Incorporating the Family as a Critical Context in Genetic Studies of Children: Implications for Understanding Pathways to Risky Behavior and Substance Use

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The availability of candidate gene markers for biobehavioral traits will undoubtedly result in increasing attention to genetic influences in studies of childhood risk factors for health behaviors. However, a strict emphasis on genomics without consideration of the social contexts that give rise to risky behaviors will miss opportunities to understand more fully the powerful effect of the family on childhood development. This article discusses the rationale for using the family as a critical context for studying the translation of genetic propensity for risky behavior into developmental pathways that span childhood and adolescence. Attention is given to the importance of family environmental factors; the emerging literature on genetic influences on potential intermediate phenotypes; the need for rich and detailed characterizations of both phenotypes and environmental risk factors embedded within genomic studies of children; and implications for interventions and preventions aimed at risky behaviors. Via discussion of these issues, pragmatic considerations of how studying families as a context may facilitate the thoughtful inclusion of children into genetic paradigms are emphasized.

Key words childhood; developmental pathways; genomics; shared environment; substance use.

Introduction

There is now a voluminous literature on the behavioral genetics of substance use in adolescence and adults. A variety of genetically informative designs have consistently indicated that heritable factors play a substantial role in the developmental pathways leading to use and abuse of a range of substances, including tobacco, alcohol, and illicit drugs. As such, it is not only tempting but logical to assume that both current and yet to be developed molecular genetic techniques should and will be put to good use, in order to understand the pathophysiology of substance use and abuse.

It is also logical to assume that genetic research on substance use could be applied not only to adults but also children and adolescents in order to generate an understanding of the antecedents of substance use and abuse. Indeed, if genetic factors are assumed to play a fundamental role in etiology, then it would seem to be of major theoretical and practical importance to identify the genetic loci that convey risk for substance use, which in principle could ultimately lead to empirically supported preventive strategies aimed at children most likely to be vulnerable to the addictive properties of substances.

Given the vast potential for genomics to fundamentally alter the study of child health, such goals may not seem to be out of the realm of possibilities. That said, the fundamental premise of this article is that genomic studies of childhood health—especially the developmental pathways to substance use and abuse—will be most productive by embracing a strong reliance on the findings and concepts generated by classical behavioral genetic methods such as the twin paradigm. Behavioral genetic strategies, when considered in a developmental framework, provide a foundation for understanding the developmental timing of genetic effects, the clinical phenotypes most sensitive to genetic influences, the intermediate phenotypes that may underlie...
genetic vulnerability, and the environmental context under which genetic effects operate (Rende & Waldman, 2006). In this article, key findings to date are presented in order to provide the beginnings of a conceptual model for rationale expansion of genomics research to the study of vulnerability to substance use and abuse in childhood.

It’s not all DNA: Shared Environment Matters

Much behavioral genetic work over the last two decades had concluded that shared environment—environmental influences that operate to produce similarities among family members independent of the influence of genes—is not a relevant etiological contributor to individual differences in psychological traits and psychiatric disorders (Rende & Waldman, 2006). It is also the case that biometrical models of adult substance abuse/dependence typically report that shared environmental influences are negligible as the bulk of familial resemblance can be explained by reference to latent genetic factors.

One of the most recent advances in behavior genetics, however, has been the accumulating recognition that “shared environment”—the latent construct that represents sources of nongenetic influences that make family members similar on a behavioral outcome—is a critical influence on the development of psychopathology and substance use in childhood and adolescence (Burt, McGue, Krueger, & Iacono, 2007; Rende & Waldman, 2006). Of particular interest is that detection of shared environmental effects have become a robust and replicable finding in behavioral genetic studies focused on adolescent risk behaviors—indeed, the magnitude of shared environmental effects during adolescence are often of similar or greater magnitude than the more typically emphasized effects of genes (Rende & Waldman, 2006). A brief review of the evidence to date is provided for initiation (and early use during adolescence) of tobacco, alcohol, cannabis, and delinquency.

Shared Environment and Tobacco Use

Recent reviews including a meta-analysis (Li, Cheng, Ma, & Swan, 2003) emphasize the importance of shared environmental factors as well as genes on smoking initiation, which typically occurs during adolescence. Although there have been fewer behavioral genetic studies of adolescent tobacco use, compared to the number of reports on adults (Maes et al., 1999; McGue, Elkins, & Iacono, 2000), the studies to date have yielded strong evidence for shared environmental influences on smoking (McGue et al., 2000; Rende, Slomkowski, Lloyd-Richardson, & Niaura, 2005; Rhee et al., 2003; Slomkowski, Rende, Novak, Lloyd-Richardson, & Niaura, 2003; White, Hopper, Wearing, & Hill, 2003), suggesting that there are etiological factors that promote twin resemblance independent of genetic relatedness and thus are thought to represent social effects. Typically, shared environmental effects have been most prominent for either initiation of smoking or an index of “ever smoking” (i.e., without taking into account intensity of smoking), leading to claims that environmental influences on initial experiences with cigarettes are not only critical (McGue et al., 2000) but perhaps even more influential than genetic contributions (Stallings, Hewitt, Beresford, Health, & Eaves, 1999; White et al., 2003).

Shared environment and alcohol use

A similarly strong literature exists supporting the significant role of shared environmental effects on adolescent alcohol use for both males and females (Hopfer, Crowley, & Hewirr, 2003). Significant shared environmental effects on adolescent alcohol use have been found in twin studies (Buster & Rogers, 2000; McGue, Iacono, Legrand, & Elkins, 2001; Rose, Dick, Viken, & Kaprio, 2001; Viken et al., 1999) as well as twin–sibling (Cleveland & Wiebe, 2003; Rende, Slomkowski, McCaffery, Lloyd-Richardson, & Niaura, 2005) and sibling/twin/adoption paradigms (Rhee et al., 2003). The convergence of evidence from different behavioral genetic studies, each of which has specific methodological strengths and weaknesses, is especially notable and indicative of the robustness of the shared environmental effect (Hopfer et al., 2003; Rende & Waldman, 2006).

Shared Environment and Cannabis Use

Shared environmental influences are not only pronounced for cannabis use in adolescence but typically exceed the effect size of heritability, particularly when assessed contemporaneously in adolescent samples rather than retrospectively in adult samples. For example, Agrawal and Lynskey (2006) provide a review of four studies of adolescent samples that measured cannabis use in adolescence (Maes et al., 1999; Miles et al., 2001; McGue et al., 2000; Rhee et al., 2003), which involved five comparisons of the effect sizes attributable to genetic and shared environmental influences. In four of the five comparisons, shared environmental effects exceeded those ascribed to genetic factors and were the primary source of influence on cannabis use; the estimate of shared environmental influence ranged from .24 to .85. Similar
evidence for the importance of shared environmental influences on cannabis use continues to emerge (Fowler et al., 2007; Lessem et al., 2006).

**Shared Environment and Delinquent Behavior**

Behavioral genetic studies of delinquent behavior are also relevant as initiation of substance use may be conceptualized as part of a spectrum of behavioral disinhibition as discussed in a later section of this article. A number of studies reflecting a variety of samples have consistently revealed shared environmental influences on adolescent delinquency (Burt, Krueger, McGue, & Iacono, 2001, Burt, Krueger, McGue, & Iacono, 2003, Burt, Krueger, McGue, & Iacono, 2007; Eaves et al., 1997; O’Connor et al., 1998; Rutter et al., 1999; Thapar et al., 2001), as confirmed in a meta-analysis of 51 twin and adoption studies (Rhee & Waldman, 2002). Rule-breaking delinquent behavior (as opposed to aggressive behavior) shows particularly strong evidence of shared environmental effects (Eley, Lichtenstein, & Moffitt, 2003; Tackett et al., 2005) and there is evidence that these findings are equally applicable to both males and females (Taylor et al., 2000), a conclusion also reached via meta-analysis (Rhee & Waldman, 2002).

**Implications for Genomic Studies in Childhood and Adolescence**

The fundamental implication from this growing body of studies is that attention to the sources of shared environmental influences on adolescent substance use and related psychopathology is required, in order to explain a large portion of the observed phenotypic variance during this developmental period. The identification of specific shared environmental risk factors may provide a platform for genomic studies, as these contextual influences will contribute to the requisite exposure to substances that proceeds genetically influenced reactivity to substances which influences likelihood of eventual progression to abuse and dependence. This point is made to remind readers that while genomic studies will offer exciting opportunities for understanding of health-related behaviors, including substance use, genetic strategies alone will not fully account for all of the salient risk factors for substance use in childhood and adolescence. Furthermore, the extensive evidence of shared environmental influences on early use of substances also underscores that not all family effects are necessarily reflections of genetic similarity. Thus, in this way, research strategies that both conceptualize and interpret genetic effects on substance use with reference to potential shared environmental influences would not only provide a platform for rationale inclusion of genetic data (e.g., by setting realistic expectations of the effect sizes of genetic effects), but also improve the resolution of models of familial transmission by sorting through particular mechanisms by which genetic vulnerabilities become expressed or shaped by environmental forces, which in part reflect social transmission within families. For example, sources of shared environmental influences may impact expression of genetic vulnerability to substances by providing social opportunities and reinforcement for initial exposure, a requisite for activation of genetic systems that are either sensitive to specific agents (e.g., nicotine) or to more general reward properties of substances.

**But What about DNA?: Genes Matter too**

Although the point was strongly made that environment, particularly shared environment, is relevant for the onset of substance use in adolescence, virtually all of the behavioral genetic studies cited above also provide evidence of genetic effects on substance use in adolescence. The combination of significant and comparable main effects of genes and shared environment on substance use in adolescence is unusual in behavioral genetic research (Rende & Waldman, 2006) and points to the strong familial currents that create risk for initiation of multiple substances. In terms of implications for genomic studies that focus on children and adolescence, it is quite clear that the expression of heritable influences on early forms of substance use operates within a rich and powerful social context and must be conceptualized accordingly.

Given this, the challenge for current and future research will be to both identify the sources of environmental effects, and to understand the meaning of genetic signals that operate in parallel and potentially in combination with social influences. The complex decisions that characterize genomic research—including determination of the type of genetic model to use, identification of potential candidate genomic regions, and evaluation of the biological plausibility of candidate gene markers—may actually profit from consideration of environmental effects as they can help to construct empirically supported etiological models that will highlight what the candidate phenotypes may be, which represents another series of substantial challenges for researchers (Prescott, Madden, & Stallings, 2006).

In the construction of etiological models, a general distinction that can be made in genetic studies of substance use is the differentiation of factors that promote likelihood of exposure to substances, versus those which
become expressed once exposure (or a particular degree of exposure) occurs. Developmentally, this distinction could signal different genetic systems: one which reflects reactivity to substances, including both substance-specific (e.g., nicotinergic receptors) systems as well as nonspecific (e.g., pertaining to reward/motivation); and another which is broader and represents a genetic liability to a number of behaviors, only some of which involve substance use. Each of these is briefly discussed below.

**Candidate Gene Studies of Adolescent Substance Use: The Example of Smoking Behavior in Adolescence**

There is an emerging body of studies which have examined links between specified candidate genes and smoking in adolescence, and which serve as exemplars for models that postulate the role of genes in early reactivity to substance exposure. What is notable about these studies is that they have focused on candidate genes, which are biologically plausible, meaning that there is evidence that they are expressed in neural systems which could logically play a role in influencing reactivity to nicotine. Furthermore, they have been attentive to the complexity of measuring substance use phenotypes, especially during the dynamic developmental period of adolescence.

We highlight studies which have examined two candidate gene systems—one related to nicotine metabolism and another involved in reward—that arguably would play a role in influencing adolescent’s reactions to nicotine as delivered via smoking history. Studies of adults have examined the role of the polymorphic hepatic enzyme CYP2A6, which functions to inactivate nicotine to cotinine. The biologically plausible argument has been that adults with a mutation that confers slow inactivation of nicotine may be less susceptible to dependence, in part because they experience longer lasting levels of nicotine which could produce negative subjective reactions such as dizziness and nausea. A recent longitudinal study of 222 adolescents (followed annually from grade 9 to grade 10) extends this model to adolescent smokers (Audrain-McGovern et al., 2007). Specifically, Audrain-McGovern et al. reported that normal metabolizers progressed to nicotine dependence at a faster rate than slow metabolizers once exposure to nicotine occurred. Interestingly, two other studies have reported the opposite finding, namely that adolescents with a CYP2A6 mutation and thus slow metabolism of nicotine are at higher risk for progressing to nicotine dependence during adolescence (Huang et al., 2005; O’Loughlin et al., 2004). One possible reason for the discrepancy may be differences in the specific types of nicotine dependence symptoms that were assessed across studies (Audrain-McGovern et al., 2007). These few studies on CYP2A6 with adolescents nicely illuminate the complexities involved in testing models linking candidate genes to complex phenotypes such as nicotine dependence, as the associations observed may be influenced by the choice of measurement strategy for the phenotype, age differences across studies, as well as other factors such as the populations studied (Audrain-McGovern et al., 2007). They also, however, serve as good examples for paradigms that test the putative role of biologically plausible candidate gene markers that may influence individual differences in reactivity to exposure to substances.

Similar good examples of genetic studies with adolescents include reports linking various candidate gene markers within the dopaminergic system (e.g., DAT1, DRD2, DRD4) and probability of smoking progression (Laucht et al., 2008; Timberlake et al., 2006). As is the case with CYP2A6, these studies provide biologically plausible rationales for examination of genetic markers within the dopaminergic system focused on the mechanisms by which exposure to nicotine increases dopamine concentrations in areas of the brain that are involved in reward. What is notable in this emerging body of work is that a number of candidate gene markers involved in the dopaminergic system have been examined, reflecting the likely possibility that genetic association studies will need to evaluate multiple genes that contribute to complex phenotypes. For example, Laucht et al. (2008) suggest that allelic variation in one gene (DRD4) is related to smoking initiation, whereas another gene (DRD2) is associated with smoking continuation and dependence.

Taken together, the emerging studies of adolescents focused on logical candidate genes offer fine templates for genetic research on adolescent substance use. In particular, the care taken to address issues of biological plausibility and the attempts to link specific aspects of the clinical phenotype to different genes is notable and provides a platform for examining the role of candidate genes on adolescent substance use.

**Multivariate Genetic Models of Substance use Risk**

Other research strategies have utilized multivariate models to examine the extent to which a latent construct of behavioral dysfunction can be developed that incorporates substance use. An excellent example of this line of thinking is provided by recent studies by McGue and colleagues (McGue, Iacono, & Krueger, 2006). They have posited that a constellation of problem behaviors that coalesce
in adolescence, including delinquency (as indexed by early contact with police), precocious sexual experience, and early use of alcohol, cigarettes, and illicit drugs, represent a generalized genetic liability to disinhibitory behavior, which manifests first in adolescence and becomes more fully expressed in adulthood as alcoholism, drug abuse, and nicotine dependence (McGue & Iacono, 2004, 2005). This speculation has been tested via application of multivariate behavioral genetic modeling of longitudinal twin data (McGue et al., 2006). First, the index of problem behavior in adolescence was found to be only modestly heritable (about 20%) and shared environmental factors were approximately double the effect size (about 40%), a finding which echoes the conclusion of the prior section of this article. In contrast, a comparable disinhibitory factor constructed during early adulthood (consisting of symptoms of nicotine dependence, alcohol abuse or dependence, drug abuse or dependence, and antisocial behavior) was found to be highly heritable (about 75%) with minimal effects of shared environment. The particularly interesting finding, however, was that there was substantial covariation between the adolescent problem behavior index and the adult disinhibitory measure, which was best explained by common genetic factors. Thus, a relatively weak genetic signal in adolescence, which occurs in the shadow of more powerful environmental influences, nonetheless seems to represent early manifestation of genetic propensity that becomes more fully expressed in early adulthood.

As discussed by Zucker (2006), complex phenotypes such as early problem behavior and disinhibitory psychopathology could be broken down into multiple underlying components (such as undercontrol, impulsivity, etc.), each of which may reflect genetic vulnerability to substance use. Such intermediate phenotypes may provide good start points for genomic research on children, which would be of relevance for the eventual development of substance abuse. Indeed, much of the relevant genetic work with children will involve isolating biobehavioral indicators of propensity for risk-taking behaviors that reflect early emerging vulnerability to a developmental pathway that could eventually result in adult substance abuse and dependence. This indirect and probabilistic chain of genetic risk that crosses developmental period along with exposure to risk environments that promote likelihood of initial exposure to substances will represent one part of a complex genetic equation of liability to abuse and dependence. Thus, genomic studies of risk for substance dependence will require recognition of developmental processes, including nongenetic effects, to be maximally informative.

There are well-articulated models that postulate indirect, longitudinal expression of genetic vulnerability to substance abuse and dependence. Hiroi and Agatsuma (2005) have provided conceptual models, which describe how specific behavioral traits such as novelty seeking may represent part of an early emerging genetic propensity for dependence and addiction and thus provide a rationale for searching for specific genes linked with such personality traits. Indeed, there is now a large literature devoted to evaluating the extent to which personality traits have a genetic basis, with most studies focusing on associations between neuroticism/harm avoidance and the serotonin transporter (SLC6A4) promoter region polymorphism (5-HTTLPR), as well as potential associations between the dopamine DRD4 exon III repeat region and novelty seeking/ extraversion (Ebstein, 2006; Hiroi & Agatsuma, 2005; Munafo, Clark, & Flint, 2005). Although there have been mixed results reported to date, and the effect sizes reported have been small (Munafo et al., 2005), the conceptual basis for linking this work with genetic models of dependence is certainly in line with the behavioral genetic evidence to date.

A particularly exciting avenue for future research research are research strategies that integrate the multivariate perspective along with testing of candidate genes. Stallings et al. (2005) have conducted a genome search, using linkage methods, to determine if there is a chromosomal region associated with indices of conduct disorder symptoms and antisocial substance dependence in a large community-based sample of 4,493 adolescents and young adults. They reported evidence of linkage to a region on chromosome 9, particularly for a composite index that combined substance use vulnerability and conduct disorder symptoms. Similarly, Dick et al. (2008) have argued that dimensional models that integrate a number of clinical phenotypes—including conduct disorder, disinhibitory personality traits, and alcohol and drug dependence—may provide traction in genetic studies. They present evidence supporting this view by showing that a single externalizing factor could be extracted from these clinical indices, and that this factor showed evidence to linkage on chromosome 7. As such, these two recent studies provide examples of newer genetic research strategies that attempt to analyze broader, higher-order clinical phenotypes which link substance use to psychopathology and personality.

**Gene–Environment Models**

It is worth noting that a number of models of genetic effects will be worth considering as this work moves
forward, and especially as it begins to extend to studies of children. Much of the work on the genetics of personality traits has focused on direct gene–behavior associations, reflecting in part the conceptual bias that personality reflects primarily heritable tendencies. When applied to developmental risk for substance use, however, other models are worth noting and have been considered. First, it is possible that such genotype–phenotype associations may account in part for genetic effects in self-initiated exposure to substances in adolescence (Prescott et al., 2006). McGue et al. (2006) have formalized this as an example of gene–environment correlation (Jaffe & Price, 2007), in that children/adolescents with a high genetic propensity toward disinhibitory psychopathology select and create risky environments in adolescence, which in turn amplifies the genetic vulnerability to the addictive property of substances once exposed. For example, children who are low on impulse control and high on novelty-seeking may be more likely to be exposed to substances via affiliation with peers who use drugs. Second, genetically influenced personality traits could serve as a diathesis in gene–environment interaction models (Moffitt, 2005; Moffitt, Caspi, & Rutter, 2005; Rutter, Moffitt, & Caspi, 2006), both in terms of initial responsivity to substances as well as to tendency toward addiction. As an example, children who are low on impulse control and high on novelty-seeking may be at risk for early exposure to substances only if they are living in a context (e.g., neighborhood) where rates of substance use are high, and conversely protected from early exposure (despite their risk via personality traits) if there are fewer environmental opportunities.

**Characterizing Phenotypes and Environments as well as Genotypes**

The overall implication thus far for genomic studies of risk for substance use, abuse, and dependence with childhood populations is that the genetically influenced traits may be somewhat removed from the eventual clinical phenotype of interest, which is not expressed until adulthood. Careful and logical consideration of what these intermediate phenotypes may be, their biological plausibility in terms of specific candidate gene regions, and the manner in which genotypes get translated into risky behavioral phenotypes that influence the likelihood of initial exposure to substances as well as reactivity to substances once sufficient exposure has occurred, will require interdisciplinary thinking and collaboration, as well as a sound developmental framework that spans from childhood to adulthood.

**Measurement of the Phenotype**

In terms of the design of genomic studies of children, important issues pertain to the measurement of phenotypes. It has long been recognized that any error in measuring the phenotype will negatively impact the ability to detect an empirical link with genetic loci. That said, more subtle issues have been shown to be relevant, such as the type of questionnaire used to measure personality traits in association studies with the serotonin transporter gene (Munafo et al., 2005). Zucker (2006) has discussed the conceptual difficulties in equating similar constructs across developmental periods (e.g., early problem behaviors in adolescence and disinhibitory psychopathology in adulthood). These difficulties will become more complex as children are included in genetic studies. Thus, developmentally sensitive approaches to construct equivalence as well as potentially important differences in phenotypic expression across developmental periods will become a requisite step in genomic studies of risk behaviors in childhood. In addition, there have been suggestions that genetic studies of personality would do well to move beyond self-report questionnaires, and consider alternatives such as experimental paradigms that approach the phenotypes in question from a neurophysiological angle, including functional imaging approaches (Ebstein, 2006). Expansion of these ideas to incorporate and/or create developmentally sensitive methods suitable for children would be useful for genomic studies and perhaps provide candidate endophenotypes for substance use risk, which in principle may reflect more strongly underlying genetic mechanisms (Rende & Waldman, 2006).

**Measurement of the Environment**

Future genomic research on childhood risk for substance use will also require more than a nod to the environment, and in fact would need to take seriously inclusion of measures of salient social influences, particularly those that reflect shared effects. Referring back to the section on shared environment, what has not been fully appreciated to date in genetic models of substance use in adolescence is that many of the salient environmental influences on substance use may be familial in origin. In addition to specifying both candidate genotypes and intermediate phenotypes, genomic research on childhood risk behaviors will profit from thoughtful measurement of candidate environmental measures, particularly those that produce similarity within family members. These can range from socioregional influences (Rose, Dick, Viken, Pulkkinen, & Kaprio, 2001) down to the level of family...
dysfunction (Kendler, Aggen, Prescott, Jacobson, & Neale, 2004) but the point is that such potentially shared environmental factors can be modeled in terms of gene–environment interplay. A particular example is the direct social influence that a sibling may have on substance use—there is now ample evidence that relationship characteristics and direct interpersonal interaction between siblings provides a source of social influence on smoking, drinking, and drug use that reflects shared environment rather than the effects of genes (Pergadia et al., 2006; Rende et al., 2005; Slomkowski et al., 2005; Vink & Boomsma, 2005). Given this, genomic studies of childhood and adolescent risk for substance use would gain traction by using a family design—such as inclusion of sibling pairs—in order to adequately capture and evaluate potential shared environmental sources of influence in the context of genetic risk.

In addition, similar to the argument made for expanding the genetic study of personality traits by using newer intensive methodologies, such opportunities exist at the level of environmental measurement as well. One paradigm is to use videotaped semi-structured discussion tasks that elicit relationship dynamics (such as between siblings or between peers), which permits the coding of microsocial interaction as it unfolds in real time (Dishion & Snyder, 2004). Dishion and colleagues have pioneered this work with particular reference to microsocial processes that convey risk for antisocial behavior and substance use (Dishion & Owen, 2002; Dishion, Nelson, Winter, & Bullock, 2004). Another methodology that has been applied to the study of substance use is Ecological Momentary Assessment (EMA). For example, the rationale for EMA is now well recognized in the smoking literature and has been well explicated (Stone & Shiffman, 2002; Stone, Shiffman, Atienza, & Nebelling, 2007). The “ecological” aspect refers to the use of technologies (e.g., PDAs, cellular phones) that allow respondents to report their behaviors in real time and in real life settings. The corresponding “momentary assessment” part of the methodology is the emphasis on acquiring instantaneous self-reports in the moment to minimize recall bias and memory distortion that is typically introduced by more retrospective accounts. This technology provides a very sensitive way to capture ecologically valid data on social context and as such could be applied within genomic studies of childhood and adolescent risk, as there are supporting data for use of EMA methods with younger populations (Henker, Whalen, Jamner, & Delfino, 2002; Whalen, Jamner, Henker, & Delfino, 2002).

Prevention and Intervention: Genotypes, Environments, and Phenotypes

Although it is premature to suggest that genomic research will clearly have implications for preventive/intervention efforts aimed at substance use, it is certainly worth considering the possibility. A primary consideration, based on the studies presented in this article, is that there is a strong familial basis to risk for substance use that is detectable from childhood to adulthood. Thus, one pragmatic consideration in designing genomic studies of risk behaviors in childhood is that some form of family design would not only be worthwhile but may be most informative. Somewhat counter-intuitively, much current genetic research is not family based, as the framework has moved to searching for gene–behavior links within large populations of unrelated individuals. Given the strong evidence of both environmental and genetic effects, which produce familial similarity for risk for substance use, family designs may permit an integrated set of findings from genomic studies that overtly incorporate measured and empirically supported environmental risk factors.

To the extent that genetic findings emerge in childhood studies, having these environmental measures captured using families will allow a more complete determination of the information yield of genomic findings with respect to prevention and intervention. Specifically, it will be important to determine if having genomic data permits either better resolution of environmental effects, or specification of which individuals are most likely to be exposed to risk environments and/or sensitive to environmental agents, including actual exposure to substances. It is worth noting that there will be a time investment in these studies to be maximally informative—it will be necessary to maintain longitudinal designs to track the expression of genotypes in childhood, expression of genotypes in adolescence, along with the relevant environmental measures at each stage. The core issue will be to improve our understanding of the developmental pathways of risk for substance use, abuse and dependence, and within this mission the unanswered question to date is the empirical yield that will be provided by having genomic data. Certainly, the hope is that developmentally and environmentally informed use of genomic information will help clarify the timing and nature of developmental risks for substance use, abuse and dependence from childhood to adulthood, permit more mechanistic understanding of both genes and environments, and ultimately be used to alter the risk pathways of vulnerable youth.
Despite the promise of genomic strategies for eventually informing public health prevention approaches, it will be imperative that guidelines be established for properly and safely incorporating children and their families in such work. There is always the potential for misinterpretation of genetic data—particularly with respect to children—leading to implications of stigma and unrealistic expectations of genetic determinism. There is also the possibility that parents can develop unnecessary concerns about other family members (e.g., siblings of childhood probands) based on insufficient information on the meaning of genetic markers (e.g., relative risks associated with having particular alleles). Another prominent issue will be assuring parents that their children’s (and perhaps their own) DNA will be used strictly for research purposes and will not be made available outside the research setting (e.g., to insurance companies, schools, etc.). We feel that these issues are of the magnitude to warrant working groups or task forces that can identify all of the sensitive areas posed by doing genomic studies with children, and thus also develop guidelines that can be used to direct the conduct of such studies in a way that fully recognizes the psychological and social risks, and benefits and provides appropriate information for dissemination to parents and their children.

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