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Genetically informative research on adolescent substance use: methods, findings and challenges

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Abstract

Objective—To provide an overview of the genetic epidemiology of substance use and misuse in adolescents.

Method—We present a selective review of genetically informative research strategies, their limitations and key findings examining issues related to the heritability of substance use and substance use disorders in children and adolescents.

Results—Adoption, twin and extended family designs have established there is a strong heritable component to liability to nicotine, alcohol and illicit drug dependence in adults. However, shared environmental influences are relatively stronger in youth samples and at earlier stages of substance involvement (e.g., use). There is considerable overlap in the genetic influences associated with the abuse/ dependence across drug classes while shared genetic influences also contribute to the commonly observed associations between substance use disorders and both externalizing and, to a lesser extent, internalizing psychopathology. Rapid technological advances have made the identification of specific gene variants that influence risks for substance use disorders feasible and linkage and association (including genomewide association studies) have identified promising candidate genes implicated in the development of substance use disorders.

Conclusions—Studies using genetically informative research designs, including those that examine aggregate genetic factors and those examining specific gene variants, individually and in interaction with environmental influences, offer promising avenues not only for delineating genetic effects on substance use disorders but also for understanding the unfolding of risk across development and the interaction between environmental and genetic factors in the etiology of these disorders.

Keywords

substance use disorders; adolescence; twin; genetics; gene by environment interaction

INTRODUCTION

The initial use of tobacco, alcohol and illicit drugs typically occurs during adolescence and some experience with these substances is now normative among adolescents in the United

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States and throughout the developed world.[1] While many youth who use drugs do so only infrequently and without experiencing any apparent adverse consequences, there are at least three principal reasons why substance use should be a major concern for child and adolescent psychiatrists: First, the acute effects of intoxication may have potentially serious long-term consequences, including increasing risks of motor vehicle and other unintentional injuries.[2] Second, a substantial proportion of adolescents report meeting criteria for abuse and/ or dependence on these substances, and substance abuse/ dependence are among the most prevalent psychiatric disorders in adolescents[3] while the majority of adults who develop a substance use disorder report onset during adolescence.[4] Finally, the age of onset of substance use is prognostic of subsequent risks for the development of abuse/ dependence and other measures of drug related harm.[5-8]

The goal of this review is to present an overview of the genetic epidemiology of substance use and misuse in adolescents. However, the study of genetic and environmental influences is predicated on an accurate understanding of the behavior being studied. As with all behavioral or psychiatric disorders there is considerable need both for precise definition and assessment of these behaviors[9] and to place them within a broader developmental framework.[10] Specific issues that need to be considered include: a) **Reliance on self report.** Although self–reports may underestimate the true extent of substance use, they are generally accepted as reliable and valid indicators of substance use.[11] Unlike some other areas of child and adolescent psychiatry where parental or other collateral reports are recognized as highly informative, parental reports of their child's substance use may be less reliable and valid as adolescents actively try to conceal the extent of their substance use from parents. While the use of biological samples (e.g., urine tests) may be ill suited for assessing lifetime patterns of substance use, they are recognized as useful in clinic referred samples and for assessing treatment compliance. b) Are DSM defined abuse and dependence criteria appropriate indices in children and adolescents? DSM[12] criteria for substance abuse and dependence were largely developed for use in adults and there have been ongoing concerns about the extent to which they may be appropriate for adolescents or young adults. Some symptoms (e.g., withdrawal) only occur after many years of heavy drinking and, given low prevalence in adolescence samples, may have limited utility for this age group.[13] Conversely, some symptoms of abuse, particularly items relating to getting into trouble with friends or family members may occur, because of parental restrictions, in adolescents who drink alcohol or use drugs only infrequently. Martin and Winters[9] described such individuals as "diagnostic imposters". Similarly, there are several dependence symptoms with high prevalence among adolescents, (particularly "tolerance" and "drinking more or longer than intended") that identify many adolescents with relatively low levels of consumption.[14] c) The extent to which normative behaviors may be indices of risk. Given that some use of tobacco, alcohol and also cannabis is normative among older teens, age of initiation and use is an important consideration: use of these substances among younger adolescents and children may be an indicator of heightened risks for the development of abuse/ dependence[15,16] and related risks.[17-19,20]

Thus, despite numerous challenges in assessing substance use disorders in adolescents, there has been increasing recognition of the public health and scientific importance of researching these behaviors; and in recent years there have been considerable advances in our understanding of them and, in particular, the mechanisms by which genetic factors may contribute to risks for substance use and substance use disorders.

METHOD

In this paper we present a selective review of genetically informative research designs and discuss key findings relating to the heritability of substance use disorders, the comorbidity

between substance use and other psychiatric disorders and gene by environmental interplay in the development of these disorders.

RESULTS

Genetically informative research approaches and their limitations

Adoption Studies—Some of the earliest findings suggesting heritable influences on substance use came from adoption studies in which offspring outcomes were compared with analogous measures in the biological and adoptive parents. Strong associations between biological parent and offspring behavior are interpreted as suggesting heritable influences, while strong associations between adoptive parent and offspring behavior suggest the role of rearing environment. While the seminal Iowa[21] and Swedish[22] adoption studies established strong correlations between biological parents and offspring diagnoses of alcohol and drug use disorders, they were based on adult samples.

The adoption design has important limitations: adoption studies have typically relied on official records to characterize biological parent psychopathology (e.g., arrest, hospitalization) and are likely to identify only severe cases. Related to this, biological parents who give their children up for adoption are not representative of the general population of biological parents. Additionally, due to both adoption agency screening and self-selection by adoptive parents, the number of adopted individuals raised in high-risk environments is likely to be limited: compared with the general population, adoptive parents are likely to be older, more affluent and less likely to show high rates of psychopathology. Furthermore, while the link between biological parents and offspring are presumed to exclude shared environment, exposure to maternal interuterine environment as well as age at adoption can result in sharing of environmental factors between biological mothers and their offspring.[23]

Twin studies—Although there have been several studies of twins reared apart,[24] because of the rarity of such pairs most research examines twins reared together. These studies compare concordance rates between members of monozygotic/identical and dizygotic/fraternal twins for a trait or disorder, with a higher degree of similarity in MZ (who share 100% of their genes) than in DZ twins (who, on average share 50% of their segregating genes) being interpreted as providing evidence for heritable influences on the behavior being studied. As shown in Figure 1, the correlation between a pair of twins can be expressed as a path diagram, where rectangles represent observed behavior and circles represent latent sources of variation: additive genetic (A), shared environmental (C) and non-shared environmental (E). Heritability is the proportion of total variance in behavior that is attributed to additive (and, in the case of broad heritability, non-additive, when they play a role) genetic factors. Several assumptions and potential limitations underlying the analysis of twin data that need to be considered[25], including: a) whether the equal environment assumption (which posits that the correlation for C is 1.0 in both MZ and DZ twin pairs) is justified. Despite concerns, general support for this assumption has been reported across a range of psychiatric phenotypes.[26] b) The assumption of random mating, the violation of which can inflate estimates of shared environment; (c) If some of the genetic variation in outcome is due to non-additive genetic effects (dominance or epistasis), the importance of shared family environmental influences may be underestimated. d) Genetic effects and gene by shared environment effects are confounded. Nonetheless, it is possible to explicitly model this gene-environment interplay by obtaining estimates of heritability that are conditioned on, or vary as a continuous function of, environmental exposure.

The Children of Twins Design—An extension of the classical twin study is the children-of-twins (COT) design which compares outcomes in offspring of twins. Using data on children of affected and unaffected MZ and DZ pairs, four groups can be defined: (1) high genetic risk and high environmental risk (parent, MZ or DZ, is affected), (2) high genetic risk but reduced environmental risk (parent is unaffected but parent's MZ twin is affected), (3) intermediate genetic risk but reduced environmental risk (parent is unaffected but parent's DZ twin is affected), and (4) children at low genetic and low environmental risk (parent and co-twin are both unaffected). The COT design allows for detection of genetic transmission that could in principle account for associations between an apparent environmental risk-factor and offspring outcomes[27]. It can also be used to detect the environmental consequences of parental substance use disorders that may or may not depend upon offspring genetic vulnerability or be masked by genetic non-additivity and therefore remain undetected in the traditional twin study design.

One of the relatively few published studies utilizing this design reported that, while offspring of MZ and DZ twins with a history of alcohol dependence were significantly more likely to exhibit alcohol abuse/ dependence than were offspring of nonalcoholic fathers, offspring of an unaffected (i.e., no history of abuse or dependence) MZ twin whose co-twin had alcohol dependence were no more likely to exhibit alcohol abuse or dependence than were offspring of nonalcoholic twins whose co-twin was also unaffected. This pattern of results suggests that a low risk environment (no exposure to paternal alcohol dependence) can ameliorate the influence of high risk genetic background.[28]

In addition to COT, extended twin designs that incorporate information on spouses of twins (i.e. to test for the assumption of random mating, or whether spousal correlations for behaviors like smoking and drinking is attributable to shared genes and environments) as well as parents and non-twin siblings have been employed [29]. Using, primarily, the classical twin design and its multivariate extensions, a host of studies have examined the sources of individual differences in alcohol, tobacco and illicit drug involvement.

Evidence for heritable influences on substance initiation and use—While it is well established that about 50-70% of the variation in alcohol use disorders is due to heritable factors,[30] initiation of alcohol use is largely influenced by shared environmental influences, with a review by Hopfer et al[31] indicating that in the region of 50-70% of variation in alcohol initiation could be attributed to shared environmental factors.

There is less evidence for the role of shared environmental influences on adolescent smoking. Several twin studies report that the heritability of smoking ranges from 25%[32] to 80%,[33] with higher heritability estimates for current smoking and regular or daily smoking. In contrast, Koopmans et al[34] found no evidence for heritable influences of smoking in adolescents aged 12-14 years – heritability increased to 27% in women aged 15-16 years and to 30-60% at ages 17-25 years. To some extent, these discrepancies are attributable to variability in definitions of smoking. Likewise, modest genetic and prominent shared environmental factors have been noted as contributors to variation in initiation of cannabis and other illicit drugs.[35]

Evidence for heritable influences on substance use disorders—Studies of alcohol, nicotine and illicit drug use disorders during adolescence are relatively uncommon as a majority of at-risk individuals meet criteria for abuse/dependence during early adulthood. Nonetheless, studies of one or more abuse/dependence symptoms during adolescence find strong evidence for the role of heritable influences (50% and greater).[36,37] While the role of shared environment appears to be non-significant in adult studies of

substance use disorders, it remains an important contributor to variation in adolescent substance use problems.[38]

The relationship between genetics of use and genetics of abuse/dependence?—Genes influencing substance initiation may also impact transitions to substance use disorders. Recognizing this conditional nature of substance use disorders, several genetic studies have modeled the genetic and environmental overlap across substance use and later abuse/dependence. Overwhelmingly, genetic influences on earlier stages of substance use have been found to be heavily correlated with genes influencing continued use and abuse/dependence – however, the source and extent of covariation differs across drugs. For instance,nearly 80-90% of the heritable influences on DSM-IV alcohol abuse/dependence overlap with indices of alcohol consumption.[39,40]. However, in adolescent samples, the overlap between use and escalation (binge drinking, getting drunk) was moderate [41]. Furthermore, particularly for alcohol, shared environment also facilitates escalation of use. A study of Finnish adolescent twins[42] examining the genetic overlap across alcohol use, frequency of consumption and problem drinking found that while drinking frequency and problem drinking shared over 50% of their genetic influences, the link between initiation and problem drinking was largely due to shared environment.

These shared environmental factors appear to be less prominent in the transitions for smoking initiation/regular smoking to nicotine dependence, with correlated genetic vulnerabilities serving as the primary source of covariation across these stages of smoking. In an adult sample, 60 -74% % of the liability to nicotine dependence was shared with earlier stages of smoking[33,43]. In contrast, Heath et al[44] reported minimal overlap between genetic influences on persistent smoking and those on initiation, leading to speculation that the etiology of persistent smoking (i.e. inability to quit) may be distinct from nicotine dependence.

Relative to alcohol, Fowler and colleagues reported significantly greater covariance between use and misuse of cigarettes and cannabis [41]. Perhaps the most convincing support for genetic overlap across stages of substance use arises from the study of cannabis and other illicit drugs, where results from adult samples show evidence for substantial genetic overlap (50-80%).[45,46] Gillespie et al[46] reported that cannabis availability accounted for 92-96% of the shared environmental (and only a modest 2-3% of the genetic) influences on cannabis initiation and abuse. The study, thus, presented two key conclusions – (a) that cannabis availability is heritable (18%), which is presumably due to individual predispositions to environmental exposure (or gene-environment correlation) and (b) that drug availability may represent a majority of shared environmental variance (C) in twin studies of substance use.

The consistent finding of genetic overlap between stages of substance use has important implications for genetic studies of adolescent cohorts. The moderate to high extent to which genetic factors are shared across stages of substance involvement suggest that a shared predisposition plays a role in trajectories of substance use and misuse. Thus, genetic factors identified in adolescents who use a substance occasionally may well be involved in later stages of dependence.

Comorbidity—Comorbidity, the occurrence of multiple psychiatric conditions in one individual, is highly prevalent and has strong implications for prognosis and course of both treated and untreated conditions.[47,48] Numerous studies have documented that use and misuse of different substances is highly correlated and that substance use and abuse/dependence are highly associated with externalizing psychopathology and, to a lesser extent, internalizing psychopathology. Multivariate twin studies can be used to model the extent to

which the same genetic factors influence vulnerability across substances and psychopathology.

Comorbidity between use of different substances—Evidence from twin studies supports the role of correlated genetic influences on use of alcohol and other drugs, as well as smoking, although to a lesser extent. For instance, Young et al[36] report genetic correlations of 0.15-0.3 between alcohol, tobacco and cannabis use. Similarly, Koopmans et al[49] reported that the genetic correlation between use of alcohol and tobacco is negligible during adolescence but is unmasked during early adulthood. Despite the reduced effect of shared genetic influences on tobacco use, Han et al[50] found evidence for a heritable (48%) common predisposition to alcohol, tobacco and drug use during adolescence.

While the genetic overlap between smoking and other forms of adolescent substance use appears to be tenuous, these links appear to be sensitive to the measures of smoking used and the comorbid drug under study. One study reported that as heritability of smoking increased, the genetic correlation between drinking and smoking also increased[34]. Smoking and cannabis use also share common genetic factors.[51] Intriguingly, two studies have reported that cannabis initiation could be linked to smoking progression, independent of its relationship with smoking initiation [52,53].

Finally, it is noteworthy that illicit drugs themselves share genetic influences to a considerable extent. One study of an adult sample reported that a single genetic factor was responsible for nearly all of the heritable influences on illicit substance use – the exception was opiate and sedative use, for which 70% and 50% of the genetic influences, respectively, were drug specific.[54]

Comorbidity between abuse/ dependence on different substances—There is robust evidence for shared genetic influences on alcohol, nicotine and drug dependence. Two studies focusing exclusively on the genetic and environmental underpinnings of illicit drug abuse/ dependence in males reported somewhat divergent results: Kendler et al[55] found no evidence for substance specific genetic influences on cannabis, sedatives, stimulants, cocaine opiates and hallucinogens. In contrast, Tsuang et al[56] reported specific genetic influences on opiate abuse, although most genetic influences were shared across these substances. Expanding this work to include licit as well as illicit drug dependence in both males and females, Kendler et al[57] concluded that there are two genetic factors (one predisposing largely to licit drug dependence and one to illicit drug dependence) underlying dependence on these drugs, although there was also evidence of quite large specific genetic influences on both nicotine and caffeine.

The extent to which these conclusions, which are based on adult samples, may generalize to adolescent samples or to earlier stages of substance use remains unclear. In adolescents, problem use of alcohol, tobacco and cannabis is influenced by correlated genetic, but not shared environmental, factors.[36] Also, Rhee et al[58] demonstrated that alcohol and drug dependence may be manifestations of a single common and heritable liability in adolescents. These authors examined multiple conceptualizations of comorbidity and determined that, in adolescents, underlying alcohol and drug dependence was a common liability and that these disorders were alternate forms of that liability. Together, these results suggest substantial overlap of both genetic and environmental factors associated with the development of abuse/ dependence across a range of licit and illicit drugs (the licit and illicit drug factors identified by Kendler et al[57] were highly correlated; r = .82). In contrast, utilizing a children-of-twins design, Volk et al[59] reported that after accounting for the offspring correlation between alcohol and nicotine dependence, there was evidence for the specificity of genetic transmission of vulnerability to alcohol and nicotine dependence.

Comorbidity with other psychiatric disorders—There is growing evidence of substantial genetic overlap of alcohol and drug use disorders with both externalizing[60-62] and internalizing disorders.[63] For example, in a study of adolescent twins Button et al[64] reported that 35% of the covariance between conduct disorder and drug use disorders could be attributed to common genetic sources and 46% to shared environmental influences. Using COT data, Knopik et al[65] demonstrated that intergenerational links between maternal alcohol dependence and offspring ADHD may be mediated by pleiotropic genetic effects, again supporting the important role of genetic influences on both within individual comorbidity and familial aggregation.

In contrast, multiple studies of adolescents suggest that associations between alcohol use and externalizing problems during adolescence are largely attributable to shared environmental influences.[66,67] While parental alcohol consumption and dependence have long been recognized as predicting both substance use and externalizing disorders in offspring, twin studies imply that parental alcohol use may link offspring alcohol involvement to other psychopathology via familial environmental mechanisms.

Smoking and externalizing problems also co-occur. Of considerable interest, the comorbidity between smoking, ADHD, conduct problems and other dimensions of delinquency has been partly attributed to maternal smoking during pregnancy (SDP). Multiple studies show increased rates of smoking and externalizing psychopathology in offspring of mothers with a history of SDP, however the extent to which the effects of SDP on offspring outcomes are genetic or environmental remain inconclusive. However, as SDP is a good indicator of maternal nicotine dependence and smoking persistence, it is often difficult to disentangle the independent effects of SDP on offspring smoking from familial transmission of vulnerability[68]. Insight into this confound may be offered by a recent study comparing related mother-offspring pairs with offspring conceived by assisted reproductive technologies, such as oocyte donations (i.e. where the mother is genetically unrelated to the offspring). This study reported that the link between ADHD and SDP was more noticeable in related pairs, thus arguing against an environmental/causal role of SDP[69]

Not surprisingly, genetic influences on adolescent illicit drug use have been linked to a general predisposition to impulsivity, disinhibition and correspondingly, to externalizing behaviors.[70] In adult samples drug dependence shares genetic influences with antisocial personality disorder and conduct disorder – for instance, Kendler et al [71] found that 64-86% of the genetic variation in these disorders was attributable to a common underlying factor.

There have been fewer studies examining the genetic comorbidity between substance involvement and internalizing disorders. For instance, shared genes only explain a modest proportion of the covariance between smoking and depressive symptoms during adolescence,[72] however, the impact of shared genetic vulnerability gains prominence during adulthood.[73,74] There also appears to be a genetic link between cannabis misuse and vulnerability to major depression in adult samples. Twins who used cannabis were more likely to also report depression and suicidality compared with co-twins who never used cannabis.[75] However, Fu and colleagues argue that genetic covariation between depression and cannabis abuse/dependence is attributable to comorbid antisocial personality disorder, albeit, perhaps to a greater extent in men.[76]

Endophenotypes—There is increasing interest in the concept of endophenotypes - defined by Gottesman and Gould[77] as a measurable index of liability to a phenotype that is often assumed to be more proximal to the biological underpinnings of the behavior. Endophenotypes are not only associated with disease (or behavior) but are transmitted in families (i.e. heritable) of affected individuals and while they may co-segregate with disease,

they are never a consequence of it. A wide variety of endophenotypes have been identified as indices of externalizing behavior. P300, for instance, reflects human cognitive ability to respond to 'oddball' stimuli. In a study of adolescent twins, reduced P300 was noted in the unaffected co-twins of twins who developed alcohol dependence during early adulthood.[78] Other commonly used endophenotypes for the study of substance use (and other psychopathology) include behavioral sensitivity (for alcohol, measured using sway scores of subjective high assessment scales)[79] and EEG activity (e.g. beta wave patterns)[80].

Genomics

With rapid technological advances, there is increasing interest in moving from delineation of latent (aggregate) genetic influences to the identification of specific gene variants that may confer risk for the development of substance use disorders. The earliest genomic efforts utilized a linkage approach (see Figure 2 (panel A)). Studies applying this method identified regions on chromosome 3 and 9 for adolescent drug dependence vulnerability[81] and for cannabis dependence symptoms. [82] The advantage of linkage analysis is that it allows for a parametric or non-parametric scan of the entire genome, which can, if well-powered, lead to discovery of novel genetic regions. However, these methods are often low resolution (a centiMorgan is equivalent to 1,000,000 bases of DNA, and linkage regions often span 10-50 cM). An alternative, hypothesis-focused technique is candidate gene analysis which characterizes a gene of putative biological importance with single nucleotide polymorphisms (SNPs) and compares the prevalence of the risk allele in those who are affected and unaffected (and can be related or unrelated, see panels B and C of Figure 2). SNPs are single base pair allelic variations that naturally occur across individuals. For instance, rs279871, is a SNP in intron 7 of the gamma-aminobutyric acid receptor A (*GABRA2*) gene. Dick and colleagues[83] demonstrated that individuals with one or more copies of the A allele were more likely to report illicit drug dependence independent of the age of onset of drug dependence. However, an increase in risk for alcohol dependence, by genotype, was only noted in those with ages of onset of alcohol dependence in their mid-twenties. Thus, the association between this polymorphism and alcohol (but not drug) dependence appeared to be absent during adolescence. Further, in an adolescent sample, Corley and colleagues[84] found several genes, including *GABRA2, CNR1* and *CHRNA2* to be associated with adolescent antisocial drug dependence.

While candidate gene studies allow the investigator to focus on a specific gene with high resolution, they preclude the possibility of gene discovery. Genomewide association studies, where SNPs are used to map the entire genome with considerable density, combine the resolution of gene association studies with the exploratory capabilities of linkage. For SUDs, such studies are fairly recent and while there are, currently, no published reports in adolescent populations, several large studies of adult samples have identified possible genetic influences on smoking[85], alcohol dependence[86] and most recently, cannabis dependence[87].

There are caveats to genomic studies of adolescents. First, twin studies suggest that genetic influences on SUDs gain prominence during early adulthood while shared environmental factors are more influential during adolescence. Second, due to the developmental course of SUDs, onsets during adolescence are uncommon, particularly in the general population. This dramatically reduces statistical power and influences the methodology for genomic studies.

The role of genes in comorbidity—While genomic findings for individual psychoactive substances are limited, the identification of genes that explain comorbidity across SUDs and with other externalizing psychopathology has shown some promise. Studies of alcohol, nicotine and drug dependence have found significant associations with

SNPs in *GABRA2*, *DRD2/ANKK1* and *CNR1*. Perhaps the most compelling of these, *GABRA2*, has also been shown to be associated with several aspects of externalizing behavior, including conduct disorder[83] and impulsivity. Thus, *GABRA2* may directly influence liability to behavioral undercontrol, which in turn, may increase an adolescent's likelihood of experimenting with and sustained use of psychoactive substances.

Gene by environment interaction—Thus far, our discussion has focused on the importance of genetic and environmental factors, *independent* of each other. However, there has been increasing interest in and recognition of the importance of gene-environment interplay in the etiology of substance use and other psychiatric disorders.[88] There are two related mechanisms by which genes work in concert with environmental exposures – gene-environment correlation and gene-environment interaction. GE correlation refers to genetic predisposition that influences our likelihood of being exposed to a certain environment. For instance, heritable influences have been found to influence deviant peer affiliations suggesting that one's own vulnerability to substance use is partly responsible for exposure to deviant peer groups. On the other hand, gene-environment interaction refers to moderation of genetic predisposition as a consequence of environmental exposure – for example, studies of adolescent Finnish twins indicated that in less stable neighborhoods there was greater evidence of genetic influence.[89] Conversely, in more supervised and restricted environments, there was less opportunity to express genetic predispositions and greater influence of environmental effects.[89,90] These analyses suggest that less restrictive environments provide greater opportunities for the expression of genetic predispositions, although again it appears that these effects may be age specific: the findings described above were reported for a sample of 16-18 year olds but using a very similar approach these authors were unable to replicate findings of significant moderation of genetic effects by socioregional factors in a younger sample of 12 to 14 year old Finnish twins.[91] Likewise, low levels of parental monitoring[92] as well as increased affiliations with substance using peers,[93] have been found to augment the importance of genetic influences of substance use.

Measured genotype x environment—As heritability can be moderated by changing environmental exposure, genotype may only influence behavior in certain environmental milieux. Some of the earliest, most influential – and arguably most controversial – work demonstrating the importance of measured gene by environment interaction was reported by Caspi et al[94] who found that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT/*SLC6A4*) gene moderated the influence of stressful life events on depression. While these results have been subject to multiple attempts at replication with mixed results (see reviews by Merikangas[95] and Caspi[96]), they have been highly influential in alerting the field to the possibility and promise of gene by environment interactions in the etiology of psychiatric and substance use disorders. In the study of environmental moderation of genotypic risk for substance involvement, Dick et al[97] recently explored the potential moderating influence of parental monitoring on the association between *GABRA2* and a broad measure of externalizing behaviors in a longitudinal sample of adolescents. Although their analyses did not focus on alcohol or other drug use, their finding that the association of *GABRA2* with externalizing trajectories diminished with high levels of parental monitoring, clearly parallel the findings above.

A further example of possible gene by environment interactions centers on the etiology of schizophreniform and related psychotic disorders, where cannabis use assumes the role of environmental exposure. Controversially, it has been proposed that adolescent cannabis use may increase risks of psychosis related disorders,[98] although only a small percentage of those using cannabis develop psychosis. Longitudinal analyses suggest a possible explanation for this apparent contradiction: adolescent onset cannabis use was strongly associated (OR=10.9) with schizophreniform disorder among individuals characterized by

the Val/ Val genotype of COMT while among individuals with one or two copies of the Met allele, adolescent onset cannabis use was not significantly associated with increased risks of schizophreniform disorder.[99] While this broad pattern of findings was reported across multiple measures of "psychosis", there have been no published replications in other general population samples. Nonetheless, parallel findings from cannabis challenge[100] and experience sampling[101] methodologies support the hypothesis that carriers of the Val/Val genotype may be particularly susceptible to the psychosis inducing effects of THC.

Environmental modification of gene expression—Epigenetics refers to heritable and de novo changes in gene expression that do not involve changes in DNA sequence[102]. Thus, individuals with the same genotype may demonstrate variations in gene expression in response to exogenous (e.g. prolonged exposure to stress) or endogenous (e.g. elevated cortisol levels in response to stress) environments. Such modification often occurs early in development[103] and mechanisms inducing epigenetic modification include gene methylation, chromatin remodeling and imprinting. Does epigenetic modification contribute to the etiology of adolescent SUDs and if so, is it a cause or consequence of SUDs? A host of epidemiological studies have shown the important role of childhood traumas, parental neglect and other early adversity on elevated risk for adolescent SUDs – to what extent these environmental risk factors induce change in expression of addiction-related genes is unknown. Furthermore, such epigenetic mechanisms may be one of several pathways from drug experimentation to persistent use and dependence. What is better understood is drug-induced neuronal plasticity - for instance, repeated cocaine administration has been found to relate to modification of neuronal plasticity and increased preference for cocaine in mice[104]. Studies in humans are largely limited by availability of tissue with gene expression congruent with activity in the central nervous system. Epigenetic modification may be gene and tissue-specific and if so, such effects will be challenging to capture within the human paradigm.

DISCUSSION

Conclusions & Future Directions

The goal of this review was to provide an overview of the genetic epidemiology of substance involvement during adolescence. We note here that there is a distinguished body of literature surrounding the behavior genetics methods described here – a review of this[105] and extensive, historical reviews of some of the issues discussed here may be found elsewhere[106,107]. However, results reviewed here (and elsewhere), from a substantial number of adoption, twin and extended family studies, have demonstrated moderate to strong genetic components to the liability to develop substance use disorders. One apparent limitation of this review and of the existing literature is that there have been few genetically informative research studies of use or abuse/ dependence on substances other than tobacco, alcohol and cannabis. This most likely reflects the relatively low base rate of use or abuse/ dependence on "hard" drugs such as cocaine or heroin among adolescents and the resultant reduction in statistical power for studying these outcomes in family based studies. Nonetheless, the extent to which the findings discussed above generalize to the use of other substances is unknown. Perhaps what is most needed in the studies of latent genetic influences on adolescent substance use is a refined investigation of how environmental risk and protective influences modify biological vulnerability. Of note, the role of stressful life events, such as childhood sexual or physical abuse on exacerbating genetic risk for subsequent development of substance use disorders, may have important implications.

Future directions

While rapid technological advances have made the search for specific gene variants influencing substance use disorders feasible, genomewide association studies of adolescent samples are lacking. Furthermore, the extent to which specific genes, individually or in concert with environmental factors, influence substance use at various developmental milestones or continuously, across the lifespan, need to be identified. How these genomic and environmental factors moderate efficacy of interventions related to adolescent substance use are increasingly under investigation and there is no doubt that a refined understanding of the genetic architecture of adolescent substance use and misuse will be of considerable clinical utility. To this end, one possible future avenue could involve the identification of genes whose measured effects could be incorporated into twin models to begin to 'explain away' the extent to which latent genetic factors influence SUDs. From a genomic perspective, the era of 'next-generation sequencing' has arrived[108] – whether deep sequencing genomic regions of interest will reveal new polymorphisms that may have considerable impact on the etiology of adolescent SUDs remains to be seen. Finally, the extent to which prolonged exposure to psychoactive substances during adolescence leads to modifications in gene expression may be an area of considerable interest. Neuroimaging studies have already begun to investigate the effects of adolescent substance use on the adolescent brain, in some instances, taking specific genes into account as well – this area will likely witness rapid development[109,110]. It is hoped, with considerable optimism, that adequately powered, genetically informative studies of adolescent substance use will soon illuminate the underpinnings of the complex architecture of adolescent substance involvement and its various comorbidities.

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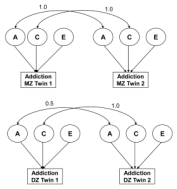

Figure 1.

A standard ACE model is depicted in a pair of monozygotic (MZ) and dizygotic (DZ) twins. Note: The rectangles represent observed behavior (phenotype) such as addiction while the circles represent latent/unmeasured contributors to variance in that behavior. A includes all segregating genes of the same ancestral origin. Heritability is A/(A+C+E). C includes those environments that make members of a twin pair similar to each other (e.g. prenatal environment, neighborhood, similar perceptions of parenting). E includes those environments that are unique to each twin (e.g. traumatic life event, differing perceptions of parenting) and measurement error.

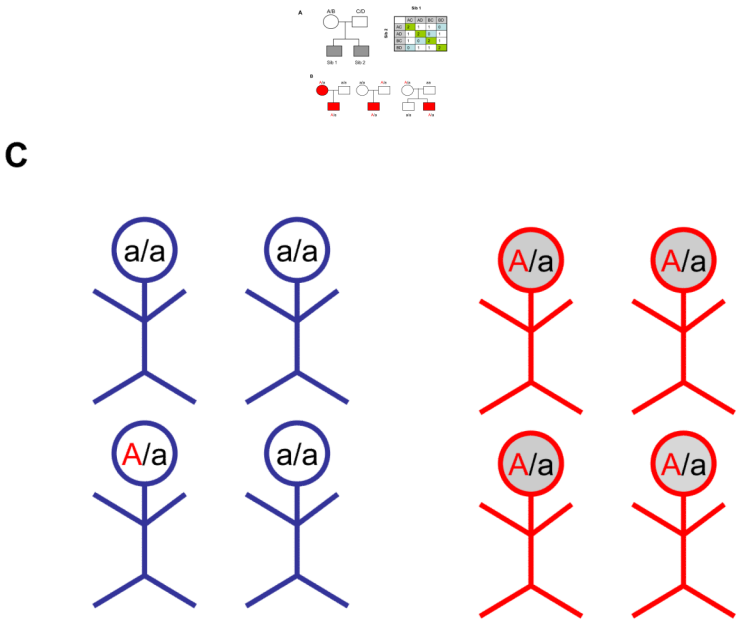

Figure 2.

Three methods for the analysis of genomic data are shown. Note: Panel A. The principle of identity-by-descent (IBD) which underlies Affected Sibling Pair (ASP) linkage analysis is shown. A genetic marker has four allelic forms (A,B,C,D) – in the pedigree, both parents are heterozygous (Mom: A/B; Dad: C/D). A pair of affected offspring (ASP, Sib 1 and 2, shaded to show affection status) are equally likely to be AC, AD, BC and BD. As shown in the table, 16 potential genotype combinations are expected in an ASP – by chance, 25%, for instance, are expected to shared both alleles IBD (IBD=2, along the diagonal). However, if a marker is close enough to a disease mutation to be transmitted more often than by chance to affected offspring, IBD=2 should exceed 25% in a pool of ASPs. This is evidence that the linkage region harbors susceptibility loci.

IBD (0)=blue cells; IBD (1)= white cells; IBD (2)= green cells

H(0): IBD (0) = 25%; IBD (1) = 50%; IBD (2) = 25%

H(A): IBD (0) < 25%; IBD (1) > 50%; IBD (2) > 25%

H(A) is evidence for linkage.

Panel B. A transmission disequilibrium test (TDT) which is the simplest form of testing for genotype-phenotype association in trios (parents and an affected offspring, shown in red) is shown. Note: A single nucleotide polymorphism with 2 alleles (A and a) where A (coded in red) confers vulnerability to disease is transmitted more often from the heterozygous (A/a) parent to the affected offspring than expected by chance alone. Extensions exist, where in addition to transmission, genotypes of siblings discordant for affection status, are also included (far left in panel B)

Panel C. The premise for an unrelated case-control association study is shown. Note: In this design that draws from a genetically homogeneous population of unrelated individuals (blue), affected individuals (shaded red circles) are assumed to be more likely to carry the risk allele (A, coded in red) than unaffected individuals (blue).