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Understanding genetic risk for substance use and addiction: A guide for non-geneticists

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ABSTRACT

There is considerable enthusiasm for the potential of genetics research for prevention and treatment of addiction and other mental disorders. As a result, clinicians are increasingly exposed to issues of genetics that are fairly complex, and for which they may not have been adequately prepared by their training. Studies suggest that the heritability of substance use disorders is approximately 0.5. Others report that family members of affected individuals experience a 4- to 8-fold increased risk of disorder themselves. Statements that addiction is "50% genetic" in origin may be taken by some to imply one's chances of developing the disorder, or that a lack of a positive family history confers immunity. In fact, such conclusions are inaccurate, their implications unwarranted given the true meaning of heritability. Through a review of basic concepts in genetic epidemiology, we attempt to demystify these estimates of risk and situate them within the broader context of addiction. Methods of inferring population genetic variance and individual familial risk are examined, with a focus on their practical application and limitations. An accurate conceptualization of addiction necessitates an approach that transcends specific disciplines, making a basic awareness of the perspectives of disparate specialties key to furthering progress in the field.

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Abbreviations: MZ, monozygotic; DZ, dizygotic.

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1. Introduction

A role for genetics in the development of substance use disorders is largely acceptable to researchers and clinicians working in the field today. Reviews of the evidence from twin and adoption studies report that the heritability of alcohol use disorders averages 0.5 to 0.6 (Schuckit, 2009; van der Zwaluw & Engels, 2009), with estimates ranging from 0.3 to 0.8 for other substances (Agrawal & Lynskey, 2006, 2008; Tsuang, Bar, Harley, & Lyons, 2001). Comparable heritability estimates are also reported for a host of sub-clinical, substance use behaviors and outcomes, including age of onset and patterns of use (Agrawal & Lynskey, 2006, 2008; Hopfer, Crowley, & Hewitt, 2003; Pagan et al., 2006; Tarter, Vanyukov, & Kirisci, 2008). Other studies report that the first-degree relatives (i.e., siblings, parents, and offspring) of individuals with substance use disorders experience a 4- to 8-fold increase in the risk of developing the disorder themselves (Merikangas & Risch, 2003b).

Despite warnings from prominent researchers in genetic epidemiology on the misinterpretation of heritability estimates (Plomin, DeFries, McClearn, & Rutter, 2008; Rutter & Plomin, 1997; Visscher, Hill, & Wray, 2008), their meaning, in particular how they capture and relay information on risk, may remain a source of some confusion to those both inside and outside of the field. How are clinicians and scientists to interpret reports of 0.5 or "50%" for heritability of substance use behaviors and disorders in their research, teaching, and practice? Is it accurate to state that addiction is "50% genetic" in origin, and, by extrapolation, "50% environmental"? How do heritability estimates relate to a "4- to 8-fold increased risk" of disorder development in family members? Finally, how should these estimates of risk be understood and communicated to help clients and families?

Amid a growing and increasingly influential field of psychiatric genetics, particularly following completion of the sequencing of the human genome, there is considerable enthusiasm for the potential of genetics research in the prevention and treatment of addiction and other mental disorders. Psychologists, psychiatrists, and other mental health clinicians are increasingly exposed to issues of genetics and population health that are fairly complex, and for which they may not have been adequately prepared by their training. The study of disorders is increasingly also taking on an interdisciplinary bent, making it insufficient for researchers and clinicians to conceptualize disorders solely from the perspective of their own discipline (see Kalant, 2010 for a thoughtful discussion of the implications for research on addiction etiology). Taking a transdisciplinary approach toward the study of a disorder necessitates the ability to read and interpret a broad array of research.

This article seeks to consider the meaning and boundaries of different types of estimates of genetic risk for alcohol and other drug use, abuse and dependence, and to provide guidance to those in the broader field in their proper use and interpretation. These risk estimates are derived from genetic epidemiology studies, where *genetic risk factors* correspond to statistical signals that emerge from genes, but that are inferred based on patterns of resemblance between relatives (Kendler, 2005). We do not aim to summarize the evidence on the role of genetics in addiction or the progress in identifying specific susceptibility genes at a molecular level (interested readers may consult Agrawal & Lynskey, 2006, 2008; Dick & Bierut, 2006; Dick, Riley, & Kendler, 2010; Gelernter & Kranzler, 2010; Schuckit, 2009). Rather, we aim to provide an introduction to the basic key concepts in statistical risk estimation in psychiatric genetics by applying them to substance use behaviors and disorder etiology.

A number of reasons underlie the rationale for a review of this nature. At a clinical level, substance use behaviors and disorders are of high relevance to psychologists (Miller & Brown, 1997). Alcohol and other drugs are commonly used and misused, and the global burden to public health is accordingly high (Rehm, Taylor, & Room, 2006; Rehm et al., 2009). Substance use disorders are also commonly comorbid with other mental disorders, and are pervasive in mental health care settings (Compton, Thomas, Stinson, & Grant, 2007; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Wang et al., 2005; Weaver et al., 2003). In addition, clinical research documents the relative effectiveness of a variety of psychotherapeutic interventions in treating individuals with substance use disorders (Miller & Wilbourne, 2002).

Aside from the direct clinical relevance, substance use behaviors and disorders also have a number of characteristics that are particularly useful for illustrating the key concepts of psychiatric genetics. These include a complex etiology with an environmental prerequisite for alcohol or other drugs, as well as burgeoning evidence for gene–environment interactions and correlations. Over and above diagnosable disorders, alcohol and other drug use behaviors and patterns are of interest in behavioral and psychiatric genetics. In addition to representing intermediate stages in the etiological mechanisms linking genes with disorders, patterns of use and sub-clinical states represent outcomes of interest in their own right, carrying significant public health burden.

In short, substance use behaviors and disorders are suitable both substantively and conceptually for this review. At the same time, however, they constitute only one of the many complex behavioral and diagnostic outcomes that are of interest to psychologists, and for which an understanding of heritability and genetic risk is essential for research and clinical work. In this sense, substance use behaviors and disorders serve the point of illustration, providing the basis for a review with broad appeal to clinicians and researchers without formal training or a solid grounding in behavioral and quantitative genetics.

In the sections that follow, heritability will first be defined and placed under the microscope, with consideration given to study designs (i.e., adoption and twin studies), their assumptions, and mathematical issues in the calculation of heritability. This will provide the necessary background with which to consider issues of interpretation and application of heritability estimates to prevention and treatment, including implications for the role played by the environment in disorder etiology. We will also explore gene–environment interactions and correlations, as these have important implications for the interpretation of heritability estimates and their application to disorder etiology. Finally, we will review methods of estimating individual risk via family studies, contrasting the calculation methods and interpretation with those of heritability.

2. Heritability defined

Conceptually, heritability (h^2) is the proportion of variability in a characteristic (i.e., an attribute, behavior, or disorder) that is caused by genetic differences in a population (Plomin et al., 2008; Teare & Koref, 2011; Visscher et al., 2008). Specifically, the differences between people on a given characteristic are assigned to genetic and non-genetic sources or causes, and the part that is due to genetic variation is reflected as a proportion of the whole (see Table 1 for a summary of this and all measures of risk discussed in this article). Mathematically, this can be expressed as:

$$h^2 = \text{Genetic variability}/\text{Total variability} \quad (1)$$

As a ratio of variances, heritability ranges from 0, indicating that all of the variance in a characteristic is attributable to non-genetic influences, to 1, indicating that all of the variability can be traced back to genetic differences. *Total variability* in Eq. (1) encompasses genetic variation plus variation due to environmental risk factors (Agrawal & Lynskey, 2008; Hopfer et al., 2003). Environmental risk factors refer broadly to all non-genetic influences, including the pre-natal environment, biological events such as illnesses that are non-genetic in origin, social and interpersonal influences, and so forth (Plomin et al.,

Table 1
Glossary of measures of risk.

Measure	Meaning	Purpose	Calculation	Health/policy implications	Example statement
Heritability	Contribution of genetic influences to individual differences in risk	Quantifies extent to which variability in risk of disorder is due to genetic differences	Genetic risk variance/total risk variance (multiply by 100 to get percentage)	Identifies portion of risk variation due to genes, informs further research to identify specific genes	Sixty percent of the variance in risk for alcohol dependence is due to genetic variation.
Absolute risk	Amount of risk for disorder in a population	Quantifies members' chances of developing the disorder	Incidence of disorder = # of new cases / # of individuals at risk (multiply by 100 to get percentage)	Needs assessment and resource allocation for prevention and treatment efforts	Four out of every 100 individuals in the US will develop alcohol dependence.
Attributable fraction	Amount of risk for a disorder in a population that is due to a particular risk factor	Quantifies the potential impact on the population of the removal of the risk factor	Incidence of disorder in the population − incidence of disorder in those without the risk factor (divide by population incidence and multiply by 100 to get percentage)	Identifies portion of risk variation due to a particular risk factor, and informs where to target prevention strategies	100% of the variance in risk for alcohol dependence is due to alcohol, as all cases of alcohol dependence could be prevented if alcohol were truly unavailable.
Relative risk	Elevation (or reduction) in the risk of a disorder associated with a given risk (or protective) factor	Quantifies the strength of the association between a risk factor and disorder	Incidence of disorder in those with the risk factor / incidence of disorder in those without the risk factor	Study etiological mechanisms and identify vulnerable subgroups of the population for prevention/intervention	The risk of alcohol dependence is elevated 4-fold in those who have an affected first-degree relative.
Relative odds (odds ratio)	Elevation (or reduction) in the odds of a disorder associated with a given risk (or protective) factor	Quantifies the strength of the association between a risk factor and disorder	Odds of disorder in those with the risk factor / odds of disorder in those without the risk factor	Study etiological mechanisms and identify vulnerable subgroups of the population for prevention/intervention	The odds of alcohol dependence are elevated 4-fold in those who have an affected first-degree relative.

2008). *Genetic variability* also represents an aggregate, which in the case of complex disorders, such as substance dependence, summarizes the total impact of a potentially large number of genes that may be widely distributed across the genome (Kendler, 2005). For instance, a total of 1500 genes have been implicated in addiction (Kalant, 2010). The effects of individual genes on complex disorders are probabilistic, rather than deterministic, and it is accordingly more appropriate in psychiatric genetics to refer to "risk genes", than to "genes for" a disorder (Smoller, Sheidley, & Tsuang, 2008).

If the genetic influences on a characteristic encompass a large number of genes, only some of which have actually been identified, where does the estimate of genetic variance come from? As with many constructs of interest to mental health and addiction researchers, it is not directly measurable, but can be inferred from the resemblance of relatives of different degrees of genetic relatedness. Before we consider these methods further, one additional clarification on terminology is needed. Strictly speaking, the term *genetic* describes outcomes that are encoded by genes or the DNA strand, whereas *heritability* assesses the degree of similarity in the expressed phenotype (i.e., the behavior, characteristic or disorder). A developmental outcome that results from the action of genes but, for all intents and purposes, shows no variability in the population (e.g., having two hands on the human body) would be genetic but not heritable. Further, it has been recognized that heritability captures variance that is explained by biological processes that are not considered to be part of the actual DNA strand, but that can nonetheless be transmitted across generations. These include epigenetic mechanisms, which represent chemical modifications that alter gene expression without altering the actual gene sequence (e.g., DNA methylation; Meaney, 2010; Zhang & Meaney, 2010; these are discussed in more detail in Section 3.1 on gene–environment interactions). This distinction may be subtle, but it is critical to understanding the meaning and limits of heritability.

2.1. Designing studies for heritability estimation

Adoption and twining provide naturally occurring experimental conditions for partitioning heritable and environmental components of variance (Table 2; Boomsma, Busjahn, & Peltonen, 2002; Haugaard & Hazan, 2003; Plomin et al., 2008). The following paragraphs provide a brief look into these study designs in turn.

2.1.1. Adoption studies

Adoption provides a setting in which two people who are genetically related do not share an environment, since the adopted children are raised in a different family in a different home. The degree to which, despite not sharing an environment, they resemble each other in terms of some characteristic captures the impact of heritable influences on that characteristic. More accurately, it captures half of the impact, as parents and offspring share only half of their *alleles*, or members of gene pairs that influence a given characteristic. That is, first-degree relatives (e.g., parents and offspring, full siblings) are 50% genetically similar. If a characteristic were fully heritable (i.e., all the variation could be attributed to genetics), we would expect the observed correlation between birth parents and adopted-away offspring to be 0.5. As such, the extent to which a characteristic is heritable in an adoption study is obtained by doubling the observed correlation between parents and offspring:

$$h^2 = 2(rPO) \quad \text{where rPO is the correlation between birth parents and adopted-away offspring} \tag{2}$$

2.1.2. Twin studies

Twin studies compare the relative degrees of similarity between MZ and DZ twins in estimating heritability. However, provided they were raised together, members of twin pairs share both genetics

Table 2
Examples of study designs and their interpretation.

Study type	Purpose	Typical research question	Yield
Adoption study	To investigate the resemblance of individuals who are genetically related but do not share a common environment	How much of the risk for alcohol dependence in the US population is due to genetic variation?	Estimates heritability
Twin study	To investigate the relative degrees of resemblance of monozygotic versus dizygotic twin pairs	How much of the risk for alcohol dependence in the US population is due to genetic variation?	Estimates heritability
Family study	To investigate the clustering of a disorder in families, without specific reference to genetic versus environmental causes	Does alcohol dependence cluster in families? How much is risk elevated because of a positive family history?	Estimates relative risk or relative odds associated with family history

and environment. *How then do twin studies manage to disentangle the influences of environment and genetics?* The resemblance of DZ twins for a given characteristic does indeed represent either or both environmental and heritable influences. The same is true for MZ twins. As a result, heritability cannot be estimated directly using the correlation between relatives, as it was in the adoption study above. Instead, if we assume that the environmental influence on a behavior is equivalent between DZ and MZ twins, then subtracting the two correlation terms will yield the part of the association that reflects the impact of heritable factors. Because DZ twins share 50% of their alleles, like any sibling pair, while MZ twins share 100% of their alleles, the difference is multiplied by 2 to obtain the entire influence of heritable factors:

$$h^2 = 2(rMZ - rDZ) \quad \text{where rMZ is the correlation between members of MZ twin pairs and rDZ is the correlation between members of DZ twin pairs} \tag{3}$$

In essence, this formula asks: *after accounting for the shared environmental factors which make siblings more alike than non-siblings, are the members of a MZ twin pair more similar to each other than the members of a DZ twin pair?* If they are, the reason is attributed to their genetic similarity.

Box 1
Heritability of alcohol dependence.

If an adoption study reveals a correlation of 0.3 between fathers and their adopted-away offspring in the risk of alcohol dependence, heritability is 0.6, suggesting that 60% of the variability in risk for alcohol dependence is caused by heritable influences. If a twin study reveals a correlation between MZ twins of 0.8 and a correlation between DZ twins of 0.5 in the risk for alcohol dependence, then heritability is estimated at 0.6 and, again, 60% of the variability in risk for alcohol dependence is attributed to heritable influences.

2.1.3. Assumptions of study designs

The assumptions that these studies make about the environment are not without controversy. Alluded to above, the estimation of heritability in adoption studies is valid only if the birth parents and adopted-away offspring have no meaningful degree of environmental similarity. To the extent that the adopted family has been selected for similarity to the birth parents (referred to as *selective placement*), this assumption maybe violated. In practice, however, by comparing the characteristics of adoptive and biological parents, numerous adoption studies have detected negligible bias due to selective placement on heritability estimates for psychological outcomes (Duyme, 1990; Leve et al., 2007; Phillips & Fulker, 1989; Plomin et al., 2008). The dissimilarity of the psychosocial environments of adoptive and biological parents is also supported by surveys of adoption agency staff on the reasons for adoption (Neil, 2000).

The internal validity of a twin study depends on MZ and DZ twins experiencing the same degree of environmental similarity during development (referred to as the *equal environments assumption*). If MZ twins experience a more similar environment relative to DZ twins and this environmental difference is associated with the outcome of interest, the estimate of heritability may be inflated. As with selective placement, the equal environments assumption has been tested empirically. This has been accomplished in a number of ways, including by assessing whether twins with greater physical resemblance, higher self- or parent-reported environmental similarity during childhood, and/or lower asserted independence are more alike in the characteristic under study (Kendler & Gardner, 1998; Mitchell et al., 2007). If so, the equal environment assumption may be violated. These studies generally support the validity of the equal environments assumption for behavioral and psychological characteristics (Derks, Dolan, & Boomsma, 2006; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Plomin et al., 2008), although one study found evidence that higher co-socialization in MZ twins contributed to higher concordance of smoking initiation, relative to DZ twins (Kendler & Gardner, 1998). Interested readers may find more detailed coverage of the assumptions of twin and adoption studies elsewhere (Cadoret, 1986; Eaves, Foley, & Silberg, 2003; Plomin et al., 2008).

2.2. Peculiarities of the familial correlation coefficient

When speaking of a continuously distributed characteristic, like age at first use of alcohol or volume of consumption during a given period of time, envisioning the "degree of family resemblance" and the "correlation between relatives" is fairly straightforward. It is a bit more complicated when the characteristic is a dichotomous disorder state. *How does one think of variability in a disorder like alcohol dependence? It is either present or absent.* The answer is that the variance estimates in Eq. (1), and the correlation coefficients in Eqs. (2) and (3), actually pertain to the *risk* of disorder rather than to the disorder itself. The totality of genetic and environmental influences underlying the expression of a disorder is hypothesized to produce a continuum of risk that is normally distributed in the population (Falconer, 1965; Plomin et al., 2008). Individuals who exceed a given threshold along this continuum of risk (i.e., their particular complement of genes and life experiences carries a high level of risk) express the disorder, or are at least classified as such according to diagnostic conventions. Heritability, then, represents the proportion of the total variability in the *risk* of disorder that can be explained by heritable influences. Likewise, the correlations that are calculated between family members in Eqs. (2) and (3) refer to their degree of similarity on the hypothetical risk continuum, rather than some form of similarity in kind, quality, or level of the disorder itself.

In addition, contrary to familiar use of correlation, the familial correlation coefficient is not squared to obtain the proportion of variance explained by heritable influences. It is itself taken as the measure of variance explained (readers not particularly interested in mathematics and statistics are invited to skip this paragraph). This peculiarity reflects the theoretical model that underlies the observed association between family members, which is best illustrated with path diagrams. Recall that the familial correlation reflects the degree of similarity between two individuals for a given characteristic, not the degree of similarity between two different characteristics. The first panel (A) in Fig. 1 presents a simple path diagram for the prediction of a measured characteristic (Y), determined by genetic (G) and environmental (E) risk factors. The standardized path coefficient summarizing the impact of heritable influences is labeled h, and squaring it

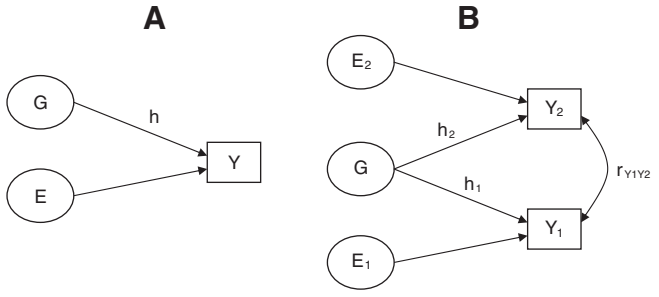

Fig. 1. Path diagrams predicting a measured characteristic (Y). Panel A: an observed characteristic (Y) is influenced by genetic (G) and environmental (E) factors. Panel B: the path model underlying adoption study designs, in which the degree of correlation between two individuals on a measured characteristic (r_{Y1Y2}) is influenced by shared genetic (G) and unique environmental (E_1, E_2) characteristics.

(i.e., h^2) would indeed yield an estimate of the proportion of variance in Y explained by these influences. The diagram is expanded in the second panel (B) to predict the characteristic in two groups of individuals (i.e., Y_1 and Y_2). Note that the two groups share genetics, but not environment (i.e., E_1 and E_2 reflect separate and uncorrelated latent variables). In this way, the diagram illustrates the theoretical model underlying adoption studies, where Y_1 and Y_2 represent the measured characteristic in birth parents and adopted-away offspring, respectively. Those familiar with path analysis will recognize that r_{Y1Y2} decomposes into the product of the two path coefficients (h_1 and h_2) via Wright's tracing rules (Wright, 1934). Conceptually, the correlation between birth parents and offspring (r_{Y1Y2}) reflects the influences of the underlying latent genetic impact on the observed characteristic in both parties (h_1 and h_2). It captures the impact of heritable influences quantified in two path coefficients and, therefore, is itself a proportion of variance. Familial correlations are, one might say, already "squared".

This section has covered the basics of heritability estimation. Examples were included for two specific types of pairings of family members (i.e., parents and offspring, and twins). Numerous other variations on this theme are possible, all involving some form of comparison of relatives who differ from each other genetically in known ways, and whose environments are assumed to differ (or not) in expected ways (e.g., full and half-siblings in the same household). In addition, as noted, the calculations outlined above reflect the classic approach to heritability estimation, and the easiest for illustration purposes. More sophisticated analytical approaches apply latent variable modeling techniques to estimate genetic and environmental variance in observed characteristics, and to allow for testing of more complex models that involve multiple characteristics (i.e., multiple dependent variables), as well as hypotheses about the interplay of genes and environment (Neale & Cardon, 1992). Given a basic understanding of heritability estimation, we can now move on to issues of interpretation.

3. Interpreting heritability for use in daily life

As we have seen, heritability is the proportion of variance explained by genetic variation. It quantifies explanatory power, akin to a *coefficient of determination* (R^2) obtained in a regression analysis. The purpose of quantitative genetics lies in explaining the differences between people in a population by examining indirectly measured aggregates of heritable and environmental variance (Neale & Cardon, 1992; Plomin et al., 2008). *There is no reference to specific genes* or their etiological mechanisms, and nothing is said about behavior, risk, or disorder status *in any one individual* within the population. The aggregate of an individual's genes is responsible for all aspects of development, including body morphology as well as behaviors and health. However, heritability does not refer to the role of genes in individual development. It considers the causes of differences between people. As noted earlier, a developmental outcome that results from the action of genes but, for all intents and purposes, shows no variability in the population (e.g., having two hands on the human body) would be genetic but not heritable. Continuing with the analogy introduced above, a model-R^2 statistic gives the analyst a possible clue about the sources of variance in the dependent variable, but it does not relay information about the status of a given subject included in the analysis. Toward a full appreciation of the meaning and limits of heritability, we will now consider gene–environment correlations and interactions, attributable fractions and models of disease causation, and the influence of non-genetic factors on heritability estimates.

3.1. The interplay of genetic and environmental influences

The above definition of heritability needs to be qualified slightly: heritability denotes the proportion of total variability that is due to heritable (i.e., h^2) and, by extension, environmental (i.e., $1-h^2$) components, *provided that there are no interactions or correlations between the genetic and environmental risk factors* (Dick et al., 2010; Sesardic, 2005). In terms of the validity of heritability, this may strike readers as a fairly tall order. Although a handle on how heritability is calculated is certainly key to understanding the genetic epidemiology literature, it is also the case that research questions have largely moved beyond partitioning the variance into heritable and environmental components, to modeling the interplay between genes and environment in the development of behavior patterns and disorders (Dick et al., 2010; Kendler, 2005; Rutter, 2007). Gene–environment correlation arises when genetic risk factors affect the likelihood of exposure to environmental risk factors. Evidence supporting the presence of gene–environment correlations include findings that a number of environmental risk factors that are implicated in psychological outcomes and disorders, including stressful life events, parenting styles, social support, marital quality, and peer deviance, are themselves heritable in part (Kendler & Baker, 2007; Kendler et al., 2007). That is, people play an active role in selecting and shaping their environments, and these processes are to some extent influenced by genetic predispositions (Dick et al., 2010).

Gene–environment interactions refer to situations in which heritable influences depend on environmental risk factors, and vice versa (Rutter, 2007; van der Zwaluw & Engels, 2009). Interaction occurs when heritable factors influence an individual's susceptibility to adverse environmental exposures or, equally, when environmental contexts affect the expression of genetic predispositions. Social control and stress processes are examples of mechanisms that may link social contexts with gene expression and subsequent behavioral and health outcomes (Shanahan & Hofer, 2005). Specifically, to the extent that one's environment limits choice or discourages particular behaviors, the heritable influence on the behavior will be lowered. Stressors, on the other hand, may serve as triggers activating a genetic predisposition. Heritability estimates for substance use behaviors have indeed been shown to vary across a number of social-contextual variables, including marital status, religiosity, and peer substance use (Button, Hewitt, Rhee, Corley, & Stallings, 2010; Dick et al., 2007; van der Zwaluw & Engels, 2009).

Operating at a more micro level, epigenetics provides a biological mechanism for gene–environment interactions (Meaney, 2010; Zhang & Meaney, 2010). Epigenetic processes represent chemical modifications that do not involve changes to the gene sequence (i.e., are not mutations), but that regulate gene expression. They provide a biological explanation for gene–environment interactions because the chemical modifications can occur in response to environmental signals, which may encompass nutritional, chemical, physical, or psychosocial agents, among others (Meaney, 2010; Wong, Mill, & Fernandes, 2011). Although this research is in preliminary stages, there is evidence implicating epigenetic processes in the etiology of addiction, occurring in response to repeated exposure to substances (McQuown & Wood, 2010; Wong et al., 2011).

As noted earlier, to the extent that gene–environment correlation and interactions are operating, heritability estimates, which rely on partitioning the variance due to heritable versus environmental risk factors, will yield an oversimplified picture of the causes of variability in behavior (Dick et al., 2010; Meaney, 2010). The end result is similar to interpreting a main effect in the presence of significant interactions in a standard regression equation. At this point, a brief foray into epidemiological literature on models of disease causation, which account for the involvement of multiple interacting risk factors, may help to illuminate some of the clinical and policy implications of behavioral and psychiatric genetics.

3.2. Attributable fractions

Applied to a disorder, the concept of heritability is akin to an *attributable fraction*, or the proportion of new cases of a disease that

can be attributed to a given risk factor (Table 1; Willet, 2002). Attributable fractions are used in epidemiology to quantify the preventive potential of interventions targeting a particular risk factor, as they convey the amount of a disease that would be eliminated if the risk factor in question were eliminated from the population (Table 1; Gordis, 2004). As an example, the World Health Organization's Global Burden of Disease project estimated that, in 2004, the attributable fraction of mortality from liver cirrhosis associated with alcohol use was 48%, indicating that alcohol use accounted for almost half of worldwide deaths from liver cirrhosis in that year (World Health Organization, 2009). Said another way, roughly half (i.e., 48%) of the annual number of deaths from liver cirrhosis could be prevented were alcohol removed from the environment.

Calculated in reference to genetic risk factors, attributable fractions are comparable to heritability estimates in that both attempt to quantify the contribution of genetic variation in population levels of disease (Khoury, Beaty, & Cohen, 1991; Willet, 2002). They are based on different methods of calculation, however: heritability estimation uses a statistical model based on partitioning components of variance, while attributable fractions correspond to differences in disease risk between exposed and non-exposed groups in the population. In contrast to attributable fractions, which only apply to binary diagnoses or disorder status, heritability can also be estimated for continuous outcomes. In terms of furthering our understanding of disorder etiology, however, if we were able to obtain the number of new cases of a disorder that were attributable to a particular susceptibility gene, the attributable fraction associated with that gene would provide a more direct quantification of genetic involvement (Khoury et al., 1991). For complex disorders that are influenced by a number of risk genes, many of which are not known, heritability calculations (via partitioning variance components) offer an alternative to directly estimating the collective genetic contribution (Willet, 2002).

One important similarity between attributable fractions and heritability is that they both pertain to the level and nature of disease burden at the population level. Although they are often expressed as a proportion, this proportion does not reflect one's chances of developing the disorder. One's risk of developing a disorder is conveyed instead by incidence rates, discussed in more detail in a later section. A particular set of genes and environmental circumstances may certainly be needed for the development of a disorder *within* an individual, and elucidating the etiological mechanisms is an important scientific endeavor. However, this is not the same question as that asked by heritability.

We have said that attributable fractions can be used to assess the preventive potential of programs targeting particular risk factors. In the case of heritability for complex disorders, like substance abuse and dependence, the practical benefits in terms of *prevention* are less obvious than they are for programs targeting specific susceptibility genes or specific environmental risk factors. However, by highlighting the causes of differences between people in their risk of disorder, even at the general level permitted by these estimates, heritability is useful in as far as it implicates genes in the causal pathway of disorder development and informs the potential of more focused molecular genetics research aimed at identifying specific genes and their etiological mechanisms of action (see Table 1, column titled *Health and policy implications*).

3.3. Necessary and sufficient causes

In characterizing the process of disease etiology, one can think of risk factors as being necessary, sufficient, or component causes of disease (Rothman & Greenland, 2005; Rothman, Greenland, & Lash, 2008). A *necessary cause* is always involved in the development of disease (i.e., the disease never occurs in its absence). A *sufficient cause* refers to a single, complete etiological mechanism or pathway. In reality, a sufficient cause does not correspond to a single risk factor, but to a set of risk factors that act in tandem to cause a disorder. Individually, these risk factors are *component causes*. They do not have to all occur at the same time, although all of the component causes in that pathway must be present in order for the disorder to occur. In other words, component causes co-participate in disorder development, and blocking any *one* of them will prevent the disorder from occurring via that mechanism. Also, for a given disorder, there is not just one, but many etiological mechanisms or sufficient causes. This is referred to as *equifinality*, the same outcome resulting from multiple, distinct pathways (Shanahan & Hofer, 2005).

These concepts have relevance for attributable fractions, introduced in the previous section. Namely, the sum of the attributable fractions associated with individual risk factors for a disorder will typically exceed 100%, and in fact has no expected upper limit (Rothman & Greenland, 2005; Rothman et al., 2008). *Is this tantamount to claiming that we can prevent more than 100% of cases of a disorder?* Not at all, it results from the fact that there are multiple pathways through which a disorder can develop, and multiple risk factors acting within each pathway. As such, the disorder can be avoided in more than one way (Willet, 2002). The attributable fraction associated with a necessary cause is 100%. Yet this does not imply the absence or irrelevance of other causal components, which may also carry substantial preventive potential. The proportion of disease associated with a single component cause or risk factor cannot exceed 100%; however, the total sum of proportions across causal components has no upper limit. As noted above, blocking any single component cause in an etiological mechanism is sufficient to block the development of the outcome via that mechanism (Rothman et al., 2008). Taking alcohol dependence as an example, if we counted the cases that were attributable to one risk factor (e.g., childhood conduct disorder) and then counted the cases that were due to a second risk factor (e.g., low parental monitoring during adolescence), we would count some cases more than once, and summing these figures may result in more cases than were present in the population (Rothman & Greenland, 2005).

Substance use behaviors and disorders have, of course, one component cause that falls under the class of *necessary*: they require the presence of a psychoactive substance. The attributable fraction of alcohol dependence associated with alcohol is 100%, meaning that all cases would be prevented in the population if alcohol was, hypothetically speaking, truly unavailable. Substance availability does not, however, constitute a *sufficient cause* of substance use disorders on its own. Although alcohol must be present for alcohol dependence to occur, exposure to alcohol does not guarantee alcohol dependence and most of those who drink do not become dependent. That is, although the attributable fraction associated with alcohol is 100%, other component causes are evidently also required in order for the disorder to develop. Similar to the elimination of alcohol, blocking one of these other component causes would also prevent development of dependence by the implicated pathway. If this component cause was particularly common in the population, then the fraction of disorder that would be prevented by its elimination could be quite substantial. The fact that there are other component causes does not detract from the preventive potential related to alcohol availability; they simply offer alternatives for tackling the problem. The prerequisite for an environmental exposure in cases of substance use problems and disorders has important public health implications. Namely, it highlights the preventive potential of strategies that target the environment, regardless of whether genes are also involved in their etiology (Merikangas & Risch, 2003a).

3.4. Instability of heritability

Faced with issues pertaining to genetics, there is a tendency to view the impacts and associations as fixed and unchanging. However, this is not the case with heritability, which is sensitive to the

characteristics of the population under study. The ways in which two (non-genetic) characteristics of populations impinge on heritability will be considered: the level of environmental variance and the age of the study population.

First, being a ratio of variance estimates, heritability is sensitive to the relative levels of genetic and environmental variability in the population under study. As a result, the estimates for a given characteristic can vary across populations. To consider an extreme case, the heritability of a behavior would be zero where there is no genetic variation (e.g., in a sample of inbred mice). That is, any variability in behavior in this situation would be due entirely to environmental factors. Equally, if a gene is involved in the development of a disorder but shows no variability between people, the heritability estimate calculated for this disorder will not reflect the risk associated with that gene (Rothman & Greenland, 2005). Heritability is also affected by environmental variation. The heritability of a given characteristic will be high in populations of low environmental diversity (e.g., uniform opportunities for food, education, health care, and so forth), relative to populations with higher environmental diversity. When environmental conditions are relatively constant or equal across a population, a larger proportion of total variability in behavior will be attributable to heritable influences, not because of some important difference in genetic makeup or any fundamental difference in the causal pathways that lead to the behavior, but simply because there is less variability that is caused by non-genetic factors.

Likewise, heritability may change *within* a population over time, if there are important changes in the environment. Heritability conveys the relative importance of genetic and environmental variation *within the existing range of environments at the time of study*. That is, the estimate applies within the current range of environments (i.e., current levels of environmental variance), and the mix of risk factors that are consequently in operation within the population. Taking alcohol dependence as an example (and assuming, for the moment, the absence of gene–environment correlations and interactions), an estimate of 60% heritability quantifies the contribution of heritable factors on disorder development, with the remaining 40% to be attributable to environmental factors. However, the number of new (*incident*) cases of alcohol dependence, and the estimate of heritability, would be expected to change if the environment were changed in some meaningful way; perhaps, for instance, by restricting alcohol availability through taxation, licensing requirements or outlet density (i.e., by altering population exposure to a *necessary* cause). In this way, the evidence for the effectiveness of policy measures based on reducing the availability of alcohol (Room, Babor, & Rehm, 2005) is not at all inconsistent with evidence for the heritability of alcohol use disorders. The same is true for evidence linking social resources in adolescence to patterns of alcohol and drug use (Barnes, Hoffman, Welte, Farrell, & Dintcheff, 2006; Guilamo-Ramos, Turrisi, Jaccard, Wood, & Gonzalez, 2004) and to developmental trajectories of use and problems over time (Chassin, Pitts, & Prost, 2002; Schulenberg et al., 2005; Tucker, Orlando, & Ellickson, 2003). The key idea is that heritability is a descriptive statistic that is dependent on local conditions, in terms of place and time. It is not a fixed property of a behavior or disorder.

Second, estimates of heritability can vary across the lifespan (Bergen, Gardner, & Kendler, 2007; Plomin et al., 2008). An estimate of heritability will, therefore, vary depending on the age range of the population under study. For many substance-related outcomes, heritable factors account for a greater proportion of variability among adults than among adolescents. In adolescent samples, a greater proportion of variance in substance use behaviors and disorders is attributable to shared environmental factors (e.g., common familial and peer influences on use; Agrawal & Lynskey, 2008; Hopfer et al., 2003; Tarter et al., 2008). Increases in heritability through adolescence and young adulthood have been found for a host of other measures, including externalizing and internalizing behaviors and symptoms, and cognitive ability (Bergen et al., 2007; Plomin et al., 2008). This age-dependency may result from the impact of genes that are expressed only once one reaches adulthood, an accumulation of many small genetic influences over time, decreased environmental variance over time, and/or increased selecting and shaping of the environment to suit (and thereby allow for expression of) one's genetic predisposition in adulthood (Bergen et al., 2007; Plomin et al., 2008).

The influence of social controls on the expression of a genetic predisposition was mentioned previously, in the discussion of gene–environment interactions. Extending this idea to age-related changes in heritability, to the extent that social controls on behavior are, on average, higher for adolescents than adults, we would expect to see reduced heritability for behavior in adolescents. Indeed, a recent longitudinal study found that the heritability of alcohol problems was attenuated with increasing religiosity when respondents were adolescents (age 12–18 years), but not once they reached young adulthood (age <30 years; Button et al., 2010). In support of social control theory, religiosity was protective of problematic alcohol use at both time points. In support of the decline in social control with age, mean religiosity was significantly lower in adulthood than in adolescence.

The age-dependency of heritability for substance use initiation, patterns of use, and disorders is relevant because adolescence is the period in which substance use is typically initiated, with disorders tending to emerge in early adulthood (Compton et al., 2007; Hasin, Stinson, Ogburn, & Grant, 2007; Substance Abuse and Mental Health Services Administration, 2009). Further, early onset of drinking and drug use is consistently associated with increased risk of developing problems and disorders (Chen, Storr, & Anthony, 2009; Grant, Stinson, & Harford, 2001). These findings underscore the high potential of preventive interventions targeting social-environmental factors in younger age groups. More generally, they highlight the relevance of integrating developmental and life course concepts into the study of addiction etiology, focusing on general and developmentally-specific transition points over the lifespan, and the resulting opportunities for targeted intervention (Dick & Bierut, 2006; Hser, Longshore, & Anglin, 2007; Tsuang et al., 2001).

3.5. Clinical implications of heritability?

In this review, discussion of the practical implications of heritability has been largely limited, thus far, to public health policies and primary prevention strategies. *Is there any use for heritability estimates in clinical settings, when individuals with substance use disorders are seeking advice for their own recovery or their children's risk of disorder?* References to the clinical uses of heritability estimates are few and far between in the literature. In a noteworthy book reviewing the clinical applications of genetic epidemiology in psychiatry, Smoller et al. (2008) caution that, because heritability does not convey the extent to which an individual patient's illness was caused by genes, and because it cannot be used to indicate the personal risk experienced by the patient's family members or children, it may be misleading or confusing in clinical contexts. Sesardic (2005) provides further conceptual clarification by drawing a distinction between disease onset and continued course. The onset of a disorder may be highly heritable, while its continued presence may be highly responsive to environmental manipulation. In other words, the "treatment" of a largely heritable disorder may nonetheless be a matter of modifying the environment. In addition, simply because the onset of a disorder is not responsive to environmental manipulation at one point in time does not mean that this will always be the case. Progress in understanding genetic and environmental causal mechanisms may illuminate new intervention targets. Whether or not the effect of a given gene is susceptible to environmental intervention will depend on how that gene exerts its effects (Rutter & Plomin, 1997). For instance, to the extent that it influences vulnerability to an environmental risk

factor, the associated risk may be offset by an environmentally-based intervention.

Ultimately, the questions about "genetics" that clinicians are most likely to face will not pertain to heritability or population distributions of risk, but to risk at the individual level. Affected individuals may wish to know the chances that their offspring or siblings will develop a substance use disorder in their lifetimes, or they may want to know more about the risk associated with a positive family history in making sense of their own experience. It is to these issues that we now turn.

4. Individual risk

It should now be apparent that a heritability estimate of 0.6 for alcohol dependence does *not* mean that an individual with an implicated genetic makeup has a 60% chance of developing alcohol dependence in their lifetime. Given a parent with alcohol dependence, it does *not* follow that you have a 60% chance of developing it yourself, nor does it mean that 60% of the alcohol that you consume is due to genetics, while environmental factors, relationships, personal choice, and so forth account for 40%. *So what is the risk conferred by an individual's genetic makeup?* Although this is not possible to delineate specifically, that does not mean that no information is available on individual risk. Estimates of the degree to which a *positive family history* is associated with elevated risk of substance use disorders are available from studies of familial aggregation (Table 2).

4.1. Family studies

Data from population health surveys and controlled family studies can be used to assess the extent to which risk is elevated among the family members of individuals with a disorder, relative to others. Controlled family studies recruit affected and control *probands*, plus their family members (e.g., siblings, parents, offspring), to allow for group comparisons of the rates of disorder among the relatives. It is from such studies that we obtain estimates such as the aforementioned "4- to 8-fold increased risk" of substance use disorders given a positive family history (Merikangas & Risch, 2003b). However, the clustering of a disorder within a family, although a necessary condition for genetic transmission, could arise from either (or both) shared genetics and environment. As such, these risk estimates *do not quantify risk that is conferred solely and uniquely by genetic risk factors*; although they nonetheless convey important information on personal risk in the face of a particular family history (Smoller et al., 2008). Although not strictly a measure of the influence of genetic variation, then, these estimates are pertinent to the current discussion and deserve some consideration.

4.2. Estimating individual risk

The measures of risk derived in these studies will be familiar to those with a background in population health or epidemiology. The incidence of a disorder in a population reflects the *absolute risk* of disorder among its members (Table 1). It quantifies the members' chances of developing the disorder during a given period of time. Incidence is a measure of risk because it captures the onset of the disorder, or the transition from a state of "health" to "disorder". However, the information provided by absolute risk is limited by the fact that the distribution of disease is not random within a population, but varies systematically according to risk factors. One's risk status *relative to others in the population* is also of interest. Because absolute risk is not calculated against any benchmark, it is not possible, in the absence of additional information, to determine whether one's risk is elevated or reduced because of a particular set of genes or circumstances. The *relative risk* and *relative odds* (also known as the *odds ratio*) both accomplish this by comparing the incidence of disorder in those with and without a positive family history (Table 1; Gordis, 2004).

The relative risk represents the ratio of incidence in those with and without a risk factor. Its calculation is based on the *probabilities* of disorder development. The relative odds, on the other hand, are based on *odds*. Odds refer to the probability that an event will occur divided by the probability that it will not occur. For instance, if 4 out of every 100 people develop alcohol dependence over the course of a longitudinal study, the incidence, or probability of developing the disorder, is 0.04, or 4%. The probability of *not* developing dependence is 0.96, or 96%, and the odds of dependence are 0.042, or 4.2% (4/96). To obtain the relative odds, the odds of disorder would be estimated for those with and without a particular risk factor, and their ratio would be taken. Rather than following a sample prospectively to assess disorder onset among those with and without a risk factor, an alternative is to recruit groups of people according to their disorder status, and compare their history of exposure to the risk factor. In this case, the odds would be calculated as the probability of having the risk factor divided by the probability of not having the risk factor, and the odds ratio would reflect the odds among those with the disorder relative to those without the disorder. Regardless of which of the two approaches is used to calculate the relative odds, the end result is the same: a measure of association between a risk factor and a disorder.

Box 2
Individual risk for alcohol dependence.

If 4 out of every 100 people *who do not have a family history of alcohol dependence* develop the disorder over the course of a study, their absolute risk of dependence is 4%. Similarly, if 20 out of every 100 people *who have a first-degree relative with alcohol dependence* develop the disorder, their absolute risk is 20%. Given these incidence rates, the relative risk of alcohol dependence associated with a positive family history is 5 (0.20/0.04). That is, having an affected first-degree relative confers a 5-fold increase in the risk of developing alcohol dependence, although it is not clear whether this is because of shared genetic risk factors, shared environmental circumstances, or both. The relative odds of alcohol dependence in this population is 6 [(0.20/0.80)/(0.04/0.96)], indicating a 6-fold increase in the odds of dependence given a positive family history, with the same caveat regarding the cause(s) of familial clustering.

The relative odds *may* be a good measure of risk provided that certain conditions are met, including that the disorder is "rare" in the population under study (e.g., incidence <10%; McNutt, Wu, Xue, & Hafner, 2003). The reason is that, as the incidence rate increases, relative risk and relative odds calculated using the same data start to diverge from each other. Once incidence exceeds approximately 10%, the divergence starts to become substantively meaningful, and the odds ratio is increasingly not a good measure of risk. Specifically, for disorders and conditions that occur commonly, an odds ratio will overestimate the relative risk associated with exposure to a given risk factor (as in the example given in Box 2). This caveat should be given more attention than it receives in studies of risk for substance use disorders, particularly when drawing from high-risk populations (i.e., in which the disorder has a substantial presence). A more in depth discussion of this methodological issue is beyond the scope of this article; readers interested in more details of the calculations of relative risk and relative odds are directed to Gordis (2004) or any other introductory epidemiology text. For our purposes, it is sufficient to recognize that the two represent alternative ways of quantifying

the strength of the association between a risk factor and disorder. The larger the relative risk (or relative odds), the stronger the association, and the more likely it is that one's disorder status will be impacted by the presence of the risk factor.

As noted above, the results of family studies converge to show an elevated risk (or odds) of substance use disorders given a positive family history. There is variation across studies depending on the methods of estimation, statistical procedures, and study design, and the caveat noted above with respect to inferring risk from odds ratios certainly applies to this area of study. Nonetheless, from the perspective of illustrating the extent of familial aggregation, it is relevant that studies report 2- to 4-fold increased risk/odds of alcohol use disorders among the first-degree relatives of those with alcohol use disorders, and 2- to 8-fold increased risk/odds of other drug use disorders among the first-degree relatives of those with drug use disorders (Beirut et al., 1998; Kendler, Davis, & Kessler, 1997; Merikangas & Avenevoli, 2000; Merikangas et al., 1998; Merikangas et al., 1998; Merikangas et al., 2009). To put these estimates into context, the lifetime prevalence of alcohol use disorders is reported to be 50% and 24% among the first-degree male and female relatives of affected probands, respectively, compared to 20% and 6% in male and female controls (Beirut et al., 1998; Schuckit & Smith, 2000). For cannabis dependence, the lifetime prevalence rates were 19%–27% among first-degree adult relatives, versus 8%–9% in controls (Beirut et al., 1998; Merikangas et al., 2009). Although rates of disorder are clearly elevated among first-degree relatives, then, it is also the case that a substantial proportion of individuals with a positive family history do not personally develop substance use disorders. Equally, the occurrence of substance use problems and disorders in individuals without a family history confirms that a lack of familial risk does not confer immunity.

It is worth noting that, in general, a positive family history does not serve as an effective screening test for substance use disorders. For a relative odds estimate of 5, a screening test based on the risk factor would have a sensitivity of approximately 14%, assuming a 5% false positive rate (i.e., 95% specificity; Wald, Hackshaw, & Frost, 1999). That is, despite being strongly associated with the disorder, the risk factor would detect only a small minority of cases. Along with the above messages regarding the risk associated with a positive family history, this information on risk prediction would likely be relevant to patients with questions about the risk experienced by their children (Smoller et al., 2008).

In concluding this section, we note also that relative risk estimates are conceivable for specific genes as they are identified and found to play role in addiction. However, because these disorders are influenced by a number of genes, the excess risk conferred by any single one would be small. This is not entirely unlike the situation for many of the environmental factors of interest in addiction etiology, which also typically have low unique explanatory power in predicting substance use behaviors and outcomes. As above, the small magnitude of the relative risks associated with individual genes has implications for their use in screening.

5. Conclusions

The purpose of this article was to demystify the literature on genetic risk estimates for substance use behaviors and disorders. The intention was not to provide a comprehensive review of findings or to cover the full breadth of work reflected in contemporary genetic epidemiology research, but to touch upon some of the basic concepts and methods of risk estimation (see Kendler, 2005 and Merikangas & Risch, 2003b for broader reviews of methodology). In genetics as elsewhere, a clear understanding of the different types of risk (i.e., absolute risk, attributable fractions, and relative risk or odds) is essential to proper interpretation of epidemiological studies.

We have seen that heritability represents an aggregated component of population-level variance, and that it is inferred, rather than directly measured, given a specific type of study design. It does not represent the impact of a single gene, nor does it speak to the risk of disorder at the individual-level. We also saw that heritability is not a fixed property of a characteristic or disorder, but can vary over time and across populations in accordance with environmental variance and age. We saw that heritability allows us to infer that genetic risk factors constitute important component causes in the etiological pathways leading to substance use behaviors and disorders; although they are far from deterministic. Viewing etiological mechanisms in this manner, it becomes apparent that studies reporting even a substantial heritable component to alcohol and drug use disorders are not at odds with studies highlighting the substantial and often pivotal role played by environment. Finally, by further reviewing basic epidemiology, we saw how the process of estimating individual risk differs from that of estimating heritability, and what can be gleaned from each type of risk estimate.

In summary, then, the genetic epidemiological literature suggests that a substantial proportion of *population* variance in risk of substance use behaviors and disorders is attributable to heritable factors. A related, but separate, line of inquiry has demonstrated elevated risk of disorder in *individuals* with a positive family history, although shared family environments complicate attribution to genetic risk factors specifically. With these caveats, the results nonetheless converge to suggest an important role for genetics in the development of addiction.

The manifestation of a substance use disorder is likely to be the end-point of a complex interplay between genes and environment, with general and age-specific behaviors and attributes deflecting the developmental trajectory toward or away from disorder status (Schuckit, 2009; Tarter et al., 2004). Far from highlighting the unimportance of environmental impacts on the determinants and distribution of substance use behaviors and disorders, the genetic epidemiology research conducted to date underscores the relative merits of a balanced approach toward prevention and intervention.

Within the realms of research and clinical work, an accurate conceptualization of addiction necessitates an approach that transcends specific disciplines (Kalant, 2010). This requires, in turn, that researchers and clinicians be able to read, understand, and interpret an increasingly broad array of literature. Equally, there is a need for those in the field to use terms that accurately describe their findings (e.g., “genetic variation explains a substantial amount of individual differences in risk for alcohol dependence”, rather than “alcohol dependence is genetic”; Neale & Cardon, 1992). With growing enthusiasm for the potential of psychiatric genetics, psychologists and other clinicians can expect to encounter concepts from, and field questions pertaining to, genetics and epidemiology. A basic awareness of the perspectives espoused by these disciplines is key to furthering progress in our understanding of addiction and in effectively communicating this understanding to those who may be at risk.

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