sup> ns for (1) & (3) + for (2) & (4)	CRHR1 rs242938 GG + for (2), ns for (1) (3) (4); rs/1876831 CC + for (1) to (4)	Gender	No	rs242938 x SLEs all ns; rs1876831 CC x SLEs + for (2) & (4), ns for (1) & (3)
Nelson et al., 2010	Australia NAG Project	563 M 565 F	M: 43.1 (9.4) F: 41.0 (8.6)	(1) Alc consumption <sup>k</sup> (2) DSM-IV AD	CSA + for (1) & (2)	H2 haplotype ns for (1) & (2)	Gender	nr	H2 haplotype x CSA – for (1) & (2)

First Author (Year)	Population	Subjects	Mean age (SD) R	Alcohol-Related Outcome	Environment Main Effect	Genetic Main Effect	Covariates	rGE	GxE
Schmid et al., 2010	Germany <i>Mannheim Study of Children at Risk</i>	125 M 145 F	19	(1) Age at first drink (2) # Drinks <sup>g</sup> (3) Max drinks/occasions <sup>g</sup> (4) # Drinking days <sup>g</sup> (5) Binge days <sup>g</sup>	Early SLEs <sup>h</sup> ns for (1); Adolescent SLEs <sup>i</sup> + for (2), (3), (5) ns for (4)	<i>CRHR1</i> rs1876831 CC – for (1); all other ns; <i>CRHR1</i> rs242938 all ns	Gender, age alc initiation, psychosocial risk factors, ext sx, parents' lifetime AUD	No	rs1876831 CC x early SLEs – for (1); rs1876831 CC x adolescent SLEs + for (2); rs242938 A allele x adolescent SLEs + for (2) & (5); All other ns <i>MAOA</i> low activity allele homozygotes x CSA ns for (1), + for (2)
Ducci et al., 2008	United States Southwest American Indian tribe	168 F AD 123 F control	37.8 (14.6)	(1) DSM-III-R AD (2) DSM-III-R AD w/ ASPD	CSA <sup>h</sup> nr	<i>MAOA</i> low activity allele ns for (1), + for (2)	None	No	<i>MAOA</i> low activity allele homozygotes x CSA ns for (1), + for (2)
Nilsson et al., 2007	Sweden <i>SALVe</i>	66 M	T1: 16 & 19 T2: 19 & 22	Past-yr alc problems	Maltx <sup>l</sup> + Poor/neutral family relations <sup>l</sup> +	<i>MAOA</i> low activity allele ns	None	No	Parametric tests: GxE ns Nonparametric tests: <i>MAOA</i> low activity allele x maltx +; <i>MAOA</i> x family relations ns
Nilsson et al., 2008	Sweden <i>SALVe</i>	114 F	T1: 16 & 19 T2: 19 & 22	Past yr: (1) Alc problems (2) Risk consumption <sup>m</sup>	Maltx <sup>l</sup> ns for (1) & (2); Poor/neutral family relations <sup>l</sup> (vs. good) + for (1) & (2)	<i>MAOA</i> low activity allele – for (1); ns for (2)	None	Maltx + <i>MAOA</i> hetero zygotes	<i>MAOA</i> high activity allele homozygotes x maltx + for (1), ns for (2); <i>MAOA</i> high activity allele homozygotes x poor/neutral family relations + for (1) & (2)
Bau et al., 2000	Brazil	115 M AD 114 control	41 R: 20–63	(1) Physiological AD sx (2) Other AD sx	Past yr SLEs <sup>n</sup> ns for (1), nr for (2)	ANKKK1 A1 allele + for (1), nr for (2)	Age	No	ANKKK1 A1 allele x SLEs + for (1), ns for (2)
Madrid et al., 2001	Honduras Mayan descent	309 M	37.8 R: 18–87	AA symptoms <sup>o</sup>	Current stress <sup>p</sup> +	ANKKK1 A1 allele ns	Marital status, religion, occupation, family income, birthplace	nr	ANKKK1 A1 allele x stress <sup>q+</sup>
van der Zwaluw et al., 2010	Netherlands <i>Longitudinal Family &amp; Health Study</i>	428 M & F	Baseline (T1): (1) at T2 <sup>a</sup>	Past week alc drinks (1) at T2 <sup>a</sup>	Low parental alc rule setting at T2 & T3 +	ANKKK1 A1 allele ns	Gender, ed, personality, smoking, parent alc use, parent behavioral	No	ANKKK1 A1 allele x low parental rule setting + for



First Author (Year)	Population	Subjects	Mean age (SD) R	Alcohol-Related Outcome	Environment Main Effect	Genetic Main Effect	Covariates	rGE	GxE
Dieck, Agrawal, et al., 2006	United States <i>COGA Study</i>	1,916 M & F from 261 multiplex AD families; 234 control families	13.4 R: 13-15 AD: 37.1 (12.3) Control: 40.6 (15.7)	(2) at T3 <sup>d</sup> Lifetime DSM-IV AD	for (1) & (2) Marital status (yes/no) - ; Marital stability (stable, divorced, never married) -	for (1) & (2) GABRA2 AA genotype +	control Gender, age	AA genotype - marital status & stability Similar ns trend in controls	(1) & (2) GABRA2 T allele x marital status & stability - ; Similar ns trend in controls
Enoch, Hodgkinson, et al., 2010	United States	577 M AD, CD &/or HD; 255 M control	Case: 45.6 (7.8) Control: 34.0 (10.1)	(1) Lifetime DSM-IV AD (2) Lifetime DSM-IV AD only (no other SUD)	Childhood trauma <sup>T</sup> + for (1) & (2)	GABRA2 haplotype (10 SNPs) ns	Age	No	GABRA2 haplotype x childhood trauma ns for (1) & (2)
Hasin et al., 2002	Israel	a. 27 recent Russian Immigrants b. 25 Sephardic Jews c. 23 other Ashkenazi	a. 42.3 (11.0) b. 36.3 (10.8) c. 48.7 (9.8)	Lifetime max drinks per drinking occasion	Exposure to env of heavy drinking: Russian immigrants (vs. Sephardic) + ; Russian immigrants (vs. Ashkenazi) ns	ADH1B*1/1 genotype (compared to 2/2 genotype) +	Gender, age, marital status, ed, family AUD hx, employment	Sephardic Jews + ADH1B*2 alleles	ADH1B*1/2 genotype was qualitatively less protective among recent Russian immigrants
Higuchi et al., 1994	Japan	1300 M & F AD a. 1979 N=400 b. 1986 N=400 c. 1992 N=500	a. 46 (10) b. 48 (9) c. 49 (11)	% AD individuals w/ ALDH2*2 allele	Yr entering tx (a,b,c) proxy for changing cultural ale-related attitudes (main effect n/a)	ALDH2*2 allele (see GxE)	None	n/a	% AD individuals w/ ALDH2*1/2 ↑ across cohorts
Irons et al., 2007	United States SIBS	180 East Asian M & F adoptees	18.4 (1.8)	Past year: (1) Quantity (2) Drunk freq	Adoptive sib past yr quantity & adoptive parent AUD hx (main effects n/a)	ALDH2*2 allele - for (1) & (2)	None	nr	§ALDH2*2 protective effect ↓ when adopted sib drank ↑ for (1) & (2); ALDH2 x parental AUD hx ns

Notes. Studies are presented alphabetically by first author within each gene. SD = standard deviation; R = range; rGE = gene-environment correlation; GxE = gene-environment interaction; + = significant positive association with alcohol-related outcome (p<0.05); - = significant negative association with alcohol-related outcome (p<0.05); nr = not reported; ns = not significant; ↑ = greater; ↓ = lower; M = male; F = female; w/ = with; env = environment; ale = alcohol; ext = externalizing; freq = frequency; sx = symptoms; hx = history; dx = diagnosis; dif = difference; T1 = time one, T2 = time two, T3 = time three; AUD = alcohol use disorder; SUD = substance use disorder; AA = alcohol abuse; AD = alcohol dependence; CD = cocaine dependence; HD = heroin dependence; SLEs = stressful life events; CSA = childhood sexual abuse; ed = education; sib = sibling; maltx = maltreatment; SNP = single nucleotide polymorphism; COGA Study = Collaborative Study on the Genetics of Alcoholism; SALVe = Survey of Adolescent Life in Vestmanland; NAG = Nicotine Addiction Genetics Project; APS = Ancestral Proportion Score; SIBS = Sibling Interaction and Behavior Study.

<sup>d</sup>Time points are 1 year apart.

- <sup>b</sup> 25-item checklist of past year SLEs from Life Events Scale for Students (Clemens & Turpin, 1996).
- <sup>c</sup> DSM-III-R AD and Feighner Criteria (Reich et al., 1998).
- <sup>d</sup> Using the Semi-Structured Assessment for the Genetics of Alcoholism II (SSAGA II) (Buchholz et al., 1994).
- <sup>e</sup> Based on largest number of drinks in 24-hour period using the SSAGA II.
- <sup>f</sup> Maltx based on (1) removal from parental care as a result of reports of abuse and neglect, and (2) state awarded temporary custody of children.
- <sup>g</sup> Assessed using the 45-day timeline follow-back (Sobell, Sobell, Leo, & Cancilla, 1988).
- <sup>h</sup> Based on a semi-structured interview.
- <sup>i</sup> Based on modified Munich Events List (Maier-Diewald, Witchen, Hecht, & Werner-Eilert, 1983).
- <sup>j</sup> Based on the Substance Use Questionnaire (Müller & Abbet, 1991) and Lifetime Drinking History (Skinner & Sheu, 1982).
- <sup>k</sup> Based on quantitative alcohol consumption factor score (Agrawal, Grant, et al. 2009).
- <sup>l</sup> Environmental variables assessed at baseline and drinking assessed at three-year follow-up.
- <sup>m</sup> Based on Alcohol Use Disorders Identification Test.
- <sup>n</sup> Based on Life Experiences Survey (Sarason, Johnson, & Siegel, 1978).
- <sup>o</sup> Based on Short version of the Michigan Alcoholism Screening Test.
- <sup>p</sup> Based on marital, economic, parental and cultural/family stress from the Hispanic Stress Inventory (Cervantes et al., 1991).
- <sup>q</sup> Post-hoc analyses indicate occupational/economic stress largely accounts for interaction.
- <sup>r</sup> Based on 28-item version of the Childhood Trauma Questionnaire (Bernstein et al., 2003).
- <sup>s</sup> Analyses based on 34 *ALDH2* deficient subjects who had ever used alcohol.

Table 4

## Summary of Findings from Studies of Gene-Environment Interactions Using Measured Genotypes

<u>Alcohol- Outcomes</u>	<u>Environmental Factors</u>			
	<u>Early Adversity/ Maltreatment</u>	<u>Family Factors</u>	<u>Socio-Cultural Changes</u>	<u>Recent Stressors</u>
Alcohol initiation	<u>Significant Result</u> <b>5-HTTLPR</b> Kaufman et al., 2007			<u>Significant Result</u> <b>CRHRI</b> Schmid et al., 2010
Adolescent & young adult alcohol consumption	<u>Significant Result</u> <b>5-HTTLPR</b> Laucht et al., 2009 <b>MAOA</b> Nilsson et al., 2007 Nilsson et al., 2008 <u>Non-Significant Result</u> <b>5-HTTLPR</b> Kaufman et al., 2007 Laucht et al., 2009 <b>MAOA</b> Nilsson et al., 2007 Nilsson et al., 2008	<u>Significant Result</u> <b>5-HTTLPR</b> Nilsson et al., 2005 <b>MAOA</b> Nilsson et al., 2008 <b>ANKKI</b> van der Zwaluw et al., 2010 <b>ALDH2</b> Irons et al., 2007 <u>Non-Significant Result</u> <b>MAOA</b> Nilsson et al., 2007 <b>ALDH2</b> Irons et al., 2007		<u>Significant Result</u> <b>5-HTTLPR</b> Covault et al., 2007 Laucht et al., 2009 <b>CRHRI</b> Blomeyer et al., 2008 Schmid et al., 2010 <u>Non-Significant Result</u> <b>5-HTTLPR</b> Covault et al., 2007 Laucht et al., 2009 <b>CRHRI</b> Blomeyer et al., 2008 Schmid et al., 2010
Adult alcohol consumption	<u>Significant Result</u> <b>CRHRI Haplotype</b> (Nelson et al., 2010)			<u>Significant Result</u> <b>ANKKI</b> Bau et al., 2000 <u>Non-Significant Result</u> <b>ANKKI</b> Bau et al., 2000
Adult alcohol use disorder	<u>Significant Result</u> <b>CRHRI Haplotype</b> Nelson et al., 2010 <b>MAOA</b> Ducci et al., 2008 <u>Non-Significant Result</u> <b>MAOA</b> Ducci et al., 2008 <sup>a</sup> <b>GABRA2</b> Enoch, Hodgkinson, et al., 2010	<u>Significant Result</u> <b>GABRA2</b> Dick, Agrawal, et al., 2006 <b>OPRMI</b> Du & Wan, 2009 <u>Non-Significant Result</u> <b>5-HTTLPR</b> Du & Wan, 2009 <b>DRD2</b> Du & Wan, 2009 <b>GABRA2</b> Dick et al., 2006a	<u>Significant Result</u> <b>ALDH2</b> Higuchi et al., 1994 <u>Non-Significant Result</u> <b>ADH1B</b> Hasin et al., 2002 <sup>b</sup>	<u>Significant Result</u> <b>ANKKI</b> Madrid et al., 2001 <u>Non-Significant Result</u> <b>5-HTTLPR</b> Dick, Plunkett, et al., 2007

<u>Alcohol- Outcomes</u>	<u>Environmental Factors</u>		
	Early Adversity/ Maltreatment	Family Factors	Socio-Cultural Changes    Recent Stressors
	<i>OPRM1</i>		
	Du & Wan, 2009		

Notes. Significant result refers to  $\geq 1$  significant GxE ( $p < 0.05$ ); Non-Significant Result refers to  $\geq 1$  non-significant GxE.

<sup>a</sup>For alcohol dependence with antisocial personality disorder.

<sup>b</sup>GxE qualitative.