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Genetic Influences on Adolescent Behavior

Danielle M. Dick, Ph.D^{a,b,c,d,*}, Amy E. Adkins, Ph.D^{a,d}, and Sally I-Chun Kuo, Ph.D^a

^aDepartment of Psychology, Virginia Commonwealth University, 806 W. Franklin Street, Richmond, VA 23284, United States

^bDepartment of African American Studies, Virginia Commonwealth University, 816 W. Franklin Street, Richmond, VA 23284, United States

^cDepartment of Human & Molecular Genetics, Virginia Commonwealth University, 1101 E. Marshall Street, Richmond, VA 23298, United States

^dCollege Behavioral and Emotional Health Institute, Virginia Commonwealth University, 816 W. Franklin Street, Richmond, VA 23284, United States

Abstract

Adolescence is a transitional, developmental phase with marked shifts in behavior, particularly as related to risk-taking and experimentation. Genetic influences on adolescent behavior also show marked changes across this developmental period; in fact, adolescence showcases the dynamic nature of genetic influences on human behavior. Using the twin studies literature on alcohol use and misuse, we highlight several principles of genetic influence on adolescent behavior. We illustrate how genetic influences change (increase) across adolescence, as individuals have more freedom to express their predispositions and to shape their social worlds. We show how there are multiple genetic pathways to risk, and how the environment can moderate the importance of genetic predispositions. Finally, we review the literature aimed at identifying specific genes involved in adolescent behavior and understanding how identified genes impact adolescent outcomes. Ultimately, understanding how genetic predispositions combine with environmental influences to impact pathways of risk and resilience should be translated into improved prevention and intervention efforts; this remains a rich area for future research.

Keywords

adolescence; genetics; alcohol use; externalizing; developmental pathways

*Corresponding Author: Danielle M. Dick, 816 W. Franklin Street, Box 842509, Richmond, VA 23284-2509; ddick@vcu.edu; fax: 804-827-0837.

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Introduction

Adolescence represents a critical link between childhood and adulthood. It is a developmental period characterized by tremendous physical changes (e.g., growth spurt, brain development, sexual maturation), psychological development (e.g., identity development), and social role transitions. One of the hallmarks of adolescence is an increase in risk taking behavior, as adolescents increasingly experiment and engage in the world. What is perhaps less widely recognized is that there are parallel dynamic changes that occur across adolescence in the importance of genetic effects. Using the literature on alcohol use and misuse as a model, we review overarching principles regarding genetic effects on adolescent behavior.

Basic methodology of genetic epidemiology: an overview of twin studies

There are several methods that have been used to study genetic influences on behavior, including family, adoption, and twin designs, each of which has its own strengths and weaknesses (Plomin et al., 2001). We focus here on twin designs, as this has been the “work horse” of behavior genetics. The relative frequency of twins, comprising about 3 in every 100 births (Hamilton et al., 2015), and the comparative ease of obtaining them through population-based (Kaprio et al., 2002) or records based (Anderson et al., 2002; Meyer et al., 1996) registries, has made this a ready design for studying genetic influences on behavior. The basic tenet of the twin design involves comparing the similarity of different types of twins who differ in their genetic relatedness. Monozygotic (MZ) twins result from a single egg fertilized by a single sperm and, accordingly, share 100% of their genetic variation and all of their shared environment when reared together. Dizygotic twins (DZs) result from two eggs, fertilized by two sperm, and therefore share, on average, just 50% of their genetic variation (as do ordinary siblings), but also share 100% of their shared environmental influences when reared together. Accordingly, comparing the similarity of MZ and DZ twins yields information about the relative importance of genetic and environmental influences. To the extent that MZs are more alike than DZs, genetic influences are implicated. If DZs are just as similar as MZs, then shared environmental processes, such as those influences found in the shared family environment, shared peers, shared schools and neighborhoods, etc., must predominate. If MZs are not exactly identical (as they would be if an outcome were 100% genetically influenced), then unique environmental processes must play a role. These could include environmental influences that are unique to an individual, such as a particular life event, stressor, or other influence not shared with their co-twin, and/or environmental events that differentially effect the co-twins (Turkheimer and Waldron, 2000).

The twin methodology can be applied to the study of virtually any behavior of interest, and probably has: a vast literature surrounds twin studies of psychopathology (Hewitt et al., 1997; McGue et al., 2006), personality (Littlefield et al., 2011; Viken et al., 2007), cognitive ability (Plomin and DeFries, 1998; Trzaskowski et al., 2013), as well as other behaviors that may seem more surprising, such as divorce (McGue and Lykken, 1992), voting behavior (Eaves et al., 1999; Hatemi et al., 2015), and well-being and life satisfaction (Archontaki et al., 2013; Sadler et al., 2011). This brings us to what has been called the first law of behavior genetics (Turkheimer, 2000): “all human behavioral traits are heritable”. A good rule of

thumb is that if you have to guess to what extent something is genetically influenced, a good guess is that “it” is about 50% heritable, regardless of what the “it” is (Polderman et al., 2015).

But these static heritability estimates fail to capture the dynamic nature of genetic effects. While demonstrating that genetic influences play a role in virtually all domains of human behavior has been an important advance, it is critical to understand the mechanisms by which genetic influences exert their effects. The dynamic shifts that occur across adolescence make this an important period during which to study genetic effects; in fact, the study of adolescent behavior illustrates many of the important principles of how genetic influences operate, which we focus on here.

Principle 1: Genetic influences change in importance across adolescence

Alcohol use is a common form of risky behavior in adolescence, and alcohol use is a developmental phenomenon. Cross-sectional and longitudinal studies of alcohol use reveal age-related patterns. Although some children begin drinking in earlier ages, alcohol use typically begins in adolescence (Faden, 2006). Between ages 12 and 21, rates of alcohol use and heavy episodic drinking increase sharply. National survey data indicate that the percentage of American youth who have ever drunk at least one whole drink rises steeply across adolescence, leveling off at about age 21 (SAMHSA, 2007). Recent national data further show that all levels of past-month alcohol use increase steadily across adolescent years, including any alcohol use, binge use, and heavy use (SAMHSA, 2014). Similarly, data from the Monitoring the Future study, a nationally representative sample of 8th, 10th, and 12th graders, demonstrate that the prevalence of binge drinking (having 5+ drinks at least once in the past two weeks) increases substantially from 8th grade to 12th grade (Johnston et al., 2016). Notably, frequency of binge drinking also increases across this developmental period. Data from the National Survey on Drug Use and Health (NSDUH) showed that the mean number of binge drinking days in the past 30 days increased continuously for both male and female adolescents from ages 12 to 20, but this rise was more dramatic for males than for females (Chen et al., 2015). Adolescence also represents an important developmental period for the development of alcohol problems. National data from NSDUH suggest that prevalence of past-year alcohol use disorder increases between ages 12 and 17 and peaks in young adulthood, between ages 18 and 25 (SAMHSA, 2014).

In the same way that alcohol use behavior shows dynamic change across the period of adolescence, twin studies demonstrate that the importance of genetic and environmental influences on alcohol use also change dramatically over this developmental period. Data from two population-based longitudinal Finnish twin studies illustrate the striking shift in the relative importance of genetic and environmental influences that occurs from early adolescence to young adulthood (Figure 1): there is a steady increase in the relevance of genetic factors on alcohol use across adolescence, and a corresponding and sharp decrease in the relevance of common environmental influences (Rose et al., 2001a; Rose et al., 2001b). These data demonstrate that while alcohol initiation is largely environmentally influenced, as has also been found in numerous other twin studies (Hopfer et al., 2003), as drinking patterns become more regular and established across adolescence, genetic factors assume

increasing importance; however, alcohol use early in adolescence is influenced largely by family, school, and neighborhood factors (Rose et al., 2001b; Rose et al., 2003). A very similar pattern of results for alcohol use was obtained by a life-history method in male twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (Kendler et al., 2008b). At age 14, all twin resemblance resulted from shared environmental factors. From ages 14 to 23, shared environment became progressively less important and genetic factors more important.

This shift in the importance of genetic influences on alcohol use outcomes has also been demonstrated with specific genes across multiple independent studies conducted by different research group. The GABRA2 receptor gene, *ALDH2*, and multiple monoamine genes were found to be associated with alcohol use outcomes in young adulthood, but not earlier in development (Dick et al., 2006b; Guo et al., 2007; Irons et al., 2012). Interestingly, genes associated with alcohol use outcomes in adulthood appear to be associated with behavior problems earlier in adolescence (Dick et al., 2006b), which brings us to Principle 2.

Principle 2: There are multiple pathways of genetic risk

These dynamic shifts in the importance of genetic effects become even more complex when viewed in the context of another important principle about genetic effects: genetic influences on an outcome can operate through multiple pathways. In the case of alcohol use, twin studies indicate that much of the predisposition to alcohol problems is not unique to alcohol problems at all – but rather is shared with a number of other psychiatric conditions that fall under the general spectrum of externalizing behavior, including other forms of drug dependence, adult antisocial behavior, and childhood conduct disorder, as well as personality traits related to impulsivity and behavioral disinhibition (Kendler et al., 2003; Krueger et al., 2002; Young et al., 2000). In fact, data from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders indicate that as much as 65% of the genetic influences on alcohol dependence is shared with these other disorders, with only ~35% of the heritability being genes that are specific to alcohol dependence (Kendler et al., 2003). These latter, more specific influences are likely to include genes that are involved in alcohol metabolism and related pathways. Genetic variation in several of the alcohol dehydrogenase (ADH) genes, as well as the gene *ALDH2* which plays the primary role in converting acetaldehyde to acetate after the metabolism of ethanol to acetaldehyde by the ADH enzymes, have been associated with susceptibility to alcohol dependence (Edenberg et al., 2006; Kuo et al., 2008; Whitfield, 1997). But many of the genes that alter susceptibility to alcohol dependence appear to exert their effects through more non-specific pathways, such as those involved in reward dependence or behavioral disinhibition. Accordingly, they impact a number of different outcomes and contribute to the substantial comorbidity that surrounds alcohol problems.

The interesting thing is that longitudinal studies indicate that the relative importance of the nonspecific genetic predisposition that impacts alcohol outcomes via general behavioral disinhibition, and the part of the genetic predisposition that is specific to alcohol, changes across adolescence. Data from two independent twin studies indicate that alcohol use and problems are more strongly influenced by the general predisposition toward externalizing behavior early in adolescence, but by late adolescence and young adulthood, alcohol-specific

genetic factors become more important (Meyers et al., 2014). Data from yet another twin study indicate that this pattern is not specific to alcohol, but rather, extends to marijuana and nicotine dependence symptoms as well (Vrieze et al., 2012). Adolescent substance use is influenced largely by nonspecific genetic factors that broadly impact externalizing outcomes, but as individuals age into adulthood, substance-specific genetic risk factors become more important. This is likely because early substance use is more experimental, and hence more strongly influenced by general disinhibitory, sensation-seeking factors; however, once substance use becomes more established and regular, genetic factors involved in drug response become increasingly important, more so than the disinhibitory disposition that contributed to initial use patterns.

This shift in the relative importance of nonspecific genetic factors that happens across adolescence is also interesting in that it parallels changes in brain development that occur across this developmental period. The striatal system, which has been related to impulsivity and reward-seeking, is known to mature earlier compared to the prefrontal cortex, which is involved in top-down cognitive control (Casey et al., 2005; Clark and Winters, 2002; Galvan et al., 2006; Giedd et al., 1999; Sowell et al., 2003). This asynchronous developmental pattern is related to increased risk-taking (Steinberg, 2004), preference for immediate over long-term gains, and increased discounting of future negative consequences (Steinberg et al., 2009). Interestingly, the importance of the part of the genetic predisposition on substance use outcomes that reflects general behavioral disinhibition peaks in adolescence at the time when brain development favors risk-taking. Further, this general genetic risk has been shown to decline earlier in females (Meyers et al., 2014; Vrieze et al., 2012), which is consistent with the earlier cortical maturation that takes place in females (Lenroot et al., 2007).

Principle 3: The environment moderates the importance of genetic influences

Adolescence is a rich area for studying gene-environment interaction since there are so many shifts in relevant environmental factors across this developmental phase. As this has become a research area of increasing interest (and there have been corresponding advances in statistical modeling to test these more complex interactions; Purcell, 2002; van der Sluis et al., 2012), a number of such interactions have been detected. Twin studies have demonstrated that genetic influences on adolescent substance use are enhanced in the presence of substance-using friends (Dick et al., 2007a), and in environments with lower parental monitoring (Dick et al., 2007b). Figure 2 illustrates the dramatic shift in the relative importance of genetic effects that can take place across different environments using data from a Finnish twin project: at the extreme low end of parental monitoring, genetic effects assumed the greatest role in impacting adolescent smoking, whereas in homes with very high parental monitoring, genetic effects played little to no role, and common environmental factors were the most important influence (Dick et al., 2007b). Similar effects have been demonstrated for more general externalizing behavior: genetic influences on antisocial behavior were higher in the presence of delinquent peers (Button et al., 2007) and in environments characterized by high parental negativity (Feinberg et al., 2007), low parental warmth (Feinberg et al., 2007), high paternal punitive discipline (Button et al., 2008), and environmental adversity more generally (Hicks et al., 2009). Socioregional, or neighborhood-level influences have also been shown to moderate the importance of genetic

influences on substance use. Genetic influences on late adolescent alcohol use and early adolescent behavior problems are enhanced in urban environments, communities characterized by greater migration, and neighborhoods with higher percentages of slightly older adolescents/young adults (Dick et al., 2009a; Dick et al., 2001; Rose et al., 2001a). These moderation effects presumably reflect differences in availability of alcohol, a range of possible different role models, neighborhood stability, and community-level monitoring across different areas. The environments for which there are demonstrated moderating effects on genetic influences in adolescence largely appear to reflect differential social control and/or opportunity, resulting in differential expression of individual predispositions (Shanahan and Hofer, 2005).

Further, it is likely that the importance of different environments as moderators of genetic effects varies across developmental stage. There is some indication of this in the Finnish twin data, where parental monitoring showed significant moderating effects on substance use starting earlier in adolescence (age 14), whereas the moderating role of peer substance use was not apparent until later in adolescence (age 17; Dick et al., 2007a). Similarly, socio-regional influences that moderated alcohol use in young adulthood did not show evidence of moderation of early adolescent alcohol use (Dick et al., 2009a). Accordingly, studying genetic influences on adolescent behavior illustrates that genetic factors can only be understood in the context of the environment, and that these interactions can also shift across developmental stage.

Principle 4: Our genetic predispositions shape our behavior in part by influencing our environments

Separating etiological risk factors into genetic and environmental factors is in some ways a misnomer, as we know that many environmental factors show evidence of genetic influence (Kendler and Baker, 2007). A systematic review of heritability of measures of the environment, to include stressful life events, parenting and family environment, social support, peer interactions, and marital quality, found that most measures of the environment yield heritability estimates in the range of 15–35%. The heritability of environmental factors reflects the fact that individuals select and shape their environmental experiences based in part on their own genetically influenced proclivities. This becomes particularly relevant in adolescence, as individuals have more freedom to select and shape their environments. Research on peer affiliation/deviance is illustrative of these unfolding processes. Twin studies and other genetically informative designs yield evidence of genetic influence on peer deviance (Kendler et al., 2008a; McGue et al., 2006) and these genetic influences on peer group deviance increase across adolescence, accounting for only 30% of the variance in peer group deviance at 8–11 years of age, but steadily rising to account for 50% of the variance in peer group deviance from age 15 onward (Kendler et al., 2007). Genetic influences on “environmental” factors is likely one of the pathways by which genetic influences increase in importance across adolescence, as adolescents increasingly gain autonomy to shape their own worlds.

Gene finding efforts

Multiple genetic methodologies have been employed to investigate the underlying genetic architecture of alcohol use and broader externalizing behaviors, including linkage analyses, candidate gene association studies and genome-wide association studies (GWAS) (Dick et al., 2015; Saccone et al., 1999; Treutlein and Rietschel, 2011; Wang et al., 2005). Linkage studies look within families to ascertain genomic regions traveling within affected (but not unaffected) family members (Hirschhorn and Daly, 2005). Looking across the genome, linkage studies allow for an unbiased interrogation. While successful in locating loci underlying traits that follow patterns of Mendelian inheritance, linkage has been much less successful for complex traits involving numerous genes and environmental influences, though there are ways in which this method can still be useful, particularly in the analysis of whole-genome sequence data (Ott et al., 2015). Association studies have become far more widely used as a statistically more robust method for complex phenotypes (Risch and Merikangas, 1996). Association studies test for genomic variants with statistically different frequencies in affected versus unaffected persons. Association analyses can be conducted within families (in which case one is testing for linkage and association (Martin et al., 2000), or, more commonly now, across families (Hirschhorn and Daly, 2005; Manolio, 2010; McCarthy et al., 2008). Genetic association is the method used in both candidate gene studies and in GWAS. Candidate gene studies involve testing for association with genes hypothesized to be involved in a phenotype (e.g., alcohol metabolizing genes for alcohol use disorders) or those previously connected to a phenotype (e.g., in previously published reports or animal studies). In contrast, GWAS take an atheoretical approach and systematically search across the genome for significant associations. Thus, GWAS combine the unbiased nature of a linkage study with the statistical power of an association study. The genome-wide search has been aided by the identification and cataloging of variants, in particular single nucleotide polymorphisms (SNPs), across the genome [see the International Hapmap Project (Barrett et al., 2005) and the 1000 Genomes Project (<http://www.1000genomes.org/>) for details]. A SNP represents a single base pair change in the DNA sequence, which may result in a change in a gene's protein product or expression. Most SNPs, however, have no apparent effect and reflect genetic diversity that has arisen over human history. The frequency and breadth of coverage of SNPs has enabled researchers to go beyond the candidate gene study design and has revolutionized genetic analyses.

The literature examining genetic influences on adolescent behavior is comprised largely of candidate gene studies. The advantage of candidate gene studies is that they potentially capitalize on known or hypothesized information about the underlying biology of the disorder under study in order to advance our understanding of genetic contributions to the outcome. The “usual suspect” candidate genes in the alcohol literature include neurotransmitters, receptors and alcohol metabolizing genes. For instance, *DRD4*, a dopamine receptor gene, has been linked to both heavy (Laucht et al., 2007) and binge (Vaughn et al., 2009) adolescent drinking as well as conduct disorder (Mota et al., 2013). A mu-opioid receptor gene, *OPRM1*, has been implicated in both alcohol misuse (Miranda et al., 2010) and “antisocial drug dependence” (Corley et al., 2008). The nicotinic receptor family has also been implicated in antisocial behavior and drug use (*CHRNA2*, Corley et al.,

2008) and adolescent binge drinking (*CHRNA4*, Coon et al., 2014). Candidate gene studies, however, have not yielded the discriminatory power many researchers predicted (Dick et al., 2015). The literature is riddled with false positive reports, stemming from problems including small sample sizes, lack of correction for multiple testing, and preferential publishing of positive (versus null) findings (Sullivan, 2007). Several scholars have spearheaded calls for a renewed interest in research integrity and a “new statistics” including more transparent methodical approaches and emphasis on effect sizes in lieu of p-values (see: Cumming, 2014; Ioannidis, 2005; Ioannidis et al., 2014). Given these concerns and difficulties with candidate gene studies, many researchers have embraced GWAS methodology.

GWAS efforts tend to focus largely on psychiatric outcomes, and on adults, since adolescents are not usually through the period of risk. Accordingly, the strategy in studying genetic influences on adolescent behavior has been to take genes identified in adult samples and study how they influence behavior earlier in adolescence. A prime example of this study model is found with *GABRA2*, the gamma-aminobutyric acid type A receptor alpha2 subunit gene. *GABRA2* was initially identified in a GWAS of adult samples as a risk factor for alcohol dependence (Edenberg et al., 2004). Dick and colleagues then investigated the role of *GABRA2* in an adolescent sample finding that the gene was significantly associated with conduct disorder in childhood (association with alcohol dependence did not reach significance until late adolescence; Dick et al., 2006a). Further studies have continued to implicate *GABRA2* in developmental paths to externalizing phenotypes (Dick et al., 2013a; Dick et al., 2013b; Dick et al., 2009b; Latendresse et al., 2015; Salvatore et al., 2015).

More recently, GWAS on adolescent externalizing traits have been published. Phenotypes include behavioral disposition (McGue et al., 2013), conduct problems (both present (Anney et al., 2008) and retrospective (Dick et al., 2011)) and alcohol problems (Edwards et al., 2015). Amongst these five published GWAS reports, only two found genomewide significant results: variants within *CIQTNF7* (as well as an intergenic SNP on both chromosomes 11 and 13) were associated with retrospectively reported conduct problems (Dick et al., 2011) and a variant located downstream from *LOC100288337* was associated with alcohol problems (Edwards et al., 2015). Furthermore, while most studies identified short lists of variants and loci at the level of trending significance, there is little overlap between studies in terms of most significant findings. This lack of consensus parallels the fate of previous GWAS in many psychiatric disorders; GWAS studies have suffered from small sample sizes and a need for more advanced technological and statistical methodologies (McCarthy et al., 2008). Recent progress in all three areas, coupled with systems and network approaches, meta-analyses, and incorporation of both rare variants and additional structural and functional genetic information in analyses has shown promising results for psychiatric disorders including autism spectrum disorders and schizophrenia (Geschwind and Flint, 2015). However, most published GWAS findings continue to account for only a small portion of the variance for substance use outcomes (e.g., Hart and Kranzler, 2015).

With individual SNPs explaining minimal variance in risk for complex traits, a complementary approach is to combine SNPs of smaller effect in order to create a polygenic risk score to test for association with a phenotype of interest. A common polygenic score

approach involves weighting alleles based on their association in a training sample and then summing across a subset of SNPs to create a score for each individual within a second sample (Purcell et al., 2009; Wray et al., 2014). One such study, published for externalizing behaviors, found that while polygenic scores cross-predicted between an adult and adolescent/young-adult sample, they still only accounted for a small amount of the variance (Salvatore et al., 2015). Thus, despite some progress in gene finding efforts using a variety of methodologies, the adolescent behavior field would benefit from large-scale, coordinated efforts to identify genes involved in key adolescent outcomes. Some of these are underway for phenotypes such as adolescent aggression (*The Eagle Consortium*, Pappa et al., 2015).

Conclusions

Adolescent behaviors, like virtually all other behavioral outcomes that have been investigated to date, show evidence of considerable genetic influence. However, genetic influences on adolescent behavior appear to be particularly dynamic, perhaps reflecting the nature of this developmental period. Parallel to the dramatic shifts in risk-taking behavior that occur across adolescence, genetic influences also increase in importance across adolescence for key behaviors, such as alcohol use and problems. Increases in genetic influence likely reflect, in part, the increasing ability of adolescents to select and shape their environments. The ability of adolescents to express their predispositions for outcomes such as substance use also varies dramatically as a function of their environments, with aspects of the home environment, peer network, and community playing a role in the extent to which genetic predispositions are engendered or diminished. Further, there are multiple pathways of genetic risk, and these too show developmental changes across adolescence. Indeed, the period of adolescence appears to be ripe with dynamic genetic effects.

Although we have made great progress in understanding how the nature of genetic effects unfolds across adolescence, there has not been equal progress in identifying specific genes that impact key adolescent outcomes. This is likely due to the inherent challenges in gene identification for complex behavioral outcomes (Dick et al., 2010; Manolio et al., 2009), coupled with the fact that the transitional nature of adolescent behavior further complicates gene identification. Most developmental studies that have incorporated genetic components have used a traditional candidate gene methodology, though more recently, GWAS data has been generated in adolescent samples and/or genes that have emerged from systematic gene identification studies have been incorporated into longitudinal designs in order to study the unfolding of risk across time. Although these studies can help elucidate the mechanisms and pathways associated with genetic risk, they are likely to remain limited in their utility until gene identification efforts are more fruitful and account for more than just a trivial portion of the variance (Salvatore et al., 2014). Further, understanding risk pathways cannot be the final step. Greater attention must be paid to how information about the unfolding of genetic risk across adolescence, in conjunction with the environment, can be used to inform prevention and intervention. Although some investigators have begun to explore these questions (Albert et al., 2015; Brody et al., 2013; Dodge et al., 2013; Dodge and McCourt, 2010), this remains an important area for future study.

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Highlights

Environments can moderate the importance of genetic predispositions.

Genetic predisposition and environments influence pathways of risky behavior.

Pathways of genetic risk show developmental changes across adolescence.

Figure 1.

Data from the Finnish twin studies demonstrating the changing degree of genetic and environmental influences across adolescence (Rose et al., 2001a; Rose et al., 2001b): genetic influences become more important, and common environmental influences become less important.

Figure 2. Changing influences on age 14 smoking frequency as a function of parental monitoring (Dick et al., 2007b). As parental monitoring increases, genetic influences become less important, and common environmental influences become more important.