A Systematic Review: Candidate Gene and Environment Interaction on Alcohol Use and Misuse among Adolescents and Young Adults

Jueun Kim, PhD¹ and Aesoon Park, PhD²

¹Department of Counseling Psychology, Handong Global University, Pohang, South Korea

²Department of Psychology, Syracuse University, Syracuse, New York

Abstract

Background and Objectives: Youth drinking is a pervasive public health concern with serious negative developmental implications. Candidate gene and environment interaction studies (cGxE) show that environmental effects on drinking behaviors may differ by individuals' genotypes. Yet little is known about whether genetic and environmental effects on drinking behaviors are developmentally specific.

Methods: This systematic review evaluated 42 cGxE studies of drinking in adolescence and young adulthood.

Results: Although there are mixed findings, studies of cGxE effects involving *DRD4*, *5-HTTLPR*, *DRD2*, and *OPRM1* genotypes showed relatively consistent patterns. The effects of under-controlled environments (e.g., low levels of parental monitoring) on early and middle adolescent drinking appeared to differ across *DRD2* or *OPRM1* genotypes. Effects of alcohol-facilitating environments (e.g., heavy drinking peers) on late adolescent and young adult drinking appeared to differ across *DRD4* or *OPRM1* genotypes. Interactions between *5-HTTLPR* genotype with stressful environments (e.g., negative life events) were found throughout adolescence and young adulthood, although there were some inconsistencies regarding the risk-conferring allele. There was limited evidence for other cGxE effects due to the small number of studies.

Conclusions and Scientific Significance: This review suggests that GxE findings may advance our knowledge regarding which developmentally specific conditions result in the expression of candidate genes that influence youth alcohol use and misuse. However, since a significant number of studies had small sample sizes and most studies had small effect sizes, findings need replication across independent studies with large samples.

Address correspondence to Aesoon Park, Ph.D., Syracuse University, Department of Psychology, 430 Huntington Hall, Syracuse NY 13244; aepark@syr.edu; Phone number: 315-443-2391; Fax number: 315-443-4085.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Introduction

Youth alcohol use and misuse is a pervasive and serious public health concern. Globally, the prevalence of monthly heavy drinking (defined as 60 or more grams of pure alcohol on at least one single occasion at least monthly) is highest between the ages of 15 and 19.¹ In the United States, risk of alcohol use disorder (AUD) is highest at 18 years of age.² Youth drinking produces a variety of harmful outcomes such as alcohol-related injuries, suicide, homicide, and alcohol poisoning.³ Youth drinking also leads to long-term negative consequences such as damage to brain development,⁴ alcoholism and drug problems later in life,⁵ and higher school drop-out rates.⁶

Genetic factors have been shown to contribute to youth drinking. A number of twin studies demonstrate that roughly 14% to 55% of individual differences in youth drinking are explained by genetic factors, although the proportion of genetic influences on drinking varies based on the specific alcohol phenotype (e.g., alcohol initiation, quantity, or frequency).⁷ In contrast to consistent findings on aggregated genetic influences, molecular genetic studies have yielded mixed findings on the role of specific genes in drinking,^{8,9} with exception of polymorphisms in alcohol metabolism genes.¹⁰ These mixed effects may be due in part to environmental factors that strengthen or weaken genetic influences on drinking behaviors. That is, individuals' genes may interact with environments to influence risk for alcohol use and misuse.

Transactional developmental theory¹¹ maintains that one's behavior is determined by the interplay between nature and nurture such that one's behavior is an expression of their inherited disposition within a given environment in a developmental period. The theory departs from a deterministic point of view and, instead, stresses an ongoing process of the mutual effects between one's characteristics and environments. This concept has allowed researchers to capture the multifaceted etiology of complex psychiatric traits and behaviors accounted for by both genes and environments. This theory has also been applied to youth drinking behaviors, and a number of gene and environment (GxE) interaction studies have tested whether the interplay between an environment and a specific genotype can affect youth alcohol use and misuse.

Examining developmental-specific cGxE effects is important because gene expression and environmental effects may occur in one developmental stage but may be suppressed in other developmental stages. For example, five monoamine genes were associated with drinking frequency during young adulthood but not during adolescence in a national large sample.¹² Also, environmental effects on drinking change over time. For example, the impact of family or community environments was larger on substance use in early adolescence while the impact of peer or school environments was larger in late adolescence ($n = 91,778$).¹³ A handful of GxE reviews on drinking behaviors exist, but none systematically address the question of whether developmentally distinct patterns emerge in youth (i.e., ages 10 – 24). A few review studies focused on developmental patterns of GxE but were not comprehensive reviews of all extant studies.^{14,15} Some GxE reviews on drinking behaviors draw general conclusions about all ages¹⁶ or focused on particular ethnic populations.^{17–19} Thus, the aim

of this paper is to comprehensively review cGxE studies to evaluate existing evidence for cGxE effects among adolescents and young adults.

Method

Inclusion and Exclusion Criteria

Articles written in English that were published in peer-reviewed journals until December 2017 were screened for inclusion. Studies were included for this review if they met all of the following criteria: (a) were comprised of youth aged 10 to 24 according to the Centers for Disease Control definition of youth (including adolescents and young adults),²⁰ (b) assessed at least one behavioral alcohol phenotype (not alcohol endophenotypes), and (c) used molecular analysis to identify participants' specific genotype. Behavioral genetic studies, including twin or adoption designs, and genome wide association studies were excluded since the current review aimed to evaluate the evidence for candidate GxE effects.

Literature Search Method

The flow of studies through the review process and the number of studies excluded are shown in Figure 1. We searched PubMed and PsycINFO databases using combinations of the following search terms: *gene and environment interaction, youth, adolescent, young adult, alcohol use, and molecular analysis*. References cited in the identified studies were also searched. Of the 183 published articles identified through the database and reference searches, 42 studies were included in the current review.

Results

Study Characteristics

Study design.—Table 1 summarizes study characteristics and main findings of the 42 identified studies. Only one out of the 42 studies used an experimental research design, and all of the other studies used a survey research design. Among the 41 studies which used a survey design, nine used cross-sectional data and 32 studies used longitudinal data. The median number of assessment waves for the longitudinal studies was two (range = 2 to 11), and the median of the length of intervals between the assessment waves was one year (range = 1 month to 19 years).

Sample characteristics.—Thirty nine studies examined only youths, and the four remaining studies^{21–24} followed up participants from youth to adulthood. Twenty four out of the 42 identified studies were conducted in the United States, and the remaining studies were conducted in Germany ($n = 7$), the Netherlands ($n = 5$), Sweden ($n = 3$), Australia ($n = 2$), Estonia ($n = 1$), and the United Kingdom ($n = 1$). Among them, one study²⁵ used one sample collected in the United States and another in the United Kingdom.

Gene and environment measures.—In this review, genes were grouped into eight different neurobiological systems: *dopamine, serotonin, opioid, corticotropin releasing hormone, GABA, circadian rhythm, alcohol metabolism, and glucocorticoid systems*. Regarding environmental measures, stressful life events ($n = 16$) and family environments (n

= 13) were most frequently examined, followed by peer environments ($n = 12$) and interventions /preventions ($n = 5$); four studies examined multiple environments.

Alcohol outcomes.—Multiple alcohol outcomes were assessed in the identified studies, with alcohol frequency ($n = 22$) and quantity ($n = 14$) as the most frequently examined outcomes, followed by binge or heavy drinking ($n = 12$; both binge and heavy drinking were commonly defined as four or more drinks (typically for women) or five or more drinks (typically for men) in one sitting in all included studies regardless of study countries with one exception of an adolescent study in the U.S., where six or more drinks in the past 6 months were used²³) and frequency of drinking to intoxication ($n = 6$). Other alcohol outcomes such as AUD symptoms ($n = 5$), the Alcohol Use Disorders Identification Test (AUDIT, $n = 4$), maximum number of alcohol drinks per occasion ($n = 3$), lifetime alcohol use ($n = 3$), negative drinking consequences ($n = 3$), intention to drink in the future ($n = 1$), age at drinking onset ($n = 1$), and frequency of three or more drinks ($n = 1$) were also examined. Among them, 22 studies examined multiple alcohol outcomes.

Review of the Extant cGxE findings

Findings of cGxE studies on youth alcohol use and misuse according to neurobiological systems are shown in Table 1. In this review, the association of each biological system with alcohol phenotypes was briefly presented before presenting cGxE findings, because evaluating cGxE effects only from the statistical point of view may yield confusing results.^{26,27} Early adolescence was defined as ages 10 to 13, middle adolescence was defined as ages 14 to 17, late adolescence was defined as ages 18 to 20, and young adulthood was defined as ages 21 to 24, in line with physical and psychological developmental stages.²⁸ Additionally, cGxE findings as a function of environmental factors are summarized in Table 2.

Dopamine System.—The dopamine system plays a prominent role in the neurobiological basis of reward, craving, and dependence,²⁹ which have been associated with alcoholism. Specifically, the risk of alcoholism has been positively associated with the genotypes that blunt dopamine receptor responsiveness and decrease dopamine metabolism.³⁰

Dopamine D4 receptor (DRD4).—Among cGxE studies of youth in the dopamine system, *DRD4* genotype was most frequently studied. As indicated in Table 1, ten studies examined interactions of *DRD4* with peer environments ($n = 6$), family environments ($n = 3$), and childhood adversity ($n = 2$; one study examined it in addition to peer environments).

Among the six studies examining peer environments, four studies particularly in late adolescence or young adulthood showed that *DRD4* variable number tandem repeat (*VNTR*) 7-repeat or long allele carriers had greater risk of drinking when exposed to alcohol facilitating peer environments, with two exceptions that showed non-significant moderating effect of *DRD4*. Specifically, peers' antisocial behaviors (e.g., cheating or theft) affected late adolescents (mixed races)' alcohol use at age 18 only among youth carrying the *DRD4* 7-repeat allele; the association did not appear among non-carriers.³¹ A similar interaction effect was reported in a study of young Caucasian adults²²: As involvement with fraternities

and sororities increased at ages 18 to 21, those carrying the *DRD4* long allele reported more alcohol dependence symptoms across their four years of college than those carrying the short allele. Similarly, when adolescents reported a higher perception of peer drinking and peer approval of drinking, *DRD4* 7-repeat allele carriers drank more frequently than non-carriers³²; in this study, this pattern of result was replicated across two independent samples at mean ages of 15 (mixed races) and 19 (Caucasians). An experimental study of Caucasian college students with a mean age of 21³³ also found that 7-repeat allele carriers consumed more alcohol in the presence of a heavy drinking confederate than in the presence of non-drinking or light drinking confederates; the association was significantly weaker among non-carriers. However, one study of mixed races showed that *DRD4* genotype did not change the effect of friends' alcohol use on drinking quantity and heavy drinking (defined as 6 or more drinks in the past 6 months) frequency at both ages 17 and 23.²³ Also, a study of mainly Caucasians in early and middle adolescence showed that, overall, *DRD4* genotype did not moderate the associations between peer drinking norms and adolescents' alcohol quantity from ages 13 to 17.³⁴

Regarding family environments, all three studies indicated that the overall effect of parenting on drinking did not differ as a function of the *DRD4* genotype in middle adolescence to young adulthood. Specifically, among Netherlands, *DRD4* genotype did not moderate the effects of parental rejection or overprotection at age 11 on youth drinking frequency at age 16.³⁵ In the same study, parents' emotional warmth increased the risk of drinking among long allele carriers as compared to non-carriers, which was unexpected given that previous studies consistently suggested parental emotional warmth to be a buffering factor in youth drinking.³⁶ Among African Americans, a family alcohol prevention program targeting parenting skills (mean ages at 11 in one sample and at 16 in another sample) was not particularly more effective for the long allele carriers compared to non-carriers in preventing later drinking or heavy drinking (ages 14 or 17).³⁷ Also, among Australians, the effect of poor adult attachment with parents on binge drinking (defined as 5 or more drinks in one day: 5+) at age 24 did not differ as a function of *DRD4* genotype.³⁸

Regarding childhood adversity, two studies in young adulthood showed conflicting findings. In one study of Caucasians,²² when youth experienced greater childhood adversity, *DRD4* long allele carriers (but not non-carriers) were more likely to show alcohol dependence symptoms from ages 18 to 34. However, in another study of Caucasians,³⁹ the effect of childhood adversity on alcohol dependence symptoms from ages 18 to 26 did not differ as a function of *DRD4* genotype.

Dopamine D2 receptor (DRD2): Five studies examined interactions between *DRD2* genotype and family environments. Among them, four studies examined the *DRD2* Taq1 polymorphism (rs18004987) and one study examined the combined effect of three other *DRD2* polymorphisms (rs6279, rs6277, and rs6275).

Four studies examining *DRD2* Taq1 rs18004987 indicated that the interactions between the *DRD2* genotype and parental rule-setting or parenting may have more prominent short-term effects (particularly during early and middle adolescence) rather than long-term effects. Specifically, when parents showed greater leniency in alcohol-related rules, early

adolescents in the Netherlands (race was not reported, age of 13) with the *DRD2* Taq1-A1 allele were more likely to consume alcohol than non-carriers concurrently⁴⁰ and one or two year prospectively.⁴¹ However, a study of Netherlands examining long-term effects showed that the effects of parents' alcohol-related rule setting at age 14 on drinking trajectories from ages 15 to 19 did not differ as a function of the Taq1 genotype.⁴² Similarly, among Netherlands, the long-term prospective effects of general parenting (rejection, overprotection, and emotional warmth) at 11 on alcohol outcome at 16 did not differ as a function of the Taq1 genotype.³⁵

A randomized prevention study examining the combined effect of *DRD2* rs6279, rs6277, and rs6275 (combined based on haplotype result in the sample) found significant cGxE effects in early (mean aged 11) and middle adolescence (mean aged 16).³⁷ In a prevention condition where parents received parenting skills training, African American youth carrying the *DRD2* CAG & CGG drank and engaged in heavy drinking less frequently at 22 to 29 months follow up than non-carriers.

Serotonin System.—Serotonin is one of the major neurotransmitters in the brain's reward system, regulating motivation and craving.⁴³ Some studies indicate that decreased levels of serotonergic functioning may increase alcohol intake.⁴⁴ All eight cGxE studies examined a single polymorphism of a serotonin transporter gene, *5-HTTLPR*.

5-Hydroxy Tryptamine Transporter Linked Promoter Region (5-HTTLPR).: Out of the eight studies, seven studies examined stressful environments and one study examined school-level drinking rates.

All seven studies that examined stressful environments showed a significant moderating role of *5-HTTLPR SLC6A4 promotor VNTR* across early, middle, late adolescence, and young adulthood. However, there were inconsistencies regarding the risk-conferring allele. That is, five studies showed that having the short or low activity allele was associated with a greater risk of drinking, but two studies showed that having the long or high activity allele was associated with greater risk. In early adolescence (mixed races), when exposed to physical, sexual, or emotional abuse at age of 10, individuals carrying a short allele initiated drinking earlier than non-carriers.⁴⁵ In middle adolescence (mixed races), when they reported high levels of family conflict at 12, youth carrying low activity allele showed higher risk of drinking at age 15 than non-carriers.²⁵ Similarly, in middle and late adolescence (Swedish; race was not reported), when they reported poor family relations, youth carrying one long and one short allele were more likely to drink and get intoxicated cross-sectionally at ages 12 and 15 in two independent samples.⁴⁶ A study of Caucasian young adults also reported that, when exposed to higher levels of negative life events, college students carrying at least one short allele were more likely to engage in binge drinking (defined as 4 or more drinks for women and 5 or more drinks for men on one setting: 4+/5+) than non-carriers.⁴⁷ A similar pattern of results was replicated in African American female (but not male) college students in another study⁴⁸: When exposed to higher levels of negative life events, female college students carrying at least one low activity allele were more likely to engage in binge drinking (4+/5+) than carriers. However, two other studies of Caucasian young adults^{49,50} showed that having the long or high activity allele was associated with a greater risk of

drinking. When they reported poor attachment to parents, two long allele carriers were more likely to engage in binge drinking at age 24, but other allele carriers were less likely to engage in binge drinking.⁴⁹ In another study, when male young adults experienced higher levels of stressful events over the past four years, carriers of two long or high activity alleles were found to consume more alcohol per drinking episode and engage in more frequent binge drinking (4+/5+) at age 19 than non-carriers.⁵⁰

Only one study (mixed races)⁵¹ examined alcohol-facilitating school environments, finding that when youth (*M* age = 16) attended a school with a high average drinking rate, carriers of the low-activity allele reported higher drinking quantity and frequency than non-carriers.

Opioid System.—The endogenous opioid system consists of β -endorphin and opioid peptides and receptors.⁵² High levels of opioid neurotransmission have been associated with higher sensitivity to the rewarding effects of alcohol.⁵³ All four cGxE studies examined a single polymorphism of an opioid receptor gene, *OPRM1* A118G single nucleotide polymorphism (SNP).

Opioid Receptor, Mu 1 (OPRM1).: Three studies examined parental monitoring and two studies examined peer environments (one study examined both parenting and peer norms).

Regarding parenting, three studies showed that early to late adolescents carrying the *OPRM1* G allele reported high-risk drinking when parents had more lenient alcohol related rules or did not closely monitor youth behaviors. For example, when exposed to low levels of parental monitoring or alcohol-related rule setting, Caucasian youth carrying the G allele were more likely to consume alcohol at age 13 ($n = 196$)⁴⁰ or develop an AUD at age 15 ($n = 104$)⁵⁴ than non-carriers. Also in middle to late adolescence, when parents showed greater leniency in alcohol-related rules at youth age of 14, adolescents carrying G allele showed a heavy drinking trajectory from ages 15 to 19, but this pattern was not shown among non-carriers.⁴²

Regarding peer environments, two studies showed that late adolescents and young adults carrying *OPRM1* G allele were more likely to be affected by peer substance use norms and more engaged in risky levels of drinking than non-carriers. Specifically, in middle adolescence (Caucasians), when peers frequently engaged in substance use including alcohol, marijuana, and other drugs, youth carrying the G allele were more likely to develop an AUD than non-carriers at age 15.⁵⁴ In young adulthood, when Caucasian youth reported that their peers drank frequently and get drunk regularly, women (not men) carrying a G allele were more likely to experience AUD symptoms at age 21 than non-carriers.²¹

Corticotropin Releasing Factor (CRF) System.—CRF stimulates the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol.⁵⁵ There is a study indicating that greater secretion of CRF may be associated with a higher risk of alcohol dependence.⁵⁶ Among three cGxE studies involving CRF related genes, two studies examined the *CRHR1* genotype and one study examined the *CRH-BP* genotype.

Corticotropin releasing hormone receptor 1 (CRHR1): Two studies showed that interaction effects of *CRHR1* with stressful life events occurred in middle and late adolescence. When 15-year-old Caucasians were exposed to many stressful life events, rs1876831 CC carriers (but not rs242938 G carriers) reported more frequent binge drinking (4+/5+) and greater maximum number of drinks than non-carriers.⁵⁷ Similarly, in another study of Caucasians, when exposed to higher levels of stressful events, rs1876831 CC carriers initiated drinking earlier than non-carriers.⁵⁸ The same study also found that, when exposed to higher levels of stressful events before age 15, rs242938 G carriers consumed a greater amount of alcohol and engaged in binge drinking (4+/5+) more often than non-carriers at age 19. In the study, *CRHR1* rs1876831 and rs242938 were found to be haplotype-tagging SNPs.

Corticotropin Releasing Hormone Binding Protein (CRH-BP): One study showed a significant interaction of *CRH-BP* with stressful life events in mid adolescence. When African American adolescents were exposed to higher levels of stressful life events at age 15, those who had *CRH-BP* rs1715749 CC genotype had higher alcohol use and misuse (heavy drinking was defined as 5 or more drinks in one setting) rates than those who had the CT or TT genotypes.⁵⁹

Circadian Rhythm.—The circadian clock mechanism maintains homeostasis by coordinating the body with the day-night cycle.⁶⁰ In some studies, disruption of the circadian rhythm has been positively associated with alcohol dependence.^{61,62} Among three cGxE studies involving circadian rhythm, two examined *PER1* rs3027172 and one examined *PER2* rs56013859.

Period Circadian Clock 1 (PER1): Two studies showed a significant interaction effect of *PER1* genotype with stressful life events in late adolescence. When youth (mixed races) experienced greater childhood trauma, *PER1* C allele carriers were more likely to develop problematic alcohol use at age 19, but this pattern was not shown among non-carriers.⁶³ In addition, when even parents experienced a great number of stressful events before the youth was born, youth (Germans; race was not reported) carrying the *PER1* C allele reported frequent heavy drinking (4+/5+) at 19, but this pattern was not found among non-carriers.⁶⁴

Period Circadian Clock 2 (PER2): One study showed that when exposed to severe stressful life events during the past four years, Caucasian youth carrying the *PER2* AA reported more alcohol dependence symptoms at age 19 than other allele carriers.⁶⁵

Gamma-Aminobutyric Acid (GABA).—*GABA* is an inhibitory neurotransmitter influencing the sedative effects of alcohol.⁶⁶ The positive association of *GABA* with the risk of alcohol dependence has been found.⁶⁷ Three cGxE studies examined *GABRA2* genotype; among them, one study examined both *GABRA2* and *GABRG1* genotypes.

GABA-A Receptor Alpha 2 (GABRA2): Among three existing cGxE studies, two studies examined substance prevention program efficacy and one study examined stressful environments, and all showed at least one significant cGxE effects across adolescence periods. When parents did not receive an alcohol prevention program on parenting skills at

adolescents aged 11 or 16, African American adolescents carrying *GABRA2* block1 (rs567926, rs534459, rs529826, and rs279858 combined based on haplotype result in the sample) CA & CG consumed more alcohol and engaged in more frequent heavy drinking (defined as 4 or more drinks on one setting) three years later than non-carriers.³⁷ Similarly, when early adolescents (mixed races) participated in substance misuse prevention at age 11, *GABRA2* rs270945 TT carriers drank less frequently and reported a lower intoxication frequency from ages 12 to 18 than non-carriers.⁶⁸ Regarding stressful environments, among Caucasians, when experienced greater childhood adversity, *GABRA2* rs270926 AA and AG carriers drank more frequently at age 15 than non-carriers.²⁴ In the study, *GABRA2* rs279826 and rs279858 were found to be in high linkage disequilibrium, and thus yielding similar patterns of cGxE results due to their functional similarity.

GABA-A Receptor Gamma Subunit 1 (GABRG1): One study reported that when parents did not receive an alcohol prevention program on parenting skills at adolescents aged 11 or 16, adolescents carrying *GABRG1* block2 (rs497565 and rs1497571 combined based on haplotype result in the sample) AGTC & AGTT consumed more alcohol and engaged in more frequent heavy drinking three years later than non-carriers.³⁷

Glucocorticoids.—Glucocorticoid receptor variants are involved in hypothalamic-pituitary-adrenocortical axis activity that modulates stress response.⁶⁹ Glucocorticoid receptors in dopaminergic neurons were found to facilitate cocaine seeking behaviors in an animal study,⁷⁰ but a link to alcohol use has not been found.

Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1): Two existing studies examined interactions of several SNPs of *NR3C1* with stressful life events or behavioral interventions in adolescence, finding overall non-significant interactions with the exception of one involving rs1255166. The effect of a behavioral problem intervention on youth trajectory of binge drinking (5+) did not differ as a function of nine SNPs individually (rs1048672, rs17209258, rs10482682, rs852980, rs2918418, rs2963149, rs4128428, rs13182800, and rs4912910).⁷¹ However, *NR3C1* rs12655166 C allele carriers showed a lower trajectory of binge drinking pattern across middle and high schools after receiving the behavioral intervention than any other carriers. This pattern appeared among African Americans but not among European Americans. Similarly, there was also no interaction effect between 10 SNPs including rs1720925, rs1048268, rs1048267, rs852980, rs2918418, rs2963149, rs4128428, rs13182800, rs4912910, and rs12655166 and past-year stressful life events on alcohol use and misuse at mean age of 15.⁵⁹

Alcohol Metabolism.—Alcohol metabolism genes are involved in encoding alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes.¹⁰ Among candidate genes, alcohol metabolism genes have been most consistently associated with drinking behavior.⁷² Three cGxE studies examined *ADH1B*, *ADH1C*, *ALDH2* genotypes respectively.

Alcohol Dehydrogenase 1B (ADH1B): One study found that when exposed to lower levels of alcohol offers or perceived peer drinking, college students of African descent carrying

*ADH1B**3 rs2066702 allele drank less frequently or were less likely to experience negative drinking consequences than non-carriers at age 20.⁷³

Alcohol Dehydrogenase 1C (ADH1C). One study found that when adolescents (mixed races) did not receive substance misuse prevention, alcohol use of *ADH1C* rs698 G allele carriers increased significantly faster between ages 11 and 14 than non-carriers.⁷⁴

Aldehyde Dehydrogenase 2 (ALDH2). One study found that when young adults reported a higher perception of peer drunkenness, East Asian college students carrying *ALDH2**2 rs678 GG consumed more alcohol at age 18 than non-carriers.⁷⁵

Other Genes. There are other genes that have limited evidence thus far. Only one study examined the *Potassium Channel, Inwardly Rectifying Subfamily J- Member 6 (KCNJ6)* rs2836016 genotype, and it found that parents' psychosocial adversity before birth had a long-term effect on youth's (German descent) alcohol dependence symptoms at age 19. However, this effect was found only among the *KCNJ6* GG allele carriers but not among AG or AA carriers.⁷⁶ Only one study examined the *Catechol-o-methyltransferase (COMT)* rs4680 genotype, and it found that low levels of parental supervision and emotional involvement at age 15 were associated with significant increases in Caucasian youth drinking between age 15 and 19. However, this pattern was found only among *COMT* Met/Met allele carriers but not among non-carriers.⁷⁷ Two studies found that *Monoamine Oxidase A (MAO-A) VNTR* genotype moderated the effects of adverse environments on youth drinking behaviors. That is, when exposed to physical/emotional maltreatment and poor family relations, male adolescents in Sweden ($n = 66$, race was not reported) carrying the *MAO-A* short allele were more likely to experience negative drinking consequences than non-carriers.⁷⁸ When youth reported poor family relations, female adolescents in Sweden ($n = 114$) carrying the *MAO-A* long allele (as opposed to the short allele in male adolescents) experienced more negative drinking consequences and AUD symptoms than non-carriers.⁷⁹ Because *MAO-A* is located on the X-chromosome (Xp11.23–11.4)⁸⁰ and males have one X chromosome and females have two, some suggested gender differences in *MAO-A* risky variants.⁸¹ However, other cGxE studies reported no gender difference in *MAO-A* risky variants.^{82–85} Thus, it is difficult to draw a conclusion regarding gender differences based on the two studies with small sample sizes. Only one study examined *Monoamine oxidase B (MAO-B)*, and it found that when exposed to physical/ emotional maltreatment or poor family relations, female adolescents who had low levels of platelet *MAO-B* activity experienced more negative drinking consequences and AUD symptoms than those who had medium and high levels of *MAO-B* activity.⁷⁹ Finally, one study examined the *Ankyrin Repeat and Kinase Domain Containing 1 (ANKK1)* genotype, and it found that the effect of an family alcohol prevention program on later drinking in middle adolescence did not differ as a function of *ANKK1* genotype.³⁷

Multi-locus index.—Four studies examined interactions between a multi-locus index summing multiple risk-conferring genotypes (i.e., non-weighted risk score) and showed significant cGxE effects in adolescents and young adults. Specifically, when parents did not receive parental training, youth drinking and heavy drinking frequency increased in middle

adolescence as youth carried more susceptible *GABRG1*, *GABRA1*, and *DRD2* genotypes (i.e., as the multi-locus index became higher).³⁷ These genes were selected based on previous candidate studies associated with alcohol use. However, when their parents received parenting skills training, youth drinking and heavy drinking frequency decreased as youth carried more susceptible genotypes. Also, a large study of mixed races ($n = 1,495$) showed that adolescents who had more risk alleles of *DAT*, *DRD2*, *DRD4*, *5-HTTLPR*, and *MAOA* (SNPs rs numbers were not stated) were more likely to be affected by parental rejection and thus initiated alcohol use before age 17.⁸³ These genes all code for proteins related to neurotransmission and have been studied to modify environmental effects on alcohol use in previous cGxE studies. Finally, young adults (mixed races) who had a medium genetic risk involving *MAOA* (rs4245145, rs2242592, rs1125394), *DRD2* rs2242592, and *LIM Domain Only 3 (LMO3)* rs7975434 risk-conferring genotypes were more likely to be affected by peer drinking norm and thus frequently engaged in binge drinking.⁸⁶ These genes were selected due to their significant associations with alcohol use in the sample. Finally, one study (mixed races) found that when early adolescents did not receive substance misuse prevention at age 11, even when their peers did not frequently use substances, those carrying more susceptible alleles of five *OXTR* SNPs (rs6770632, rs53576, rs2254298, rs4686302, rs1488467) drank more frequently at age 14 than the low genetic risk group.⁸⁷

Discussion

The current review summarized and evaluated cGxE studies on youth alcohol outcomes. Most of the candidate genes examined had limited evidence for developmentally specific cGxE effects on youth drinking due to the small number of studies. However, studies of *DRD4*, *5-HTTLPR*, *DRD2*, and *OPRM1* genotypes provided some evidence for cGxE effects on youth drinking. Findings showed that the effects of under-controlled environments (e.g., low levels of parental monitoring) on drinking may differ as a function of *DRD2* and *OPRM1* genotypes in early and middle adolescence. Also, the effects of alcohol-facilitating environments (e.g., heavy drinking peers) on drinking may differ as a function of *DRD4* and *OPRM1* genotypes during late adolescence and young adulthood. Finally, the effect of stressful environments on youth drinking seems to differ as a function of *5-HTTLPR* genotype across adolescence and young adulthood. However, because there were inconsistencies regarding the risk-conferring allele, the result should be interpreted with caution and more studies about robust neurobiological evidence are needed.

Overall, our results are consistent with current development models of youth alcohol misuse. The cGxE findings involving dopamine and opioid genotypes are in line with a deviance proneness pathway in which youth's heritable proneness to deviant behaviors is actualized when exposed to alcohol promoting environments.^{88,89} Similarly, in line with behavioral inhibition theory,⁹⁰ genetic liability conferred by dopamine and opioid genotypes may make it harder for some individuals to inhibit problematic behaviors, particularly when exposed to alcohol-promoting and under-controlled environments. In fact, dopamine and opioid systems have been found to be involved in reward seeking or inhibitory control neural pathways,^{91,92} and neuro-imaging studies showed that subgroups of dopamine and opioid genotypes had higher sensitivity and lower levels of impulse control to reward predictive cues.^{93,94} On the

other hand, the results of serotonin or stress hormone related genotypes are in line with an internalizing pathway in that youths drink alcohol as a means of regulating stress and negative affect.⁹⁵ A meta-analysis⁹⁶ has shown that subgroups of serotonin genotypes had higher levels of hypothalamic-pituitary-adrenal (HPA) axis activity, which is involved in stress response to adverse environments. That is, youth with risky serotonin and stress hormone genotypes may be more responsive to the stress-dampening effects of drinking. To further examine this potential pathway, future research should examine coping motives (e.g., drinking to forget worries) and tension reduction expectancies (e.g., evaluating tranquilizing effects of alcohol favorably) as potential psychological mechanisms underlying the observed cGxE effects.

A number of limitations also exist in interpreting the reviewed literature. Most critically, a number of studies were underpowered. Growing concern has been raised about the high potential for false positives in cGxE studies, and the importance of utilizing large sample sizes in cGxE studies has been highlighted⁹⁷. For example, a review of 103 cGxE studies⁹⁸ demonstrated that, with an exception of very large cGxE effect sizes, the required sample size to reach the statistical power of 80% is 600 participants or more. Out of the 42 reviewed studies in the current review, 30 studies had smaller sample sizes than 600 and seven studies had sample sizes around or under 200, which may have resulted in false positive or false negative findings. Also, the overall cGxE effect sizes have been suggested to be small except for a few genes such as *COMT* and *OPRM1*.^{54,77} Given the small effect sizes for many significant findings (as shown in Table 1), it is crucial to replicate existing studies to address potential publication bias or statistical artifact. Finally, in case of studies combining different variants, there is little evidence presented to suggest that joint contributions would be necessary or sufficient to encapsulate genetic risk for alcohol use. It was not reported whether the variants are related each other or how much more information is provided when combined than individual candidate genes in isolation.

Overall our understanding of the complex patterns involving interplay between genetics and environments is still in the beginning stages, but the current review adds to the understanding of developmentally specific cGxE effects with regard to youth drinking. In future studies, it will be important to examine whether cGxE studies on youth drinking show different patterns of results from those on adult drinking. In youth, *OPRM1*, *5-HTTLPR*, *DRD4*, and *DRD2* genotypes were most frequently examined, and a majority of studies involving those genes showed significant interaction effects with family, peer, and/or stressful environments. However, in adults, cGxE studies involving *OPRM1*, *5-HTTLPR*, *DRD4*, and *DRD2* genotypes tended to show either non-significant^{22,99} or mixed^{100,101} interaction effects. Instead, in adults, the *MAO*, *CRHR1*, and *GABRA* genotypes consistently showed significant interaction effects with childhood maltreatment,^{85,102} marital status,¹⁰³ and stressful life events.¹⁰⁴ Thus, future studies would benefit from using long-term longitudinal data to test potentially different patterns of cGxE effects over the course of adolescence versus adulthood.

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Figure 1.
Flow diagram for studies selected for this review.

Candidate gene and environment interaction effects on youth drinking: Study characteristics and core findings, by gene (studies ordered form early adolescence to young adulthood)

Table 1

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core G×E finding (ES; Effect size)
DRD4					
Creemers et al. ³⁵	<ul style="list-style-type: none"> ■ $n = 1,192$ ■ M age = 11 at T1 ■ Netherlands; race was not reported 	<ul style="list-style-type: none"> ■ Frequency of drinking at 16 [regular vs irregular drinkers] 	<ul style="list-style-type: none"> ■ DRD4 VNTR (long allele [-repeat]) 	<ul style="list-style-type: none"> ■ Parental rejection at 11 (E_1) ■ Parental overprotection at 11 (E_2) ■ Parental emotional warmth at 11(E_3) 	<ul style="list-style-type: none"> ■ $G \times (E_1 \text{ or } E_2) = A$ ns (OR= 0.79-1.23) ■ $G \times E_3 \uparrow = A \uparrow$ (OR =1.93)
Brody et al. ³⁷	<ul style="list-style-type: none"> ■ Combined $n > 900$ ■ Sample 1: M age = 11 at T1 & Sample 2: M age = 16 at T1 ■ African American 	<ul style="list-style-type: none"> ■ Frequencies of drinking & heavy drinking (4+) at 11 & 14 for Sample 1, at 16 & 17 for Sample 2 	<ul style="list-style-type: none"> ■ DRD4 VNTR (long allele [-repeat]) 	<ul style="list-style-type: none"> ■ Prevention program on family communication & support at 11 for Sample 1 & at 16 for Sample 2 	<ul style="list-style-type: none"> ■ $G \times E = A$ ns (no ES)
Griffin et al. ³¹	<ul style="list-style-type: none"> ■ $n = 414$ ■ M age = 13 at T1 ■ Mixed races in the U.S. 	<ul style="list-style-type: none"> ■ Lifetime ever use and drinking frequency at 18 	<ul style="list-style-type: none"> ■ DRD4 VNTR (7-repeat allele) 	<ul style="list-style-type: none"> ■ Antisocial peer pressure at 13 	<ul style="list-style-type: none"> ■ $G \times E \uparrow = A \uparrow$ ($R^2 = 0.03$)
Van der Zwaluw et al. ³⁴	<ul style="list-style-type: none"> ■ $n = 308$ ■ M age = 13 at T1 ■ Mainly Caucasians in the Netherlands 	<ul style="list-style-type: none"> ■ Drinking quantity at 13 to 17 	<ul style="list-style-type: none"> ■ DRD4 VNTR (long allele [-repeat]) 	<ul style="list-style-type: none"> ■ Sum of perceived past-week drinking quantity & frequency of best friends at 13 to 17 	<ul style="list-style-type: none"> ■ M age 13, 14, 15, & 17, $G \times E = A$ ns (-0.11 β 0.00) ■ M age 16, $G \times E \uparrow = A \uparrow$ ($\beta = -0.12$)
Olsson et al. ³⁸	<ul style="list-style-type: none"> ■ $n = 839$ ■ M age = 14 at T1 ■ Australian ethnicity 	<ul style="list-style-type: none"> ■ Binge drinking (5+) at 24 	<ul style="list-style-type: none"> ■ DRD4 VNTR (7R+ = 5,6,7,&8 repeat alleles) 	<ul style="list-style-type: none"> ■ Adult attachment with parents at 24 	<ul style="list-style-type: none"> ■ $G \times E = A$ ns (no ES)
Park et al. ³²	<ul style="list-style-type: none"> ■ Sample 1 ■ $n = 174$ ■ M age = 14 at T1 ■ Mixed races in the U.S. 	<ul style="list-style-type: none"> ■ Sample 1 ■ Drinking frequency at 15 	<ul style="list-style-type: none"> ■ DRD4 VNTR (7-repeat allele) 	<ul style="list-style-type: none"> ■ Sample 1 ■ Peer drinking norms at 14 	<ul style="list-style-type: none"> ■ Sample 1 ■ $G \times E \uparrow = A \uparrow$ ($d = 0.94$)
	<ul style="list-style-type: none"> ■ Sample 2 ■ $n = 234$ ■ M age = 18 at T1 ■ Caucasians in the U.S. 	<ul style="list-style-type: none"> ■ Sample 2 ■ Drinking frequency at 19 (A_1) & at 20 (A_2) 		<ul style="list-style-type: none"> ■ Sample 2 ■ Peer drinking norms at 18 (E_1) & at 19 (E_2) 	<ul style="list-style-type: none"> ■ Sample 2 ■ $G \times E \uparrow = A_1 \uparrow$ ($d = 0.40$) ■ $G \times E_2 \uparrow = A_2$ ns ($d = 0.08$)
Mrug et al. ²³	<ul style="list-style-type: none"> ■ $n = 340$ ■ M age = 17 at T1 ■ Mixed races in the U.S. 	<ul style="list-style-type: none"> ■ Average alcohol consumption per day (A_1) at 17, 23, 29, & 33 20 (A_2) 	<ul style="list-style-type: none"> ■ DRD4 VNTR (long allele [-repeat]) 	<ul style="list-style-type: none"> ■ Perceived percentage of close friends considered to be heavy 	<ul style="list-style-type: none"> ■ M age 17, 23, & 29, $G \times E = A$ ns (no ES) ■ M age 33, $G \times E \uparrow = A_1 \uparrow$

DOPAMINE SYSTEM

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
Park et al. ²²	<ul style="list-style-type: none"> ■ $n=234$ ■ $M_{age}=18$ at T1 ■ Caucasians in the U.S. 	<ul style="list-style-type: none"> ■ Frequency of heavy drinking (6+/6 months) (A_2) at 17, 23, 29, & 33 ■ Alcohol dependence trait at 18 to 21 (A_1), at 25 to 34 (A_2), at all 20 (A_2) periods (A_3) 	<ul style="list-style-type: none"> ■ DRD4 VNTR (long allele [-repeat]) 	<ul style="list-style-type: none"> ■ Fraternity or Sorority involvement at 18 to 21 (E_1) ■ Delayed adult role transition at 25 to 34 (E_2) ■ Childhood adversity (E_3) 	<ul style="list-style-type: none"> ■ Age 18-21, $G \times E_1 \uparrow = A_1 \uparrow$ ($\beta = 0.26$) ■ Age 25-34, $G \times E_2 = A_2$ ns ($\beta = -0.10$) ■ Age 18-34, $G \times E_3 \uparrow = A_3 \uparrow$ ($\beta = 0.22$)
Carlson et al. ³⁹	<ul style="list-style-type: none"> ■ $n=367$ ■ $M_{age}=18$ at T1 ■ Caucasians in the U.S. 	<ul style="list-style-type: none"> ■ Alcohol dependence symptoms at 18 to 26 (A_1) and at 26 (A_2) 	<ul style="list-style-type: none"> ■ DRD4 VNTR (7-repeat allele) 	<ul style="list-style-type: none"> ■ Childhood adversity (E_1) ■ Work and family role at 26 (E_2) 	<ul style="list-style-type: none"> ■ $G \times E_1 = A_1$ ns (no ES) ■ $G \times E_2 = A_2$ ns (no ES)
Larsen et al. ³³	<ul style="list-style-type: none"> ■ $n=113$ ■ $M_{age}=21$ ■ Caucasians in the U.S. 	<ul style="list-style-type: none"> ■ Drinking quantity 	<ul style="list-style-type: none"> ■ DRD4 VNTR (7-repeat allele) 	<ul style="list-style-type: none"> ■ Heavy drinking peers in lab environment 	<ul style="list-style-type: none"> ■ $G \times E \uparrow = A \uparrow$ ($np^2 = 0.11$)
DRD2					
Creemers et al. ³⁵	<ul style="list-style-type: none"> ■ $n=1,192$ ■ $M_{age}=11$ at T1 ■ Netherlands; race was not reported 	<ul style="list-style-type: none"> ■ Frequency of drinking at 16 	<ul style="list-style-type: none"> ■ DRD2 TaqIA ($A1A1/A1A2$) 	<ul style="list-style-type: none"> ■ Parental rejection at 11 (E_1) ■ Parental overprotection at 11 (E_2) ■ Parental emotional warmth at 11 (E_3) 	<ul style="list-style-type: none"> ■ $G \times (E_1 \text{ or } E_2 \text{ or } E_3) = \text{all } A$ ns (OR=0.89-1.10)
DOPAMINE SYSTEM					
Brody et al. ³⁷	<ul style="list-style-type: none"> ■ Combined $n > 900$ ■ Sample 1: $M_{age}=11$ at T1 & Sample 2: $M_{age}=16$ at T1 ■ African American 	<ul style="list-style-type: none"> ■ Frequencies of drinking & heavy drinking (4+) at 11 & 14 for Sample 1, at 16 & 17 for Sample 2 	<ul style="list-style-type: none"> ■ DRD2 (CAG & CGG) 	<ul style="list-style-type: none"> ■ Prevention program on family communication & support at 11 for Sample 1 & at 16 for Sample 2 	<ul style="list-style-type: none"> ■ $G \times \text{no } E = A \uparrow$ (no ES)
Pieters et al. ⁴⁰	<ul style="list-style-type: none"> ■ $n=196$ ■ $M_{age}=13$ ■ Mixed races in the Netherlands 	<ul style="list-style-type: none"> ■ Drinking quantity 	<ul style="list-style-type: none"> ■ DRD2 TaqIA ($A1A1/A2A1$) 	<ul style="list-style-type: none"> ■ Parental alcohol related rule setting 	<ul style="list-style-type: none"> ■ $G \times E \uparrow = A \uparrow$ ($\beta = -0.33$)
Van der Zwaluw et al. ⁴¹	<ul style="list-style-type: none"> ■ $n=428$ ■ $M_{age}=13$ at T1 ■ Netherlands; race was not reported 	<ul style="list-style-type: none"> ■ Drinking quantity at 13 to 15 	<ul style="list-style-type: none"> ■ DRD2 TaqIA ($A1A1/A1A2$) 	<ul style="list-style-type: none"> ■ Parental alcohol related rule setting at 13 & 14 	<ul style="list-style-type: none"> ■ $G \times E \uparrow = A \uparrow$ ■ Age 13→14 ($\beta = -0.19$ - -0.17) ■ Age 14→15 ($\beta = -0.25$ - -0.16)
Van der Zwaluw et al. ⁴²	<ul style="list-style-type: none"> ■ $n=596$ ■ $M_{age}=14$ at T1 ■ Netherlands; race 	<ul style="list-style-type: none"> ■ Drinking quantity at 15 to 19 	<ul style="list-style-type: none"> ■ DRD2 TaqIA (TT= $A1A1$/CT= $A1A2$) 	<ul style="list-style-type: none"> ■ Parental alcohol related rule setting at 14 	<ul style="list-style-type: none"> ■ $G \times E = A$ ns (OR=0.86-1.06)

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
was not reported					
ANKK1 ■Brody et al. ³⁷	■Combined n > 900 ■Sample 1: M age = 11 at T1 & Sample 2: M age = 16 at T1 ■African American	■Frequencies of drinking & heavy drinking (4+) at 11 & 14 for Sample 1, at 16 & 17 for Sample 2	■ANKK1 (TTAG) (G ₃)	■Prevention program on family communication & support at 11 for Sample 1 & at 16 for Sample 2	■G × E = A <i>ns</i> (no ES)
KCNJ6 Clarke et al. ⁷⁶	■n = 261 ■M age = 3 months at T1 ■German descent	■AUDIT at 19	■KCNJ6 (GG)	■Psychosocial adversity (E ₁) ■Stressful life events for the past 4 years at 19 (E ₂)	■G × E ₁ = A [†] (α = 0.43) ■G × E ₂ = A <i>ns</i> (β = 0.35)
MAO-A Nilsson et al. ⁷⁸	■n = 66 ■M age = 16 & 19 at T1 ■Sweden; race was not reported	■Alcohol related problem behavior at 19 & 22	■MAO-A-VNTR (short variants = 3 repeat)	■Poor family relations at 16 & 19 (E ₁) ■Lifetime maltreatment/sexual abuse at 16 & 19 (E ₂)	■G × E ₁ or E ₂ = A <i>ns</i> (no ES) ■G × (E ₁ + E ₂) [†] = A [†] (no ES)
Nilsson et al. ⁷⁹	■n = 114 ■M age = 16 & 19 at T1 ■Sweden; race was not reported	■Alcohol related problem behavior at 19 & 22 (A ₁) ■AUDIT at 19 & 22 (A ₂)	■MAO-A-VNTR (long variants = 4 repeats)	■Family relations at 16 & 19 (E ₁) ■Lifetime maltreatment/sexual abuse at 16 & 19 (E ₂)	■G × E ₁ = all A _s [†] (no ES) ■G × E ₂ = A ₁ (no ES) ■G × E ₂ = A ₂ <i>ns</i> (no ES)
DOPAMINE SYSTEM MAO-B Nilsson et al. ⁷⁹	■n = 114 ■M age = 16 & 19 at T1 ■Sweden; race was not reported	■Alcohol related problem behavior at 19 & 22 (A ₁) ■AUDIT at 19 & 22 (A ₂)	■Platelet MAO-B (low level activity)	■Family relations at 16 & 19 (E ₁) ■Lifetime maltreatment/sexual abuse at 16 & 19 (E ₂)	■G × (E ₁) [↓] or E ₂ [†] = all A _s [†] (no ES)
COMT Laucht et al. ⁷⁷	■n = 285 ■M age = 15 at T1 ■Predominantly (>99%) European descent in Germany	■Drinking quantity at 15 & 19 (A ₁) ■Drinking frequency at 15 & 19 (A ₂)	■COMT rs4680 (Met/Met)	■Parental supervision at 15 (E ₁) ■Parental involvement at 15 (E ₂) ■Adolescent autonomy at 15 (E _{3E})	■G × E ₁ = all A _s [†] (β = -1.32 - -0.96) ■G × E ₂ = A ₁ [†] (β = -1.05) ■G × E ₃ = all A _s <i>ns</i> (β = -0.25 - 0.17)
SEROTONIN SYSTEM 5-HTTLPR Kaufman et al. ⁴⁵	■n = 127 ■M age = 10 at T1	■Alcohol ever use at 12 (A ₁)	■5-HTTLPR SLC6A4 promotor	■Lifetime maltreatment (physical)	■G × E ₁ = A ₁ [†] (no ES) ■G × E = A ₂ <i>ns</i> (no ES)

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core G×E finding (ES; Effect size)
Kim et al. ²⁵	<ul style="list-style-type: none"> ■Mixed races in the U.S. ■Sample 1 <ul style="list-style-type: none"> ■$n = 4,916$ ■M age = 12 at T1 ■Caucasian in the U.K. 	<ul style="list-style-type: none"> ■Episodes of intoxication at 12 (A_2) 	VNTR (LS)	abuse, sexual abuse, neglect, & domestic violence) at 10	<ul style="list-style-type: none"> ■Sample 1 <ul style="list-style-type: none"> ■$G \times E = A_1 \& A_2$ ns ($\beta = 0.02 - 0.09$) ■$G \times E^\dagger = A_3^\dagger$ ($\beta = 0.19$)
		<ul style="list-style-type: none"> ■Sample 1 <ul style="list-style-type: none"> ■Drinking frequency at 12 & 15 (A_1) ■Maximum drinks at 12 & 15 (A_2) ■Frequency of 3 or more drinks at 12 (A_3) ■Sample 2 <ul style="list-style-type: none"> ■Drinking frequency at 15 (A_1) ■Intoxication frequency at 15 (A_2) 	<ul style="list-style-type: none"> ■5-HTTLPR ($S'L'/S'S'$) 	<ul style="list-style-type: none"> ■Sample 1 <ul style="list-style-type: none"> ■Family conflict at 12 ■Sample 2 <ul style="list-style-type: none"> ■Family conflict at 15 	
Olsson et al. ³⁸	<ul style="list-style-type: none"> ■$n = 752$ ■M age = 24 ■Australian ethnicity 	<ul style="list-style-type: none"> ■Ever binge drinking 	<ul style="list-style-type: none"> ■5-HTTLPR (SS & SL; protective allele) 	<ul style="list-style-type: none"> ■Adult attachment typically with parents 	<ul style="list-style-type: none"> ■Sample 2 <ul style="list-style-type: none"> ■$G \times E = A_1$ ns ($\beta = 0.28 - 0.44$) ■$G \times E^\dagger = A_2^\dagger$ (cross-sectional, $\beta = 0.57$; longitudinal, $\beta = 0.48$) $G \times E^\dagger = A_1^\dagger$ (OR = 1.41)
Daw et al. ⁵¹	<ul style="list-style-type: none"> ■$n = 14,560$ ■M age = 16 ■Mixed races in the U.S. 	<ul style="list-style-type: none"> ■Drinking quantity (A_1) ■Drinking frequency (A_2) 	<ul style="list-style-type: none"> ■5-HTTLPR ($S'L'/S'S'$) 	<ul style="list-style-type: none"> ■School-level frequency of drinking 	<ul style="list-style-type: none"> ■$G \times E^\dagger = A_1^\dagger$ (no ES) ■$G \times E^\dagger = A_2$ ns (no ES)
Nilsson et al. ⁴⁶	<ul style="list-style-type: none"> ■$n = 200$ ■M age = 16 & 19 ■Sweden; race was not reported 	<ul style="list-style-type: none"> ■Drinking quantity per year (A_1) ■Intoxication frequency (A_2) 	<ul style="list-style-type: none"> ■5-HTTLPR (LS) 	<ul style="list-style-type: none"> ■Family relations 	<ul style="list-style-type: none"> ■$G \times E^\dagger =$ all $As^\dagger$ (no ES)
Covault et al. ⁴⁷	<ul style="list-style-type: none"> ■$n = 295$ ■M age = 18 at T1 ■Caucasians in the U.S. 	<ul style="list-style-type: none"> ■Drinking frequency at 18 & 19 (A_1) ■Heavy drinking (4+/5+) frequency at 18 & 19 (A_2) ■Intention to drink at 18 & 19 (A_3) 	<ul style="list-style-type: none"> ■5-HTTLPR (SS) 	<ul style="list-style-type: none"> ■Past-year stressful life events at 18 & 19 	<ul style="list-style-type: none"> ■$G \times E^\dagger =$ all $As^\dagger$ ($R^2 = 0.01 - 0.04$)
Kranzler et al. ⁴⁸	<ul style="list-style-type: none"> ■$n = 393$ ■M age = 20 at T1 ■African descents in the U.S. 	<ul style="list-style-type: none"> ■Drinking frequency at 20 (A_1) ■Frequency of heavy drinking (4+/5+) at 20 (A_2) 	<ul style="list-style-type: none"> ■5-HTTLPR SLC6A4 promotor VNTR ($S'L'/S'S'$) 	<ul style="list-style-type: none"> ■Past-year stressful life events at 20 	<ul style="list-style-type: none"> ■Among women, $G \times E^\dagger =$ all $As^\dagger$ (no ES) ■Among men, $G \times E =$ all As ns (no ES)
Laucht et al. ⁵⁰	<ul style="list-style-type: none"> ■$n = 309$ ■M age = 3 months at T1 ■Predominantly (>99%) European descent in Germany 	<ul style="list-style-type: none"> ■Drinking quantity at 19 (A_1) ■Frequency of binge drinking (4+/5+) at 19 (A_2) 	<ul style="list-style-type: none"> ■5-HTTLPR (LL or L'L') 	<ul style="list-style-type: none"> ■Psychosocial adversity for a year prior to birth (E_1) 	<ul style="list-style-type: none"> ■$G \times E^\dagger = A_1$ ns ($\beta = -0.32 - 0.34$) ■$G \times E^\dagger = A_2^\dagger$ ($\beta = -0.40 - 0.42$)

SEROTONIN SYSTEM

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
OPRM1 Chassin et al. ²¹	■ $n = 238$ ■ M age=12 at T1 ■ Caucasian in the U.S.	■ AUD symptoms at mean ages of 21 (A_1), at 26 (A_2), & at 34 (A_3)	■ OPRM1 (AG/GG)	■ Recent stressful events at 19 (E_2)	■ $G \times E_2 \uparrow =$ all $A_3 \uparrow$ ($\beta = -0.42 - 0.70$)
	■ $n = 196$ ■ M age=13 ■ Mixed races in the Netherlands	■ Drinking quantity	■ OPRM1 (AG&GG)	■ Descriptive & injunctive peer drinking norms at mean ages of 21 (E_1), at 26 (E_2), & at 34 (E_3)	■ women at 21, $G \times E_1 \uparrow = A_1 \uparrow$ (no ES) ■ men at 21, $G \times E_1 = A_1$ ns (no ES) ■ $G \times E_2 = A_2$ ns (no ES)
	■ $n = 596$ ■ M age=14 at T1 ■ Netherlands; race was not reported	■ Drinking quantity at 15 to 19	■ OPRM1 (AG/GG)	■ Parental alcohol related rule setting	■ $G \times E_2 = A_2 \uparrow$ ($\beta = -0.26$)
CRHR1 Blomeyer et al. ⁵⁷	■ $n = 104$ ■ M age=15 ■ Caucasians in the U.S.	■ Adolescent AUD	■ OPRM1 (AG/GG)	■ Parental alcohol related rule setting at 14	■ $G \times E_1 \uparrow = A_1 \uparrow$ (OR = 1.87 - 3.20) ■ Moderate vs light drinkers - $G \times E_2 = A$ ns (OR = 0.58)
	■ $n = 280$ ■ M age=15 ■ Predominantly (>99%) European descent in Germany	■ Average alcohol quantity (A_1) ■ Past-month drinking frequency (A_2) ■ Maximum number of drinks (A_3) ■ Frequency of heavy drinking (4+/5+) (A_4)	■ CRHR1 rs242938 (AG/GG) (G_1) rs1876831(CC) (G_2)	■ Parental monitoring (E_1) ■ Deviant peer affiliation (E_2)	■ $G \times E_1 \downarrow$ or $E_2 \uparrow = A_1 \uparrow$ (E_1 ; OR = 0.19) (E_2 ; OR = 7.64)
	■ $n = 270$ ■ M age=15 at T1 ■ Predominantly (>99%) European descent in Germany	■ Age at drinking onset at 15 & 19 (A_1) ■ Drinking quantity (A_2) at 19 ■ Maximum drinks (A_3) at 19 ■ Drinking frequency (A_4) at 19 ■ Binge drinking (4+/5+) frequency (A_5) at 19	■ CRHR1 rs242938 (AG/GG) (G_1) rs1876831(CC) (G_2)	■ Stressful life events for the past 3 years	■ G_{1A} , $E =$ all As ns (no ES) ■ G_{2A} , $E = A_1$ & A_2 ns (no ES) ■ G_{2A} , $E \uparrow = A_3 \uparrow$ & $A_4 \uparrow$ (no ES)
ORTTCTROPIN Schmid et al. ⁵⁸				■ Childhood stressful life events for past 2 years before drinking onset at 2 to 15 (E_1) ■ Current stressful life events for the past 4 years at 19 (E_2)	■ $G_1 \times E_1 = A_1$ ns (HR = 1.04) ■ $G_1 \times E_2 \uparrow = A_2 \uparrow$ & $A_5 \uparrow$ ($\beta = 0.60 - 0.63$) ■ $G_2 \times E_1 = A_1 \uparrow$ (HR = 1.10) ■ $G_2 \times E_2 \uparrow = A_2 \uparrow$ ($\beta = -0.36$)
CRH-BP					

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
Goyal et al. ⁵⁹	<ul style="list-style-type: none"> ■ $n = 541$ ■ M age = 15 ■ African Americans in the U.S. 	<ul style="list-style-type: none"> ■ Alcohol use/misuse including drinking frequency, quantity, heavy drinking (5+) frequency 	<ul style="list-style-type: none"> ■ CRHBP rs1715749 (G_1) (CC) 7 other SNPs 	<ul style="list-style-type: none"> ■ Stressful life events for the last 12 months 	<ul style="list-style-type: none"> ■ $G_1 \times E_1^{\dagger} = A^{\dagger}$ ($R^2 = 0.09$) ■ All other $G_{3 \times} E = A$ ns (no ES)
GABRA2 & GABRG1					
Brody et al. ³⁷	<ul style="list-style-type: none"> ■ Combined $n > 900$ ■ Sample 1: M age = 11 at T1 & Sample 2: M age = 16 at T1 ■ African Americans in the U.S. 	<ul style="list-style-type: none"> ■ Frequencies of drinking & heavy drinking (4+) at 11 & 14 for Sample 1, at 16 & 17 for Sample 2 	<ul style="list-style-type: none"> ■ GABRG1 Block1 (G_1) ■ GABRG1 Block2 (AGTC & AGTT) (G_2) ■ GABRA2 Block1 (CA & CG) (G_3) 	<ul style="list-style-type: none"> ■ Prevention program on family communication & support at 11 for Sample 1 & at 16 for Sample 2 	<ul style="list-style-type: none"> ■ $G_{1 \times} E = A$ ns (no ES) ■ $G_{2 \times} E = A^{\dagger}$ (no ES) ■ $G_{3 \times} E = A^{\dagger}$ (no ES)
Russell et al. ⁶⁸	<ul style="list-style-type: none"> ■ $n = 1,920$ ■ M age = 11 at T1 ■ Mixed races in the U.S. 	<ul style="list-style-type: none"> ■ Change of past-month drinking frequency and drunkenness from 12 to 18 	<ul style="list-style-type: none"> ■ GABRA2 rs279845 (TT; protective) 	<ul style="list-style-type: none"> ■ Substance misuse intervention at 11 	<ul style="list-style-type: none"> ■ $G \times \text{yes } E = A^{\dagger}$ (IRR = 0.50 at 13)
GABA					
Kiive et al. ²⁴	<ul style="list-style-type: none"> ■ $n = 583$ ■ M age = 15 at T1 ■ Caucasians in Estonia 	<ul style="list-style-type: none"> ■ Frequency of typical alcohol consumption at 15 (A_1) ■ Alcohol Use Disorder at 25 (A_2) 	<ul style="list-style-type: none"> ■ GABRA2 rs279826 (AA & AG) (G_1) ■ rs279858 (AA & AG) (G_2) 	<ul style="list-style-type: none"> ■ Early life stress in childhood (E_1) ■ Current life stress in the last 5 years at 25 (E_2) 	<ul style="list-style-type: none"> ■ $G_1 \times E_1^{\dagger} = A_1^{\dagger}$ (no ES) ■ $G_1 \times E_1^{\dagger} = A_2^{\dagger}$ (OR = 1.40) ■ $G_1 \times E_2^{\dagger} = A_2^{\dagger}$ (no ES) ■ $G_2 \times E_2^{\dagger} = A_2^{\dagger}$ (no ES)
CIRCADIAN RHYTHM					
Dong et al. ⁶⁴	<ul style="list-style-type: none"> ■ $n = 273$ ■ M age = 3 months at T1 ■ Germans; race was not reported 	<ul style="list-style-type: none"> ■ Frequency of heavy drinking (4+/5+) per month at 19 (A_1) ■ Average drinking quantity at 19 (A_2) 	<ul style="list-style-type: none"> ■ PER1 (CT & CC) 	<ul style="list-style-type: none"> ■ Psychosocial adversity for a year prior to birth measured at 3 months 	<ul style="list-style-type: none"> ■ $G \times E^{\dagger} = A1^{\dagger}$ ($\beta = 0.62$) ■ $G \times E^{\dagger} = A_2$ ns ($\beta = -0.14$)
Baranger et al. ⁶⁵	<ul style="list-style-type: none"> ■ $n = 665$ ■ M age = 19 ■ Mixed races in the U.S. 	<ul style="list-style-type: none"> ■ AUDIT 	<ul style="list-style-type: none"> ■ PER1 (CT & CC) 	<ul style="list-style-type: none"> ■ Early life stress in childhood 	<ul style="list-style-type: none"> ■ $G \times E^{\dagger} = A^{\dagger}$ ($\beta = 0.09$)
PER2					
Blomeyer et al. ⁶⁵	<ul style="list-style-type: none"> ■ $n = 131$ regular drinkers ■ M age = 19 ■ Predominantly (>99%) European descent in Germany 	<ul style="list-style-type: none"> ■ Drinking frequency (A_1) ■ Drinking quantity (A_2) ■ AUDIT (A_3) 	<ul style="list-style-type: none"> ■ PER2 (AA) 	<ul style="list-style-type: none"> ■ Stressful events for the past 4 years 	<ul style="list-style-type: none"> ■ $G \times E = A_1$ or A_2 ns (no ES) ■ $G \times E^{\dagger} = A_3^{\dagger}$ (no ES)
NR3C1					
Zheng et al. ⁷¹	<ul style="list-style-type: none"> ■ $n = 552$ ■ M age = 6 at T1 ■ Caucasians $n = 270$; African Americans n 	<ul style="list-style-type: none"> ■ Trajectories of binge drinking (5+) frequencies from grade 7 to 2 years 	<ul style="list-style-type: none"> ■ NR3C1 rs12655166 ($G1$: C; protective allele) Other 9 SNPs 	<ul style="list-style-type: none"> ■ Multi-component behavioral problem intervention from grade 1 	<ul style="list-style-type: none"> ■ $G1 \times E = A^{\dagger}$ (African Americans only) (OR = 1.63)
GLUCOCORTI-COID					

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
Goyal et al. ⁵⁹	= 282 in the U.S. ■ $n = 541$ ■ $M_{age} = 15$ ■ African Americans in the U.S.	post-high school ■ Drinking frequency, quantity, and heavy drinking (5+) frequency	■ NR3C1 9 SNPs	to 10 ■ Stressful life events for the last 12 months	■ All other 9 Gs $\times$ E = A ns (no ES) ■ All G $\times$ E $\uparrow$ = all As ns (no ES)
ADH1B, ADH1C, & ADH4					
Cleveland et al. ⁷⁴	■ $n = 1,815$ ■ $M_{age} = 11$ at T1 ■ Mixed races in the U.S.	Change of alcohol initiation and being drunk between 11 and 14 (A1) ■ Change of alcohol initiation and being drunk between 15 and 17(A2)	■ ADH1B (A) (G1) ■ ADH1C (G) (G2) ■ ADH4 (A) (G3)	■ Substance misuse intervention at 11	■ G1 $\times$ E = A ns (no ES) ■ G2 $\times$ no E = A1 $\uparrow$ (no ES) ■ G2 $\times$ no E = A2 ns (no ES) ■ G3 $\times$ E = A ns (no ES)
Desalu et al. ⁷³	■ $n = 241$ ■ $M_{age} = 20$ ■ African descent	■ Frequency of drinking (A1) ■ Negative drinking consequences (A2)	■ ADH1B (*3; protective allele)	■ Alcohol offer (E1) ■ Perceived peer drinking norm (E2)	■ G $\times$ E1 = all As $\downarrow$ (IRR = 1.14–1.21) ■ G $\times$ E2 = A1 ns (IRR = 1.21) ■ G $\times$ E2 = A2 $\downarrow$ (IRR = 1.41)
O'Shea et al. ⁷⁵	■ $n = 318$ ■ $M_{age} = 18$ ■ East Asians	■ Drinking quantity	■ ALDH2 *2 (GG)	■ Perceived peer drunkenness	■ G $\times$ E $\uparrow$ = A $\uparrow$ (no ES)
ALCOHOL DEHYDROGENASE					
Sum of GABRG1, GABRA1, & DRD2 risk alleles					
Brody et al. ³⁷	■ Combined $n > 900$ ■ Sample 1: $M_{age} = 11$ at T1 & Sample 2: $M_{age} = 16$ at T1 ■ African American in the U.S.	■ Frequencies of drinking & heavy drinking (4+) at 11 & 14 for Sample 1, at 16 & 17 for Sample 2	■ GABRG1 Block1 (GT) ■ GABRA2 Block 1(CA & CG) ■ DRD2 (CAG & CGG)	■ Prevention program on family communication & support at 11 for Sample 1 & at 16 for Sample 22	■ G index $\times$ no E = A $\uparrow$ ($\beta = -0.65$)
Sum of five OXTR SNPs risk alleles					
Cleveland et al. ⁸⁷	■ $n = 1,418$ ■ $M_{age} = 11$ at T1 ■ Mixed races in the U.S.	■ Sum of alcohol initiation and being drunk at 14	■ OXTR 5 SNPs	■ Peer substance use (E1) at 11 ■ Substance misuse intervention (E2) at 11	■ G index $\times$ E1 = A ns (no ES) ■ G index $\times$ E2 = A ns (no ES) ■ G index $\uparrow$ $\times$ E1 $\downarrow$ $\times$ E2 = A $\uparrow$ (no ES)
MULTI-LOCUS INDEX					
Sum of DAT1, DRD2, DRD4, 5-HTTLPR, & MAOA risk alleles					
Stogner et al. ⁸³	■ $n = 1,495$ & ■ $M_{age} = 16$ at T1 ■ Mixed races in the U.S.	■ Alcohol ever use at 17	■ DAT (10-repeat) ■ DRD2 (A1) ■ DRD4 (7-repeat) ■ 5-HTTLPR (short)	■ Perceived parental rejection at 16	■ G index $\times$ E $\uparrow$ = A $\uparrow$ (OR = 1.13)

Citation	Sample Characteristic	Alcohol outcome (A)	Gene (Risky allele) (G)	Environment (E)	Core GxE finding (ES; Effect size)
Sum of DRD2, MAOA, & LMO3 risk alleles					
Guo et al. ⁸⁶	■Sample 1 ■n = 1,003 ■M age = college students (no age) ■Mixed races in the U.S	■Sample 1 ■Heavy drinking frequency (A ₁) ■Past two weeks heavy drinking (definition was not stated) ■Sample 2 ■Heavy drinking (definition was not stated) frequency (A ₁) at 22	■ MAOA (low activity) ■DRD2 (rs4245145, rs22424592, rs1125394) MAOA LMO3	■Sample 1 ■Roommate's drinking ■Sample 2 ■Friend's drinking at 15	■Sample 1; Medium risk of G index ■G × E↑ = A ₁ ↑(β = 0.95) ■G × E ↑ = A2↑(β = 0.88) ■Sample 2; Medium risk of G index ■Gx E↑ = A1 ↑(β = 1.1)
MULTI-LOCUS INDEX					

Note. For studies that examined more than one gene, the results were presented separately for each gene. GxE = gene and environment interaction; ns = not significant; ↑ = greater levels or increased effects; ↓ = lower levels or decreased effects; no ES = no GxE interaction effect size is reported; SNP = Single-Nucleotide Polymorphism; ADH = alcohol dehydrogenase; AUD = Alcohol Use Disorder; AUDIT = Alcohol Use Disorders Identification Test; ANKK1 = ankyrin repeat and kinase domain containing 1; COMT = catechol-o-methyltransferase; CRHR1 = corticotropin releasing hormone receptor; CRHBP = Corticotropin Releasing Hormone Binding Protein; DRD2 = dopamine receptor d2; DRD4 = dopamine receptor d4; GABA = gamma-aminobutyric acid; GABRG1 = gaba-a receptor, gamma subunit1; GABRA2 = gaba-a receptor alpha2 subunit; KCNJ6 = potassium channel, inwardly rectifying subfamily J, LMO3 = LIM Domain Only 3, Member 6; MAO-A-VNTR = monoamine oxidase a variable number tandem repeat; MAO-B = monoamine oxidase b; NR3C1 = Nuclear Receptor Subfamily 3 Group C Member 1, OPRM1 = μ-opioid receptor, mu 1; PER1 = period circadian clock 1; PER2 = period circadian clock 2; 5-HTTLPR = 5-htt linked promoter region; 5-HTTLPR-L = long allele; S = short allele; S' = low activity allele; L' = high activity allele; OR = Odds Ratio; β = standardized regression coefficient; R² = coefficient of determination; HR = hazard ratio; ηp² = eta squared; RR = relative risk ratio; IRR = incidence rate ratio; 4+/5+ = 4 standard drinks or more for women and 5 standard drinks or more for men.

*The findings on MAO-A, MAO-B, and COMT are summarized under dopamine system for simplicity, although their functions are not limited to dopamine system.

Table 2

Summary of the extant youth cGxE findings as a function of environmental factors. Studies that showed statistically significant GxE effects on youth drinking behaviors are marked with an asterisk. Studies that found non-significant GxE effects are written in italic font style. Studies that examined other environments were not included in the table. Two studies that examined intervention effects were not included in the table (Russell et al.⁶⁸, Cleveland et al.⁷⁴, Zheng et al.⁷¹)

Gene	Family Environment	Stressful Environment	Peer Environment
DRD4	Parenting style (Creemers et al. ³⁵ *) <i>Family prevention (Brody et al.³⁷)</i> <i>Adult attachment with parents (Olsson et al.³⁸)</i>	Childhood adversity (Park et al. ²² *) <i>Childhood adversity (Carlson et al.³⁹)</i>	Greek organization involvement (Park et al. ²² *) Heavy drinking confederates (Larsen et al. ³³ *) Drinking peer norm (Van der Zwaluw et al. ³⁴ *) <i>Drinking peer norm (Mrug et al.²³)</i> Anti-social peer pressure (Griffin et al. ³¹ *) Perceived drinking peer norm (Park et al. ³² *)
DRD2	Alcohol related rule setting (Van der Zwaluw et al. ⁴¹ ; Pieters et al. ⁴⁰ *) <i>(Van der Zwaluw et al.⁴²)</i> <i>Parenting (Creemers et al.³⁵)</i> Family prevention (Brody et al. ³⁷ *) <i>Family prevention (Brody et al.³⁷)</i>		
ANKK1			
KCNJ6			
MAO-A	<i>Poor family relationship (Nilsson et al.⁷⁸)</i> Poor family relationship (Nilsson et al. ⁷⁹ *)	Psychosocial adversity before birth; <i>Current stressful life events</i> (Clarke et al. ⁷⁶) Lifetime maltreatment and poor family relationship (Nilsson et al. ⁷⁸ *) <i>Lifetime maltreatment (Nilsson et al.^{78, 79})</i>	
MAO-B	Poor family relationship (Nilsson et al. ⁷⁹ *)	Lifetime maltreatment (Nilsson et al. ⁷⁹ *)	
COMT	Parenting style (Laucht et al. ⁷⁷ *)		
5-HTTLPR	Insecure attachment (Olsson et al. ³⁸ *) Poor family relationship (Nilsson et al. ⁴⁶ *) Family conflict (Kim et al. ²⁵ *)	Sum of stressful life events (Kaufman et al. ⁴⁵ ; Laucht et al. ⁵⁰ ; Kranzler et al. ⁴⁸ ; Covault et al. ⁴⁷ *)	School level frequency of alcohol (Daw et al. ⁵¹ *)
OPRM1	Parental monitoring (Miranda et al. ⁵⁴ *) Alcohol related rule setting (Van der Zwaluw et al. ⁴² ; Pieters et al. ⁴⁰ *)		Alcohol peer norm (Chassin et al. ²¹ *) Substance peer norm (Miranda et al. ⁵⁴ *)
CRHR1		Sum of stressful life events (Blomeyer et al. ⁵⁷ ; Schmid et al. ⁵⁸ *)	
CRHBP		Sum of stressful life events (Goyal et al. ⁵⁹ *)	
GABA receptors	Family prevention (Brody et al. ³⁷ *)	Stressful life events (Kiive et al. ²⁴ *)	
PER1		Psychosocial adversity before birth (Dong et al. ⁶⁴ *) <i>Early life stress in childhood (Baranger et al.⁶⁵)</i>	

Gene	Family Environment	Stressful Environment	Peer Environment
PER2		Sum of stressful life events (Blomeyer et al. ⁶⁵)*	
NR3C1		Sum of stressful life events (Goyal et al. ⁵⁹)*	
ADH & ALDH			Peer drinking (O'Shea et al. ⁷⁵)* Perceived drinking peer norm (Desalu et al. ⁷³)*
Multi-locus index	Family prevention (Brody et al. ³⁷)* Parental rejection (Stogner et al. ⁸³)*		Alcohol peer norm (Guo et al. ⁸⁶)* <i>Peer substance use (Cleveland et al.⁸⁷)</i>