Twin Studies of Psychiatric Illness

An Update

Kenneth S. Kendler, MD

This overview presents selected recent developments in twin studies of adult psychiatric disorders. Subjects examined include the generalizability of heritability estimates, the impact of sex on patterns of familial transmission, gene-environment interaction, twin studies of anxiety and eating disorders, the so-called family environment, special issues raised by twin studies of drug use and abuse, and gene-environment correlation. The studies reviewed suggest that (1) the heritability of many behavioral traits may be greater in permissive than in restrictive environments and, (2) for psychiatric and drug abuse disorders, genes probably work through both traditional within-the-skin physiological pathways and outside-the-skin behavioral pathways. In the latter, genes affect aspects of the social environment, such as exposure to stressful life events and levels of social support, which in turn feed back on risk of illness. Twin studies remain a vibrant part of the field of psychiatric genetics and an important complement to and context for current efforts to localize individual susceptibility genes.

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In 1993, I reviewed in this journal the accomplishments and future prospects of twin studies of psychiatric illness.1 I herein provide an overview of selected developments in this vibrant field, focusing on adult psychiatric and drug abuse disorders. Areas were chosen to illustrate important themes in current research.

THE CROSS-TIME AND CROSS-SAMPLE GENERALIZABILITY OF HERITABILITY ESTIMATES

An important first goal of twin studies is to estimate heritability—the proportion of individual differences in risk in a population at a given time that are due to genetic differences among individuals. Because a heritability estimate is a population- and time-specific “snapshot,” it is important to know how stable such estimates are across space and time. The field has accumulated enough data to initially address this question.

Before 1990, only schizophrenia had been studied frequently enough in twins to examine meaningfully the homogeneity of heritability estimates. Several reviews tw con-1006-1014 cuded that these studies were essentially replications of one another. For example, an examination of 9 studies in 1983 showed that most estimates of the heritability of liability to schizophrenia were between 0.60 and 0.80, with a weighted mean of 0.68. Three new studies have been published since then from Norway, Germany, and Finland.6 The 2 Scandinavian studies produced heritability estimates (approximately 0.70 and 0.83) consistent with earlier reports. The sample size of the German study was too small for useful heritability analyses, but the concordance rates (0.79±0.11 in monozygotic and 0.17±0.11 in dizygotic twins) were within range of those reported previously. In addition, an updated and expanded report on the Maudsley Twin Series reported heritabilities for varying definitions of schizophrenia ranging from 82% to 84%.7

Enough twin studies of major depression (MD) and alcoholism have been

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published to also examine the homogeneity of results. For MD, a meta-analysis examined 11 samples derived from 5 reports. The estimated heritability of liability to MD was homogeneous across samples, with a jointly estimated heritability of 0.33 (95% confidence interval, 0.26-0.39). Six population-based twin studies of alcoholism have been published since 1992 (Table 1). The consistency of heritability estimates across samples, ranging from only 0.52 to 0.64, is striking.

We can now examine whether levels of heritability differ meaningfully among psychiatric disorders. The current literature suggests that schizophrenia is more heritable than alcoholism, which in turn is more heritable than MD.

Variations in heritability estimates across samples could be due to genetic or environmental differences between populations. By studying different historical cohorts from the same population, it is possible to examine specifically the impact of changing social conditions on the heritability of psychiatric syndromes.

Sweden established temperance boards to register and treat individuals with alcohol abuse seen in legal or medical settings. Information on temperance board registration was available for all male-male Swedish twin pairs born between 1902 and 1949. The sample was large enough to divide into 4 birth cohorts, each containing more than 1900 twin pairs. The frequency of registrations was similar across cohorts. Model fitting suggested that genetic and familial-environmental risk factors account for 54% and 14% of the liability to temperance board registration, respectively. These estimates were stable across the 4 birth cohorts. Despite wide-ranging changes in economic and social conditions in Sweden during the first half of the 20th century, the etiologic importance of genetic factors in alcohol abuse remained stable.

For schizophrenia, MD, and alcoholism, current evidence suggests that heritability, as estimated from twin studies, is reasonably stable across the time periods and populations that have to date been studied. We recently reached a similar conclusion for smoking initiation and nicotine dependence—related measures, such as smoking persistence. However, with the exception of one Japanese twin study of schizophrenia, all other studies used populations that were largely or entirely of Western European extraction. Whether these heritability estimates would extrapolate to other major ethnic groups is unknown.

SEX AND DISEASE LIABILITY

Although sex has long been a key variable in psychiatric epidemiology, where it has proven to be an important risk factor for many psychiatric disorders, it has played a less central role in psychiatric genetics. For example, until recently, many twin studies of psychiatric illness excluded opposite-sex dizygotic pairs—the twin type most informative for sex differences. Indeed, opposite-sex dizygotic pairs are probably nature’s best experiment for the study of sex differences in humans. In such pairs, 2 individuals—one male and one female—are conceived at the same time, develop in the same womb, are born at the same time, and reared in the same family.

Two important questions can be asked about the impact of sex on genetics. First, is the magnitude of genetic and environmental effects equal in men and women? Second, are the genes that influence liability to illness the same in the 2 sexes? The answer to this latter question is quantified in the genetic correlation, which usually ranges from zero (indicating entirely separate genes influencing the trait in the 2 sexes) to unity (meaning that all the genes that affect risk of illness in one sex act similarly in the other).

Our most recent field study in the Virginia Twin Registry contained more than 1400 pairs of opposite-sex dizygotic twins, and initial analyses have revealed some surprising results. For DSM-III-R—defined MD, using 1 wave of interviews in more than 3700 complete twin pairs, we found that although the level of heritability was similar in men and women, the genes influencing liability were not entirely the same. The genetic correlation was estimated at 0.52. We have recently repeated these analyses using 2 waves of interviews for lifetime MD, thereby increasing power through a reduction in error variance. For DSM-III-R criteria, we found a very similar estimate for the genetic correlation, but also found evidence for greater heritability of MD in women than men. We also addressed a similar question for al-

Table 1. Population-Based Twin Studies of Alcoholism

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Sample</th>
<th>Assessment</th>
<th>Sex</th>
<th>No. of Pairs</th>
<th>Correlation in Liability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendler et al, 1992</td>
<td>Va TR</td>
<td>PI-AD</td>
<td>F</td>
<td>590</td>
<td>0.54</td>
</tr>
<tr>
<td>Reed et al, 1996</td>
<td>NAS TR</td>
<td>Medical diagnosis</td>
<td>M</td>
<td>11,666</td>
<td>0.59</td>
</tr>
<tr>
<td>True et al, 1996</td>
<td>Viet TR</td>
<td>PI-AD</td>
<td>M</td>
<td>1,664</td>
<td>0.55</td>
</tr>
<tr>
<td>Kendler et al, 1997</td>
<td>Sw TR</td>
<td>TBR</td>
<td>M</td>
<td>3,185</td>
<td>0.54</td>
</tr>
<tr>
<td>Heath et al, 1997</td>
<td>Aus TR</td>
<td>PI-AD</td>
<td>M</td>
<td>396</td>
<td>0.64</td>
</tr>
<tr>
<td>Prescott et al, 1999</td>
<td>Va TR</td>
<td>PI-AD†</td>
<td>M</td>
<td>863</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Va TR indicates Virginia Twin Registry; NAS TR, National Academy of Sciences Twin Registry; Viet TR, Vietnam Era Veteran Twins Registry; Sw TR, Swedish Twin Registry; Aus TR, Australian Twin Registry; PI-AD, Personal Interview for Alcohol Dependence; TBR, Temperance Board Registration; and ellipses, not presented.
†By DSM-III-R or DSM-IV.
Table 2. Selected Studies Suggesting Changing Heritability of Behavioral Traits in Different Environments

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Measure</th>
<th>Sample</th>
<th>Environmental Variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heath et al, 1985</td>
<td>Years of education</td>
<td>Male twins from Norwegian Twin Registry</td>
<td>Pre- vs post-World War II historical cohort</td>
<td>Higher heritability in more recent cohorts where school advancement more merit based</td>
</tr>
<tr>
<td>Heath et al, 1989</td>
<td>Alcohol consumption</td>
<td>Twins from Australian Registry</td>
<td>Marital status</td>
<td>Greater heritability in single vs married individuals</td>
</tr>
<tr>
<td>Fishbein et al, 1990</td>
<td>Reading and math achievement</td>
<td>Swedish twin school children</td>
<td>Permissive vs restrictive class</td>
<td>Higher heritability in permissive vs restrictive class</td>
</tr>
<tr>
<td>Lichtenstein et al, 1992</td>
<td>Educational achievement</td>
<td>Swedish twins raised together and apart</td>
<td>Historical cohort</td>
<td>Higher heritability in those &lt;60 vs &gt;60 years of age</td>
</tr>
<tr>
<td>Dunne et al, 1997</td>
<td>Age at first intercourse</td>
<td>Australian Twin Registry</td>
<td>Historical cohort</td>
<td>Greater heritability in more recent cohorts</td>
</tr>
<tr>
<td>Rowe et al, 1999</td>
<td>Aggression</td>
<td>US adolescent twins and siblings</td>
<td>Family warmth</td>
<td>Greater heritability in schools with higher mean family warmth</td>
</tr>
<tr>
<td>Boomsma et al, 1999</td>
<td>Disinhibition</td>
<td>Dutch adolescent twins</td>
<td>Religious upbringing</td>
<td>Higher heritability in those with a nonreligious vs religious upbringing</td>
</tr>
<tr>
<td>Rowe et al, 1999</td>
<td>Vocabulary IQ</td>
<td>US adolescent twins and siblings</td>
<td>Parental education</td>
<td>Greater heritability in more highly educated families</td>
</tr>
<tr>
<td>Kendler et al, 2000</td>
<td>Regular tobacco use</td>
<td>Female-female Swedish twins reared together and apart</td>
<td>Historical cohort</td>
<td>Greater heritability in more recent cohorts with higher levels of tobacco use</td>
</tr>
</tbody>
</table>

cohol dependence, this time using DSM-IV criteria. The best-fit model included a modestly higher heritability in women than in men and a genetic correlation estimated at +0.48. Although our results for alcoholism were not replicated by the most comparable other study, they nonetheless raise the possibility that differences in the sexes, at the levels of biological, psychological, or social systems, are of sufficient magnitude to elicit different genetic risk factors for common psychiatric and drug abuse disorders.

GENE-ENVIRONMENT INTERACTION

Most traditional genetic analyses assume that the effects of genes and environment are additive or, to put it into other words, the impact of genetic factors is the same across diverse environments. Until recently, studies of gene-environment interaction in psychiatry were restricted to adoption designs in which genetic risk was reflected by the diagnostic status of biological relatives and rearing environmental risk was indexed by characteristics of the adoptive family. As indicated in Table 2, twin studies have now considerably expanded the range of environments that have been investigated. In particular, several studies have examined differences across historical cohorts in the heritability of a range of behavioral traits, including educational achievement, age at first intercourse, and regular tobacco use. Heritability was consistently higher in more recent cohorts.

To explain this pattern, let us examine the study of regular tobacco use in Swedish twins reared together and reared apart who were born between 1890 and 1958. In male twins, the frequency of regular tobacco use and heritability was constant over cohorts. In female twins, by contrast, regular tobacco use was rare for those born before 1925 and only reached levels comparable to men in those born after 1940. More remarkably, heritability of regular tobacco use similarly increased from zero in those born before 1910 to levels comparable to those seen in men (around 60%) for those born after 1940. This pattern of findings is most likely driven by greater accessibility to tobacco products for women in Sweden during the 20th century. Greater opportunity for tobacco use in women in the late 20th century allowed the expression of susceptibility genes that might have been “silent” earlier in the century when many women had limited access to tobacco.

This hypothesis—higher heritability in environments that provide a greater diversity of exposures—is supported by other studies. Social mores about sexuality have liberalized in Australia in recent years, and the heritability of age at first intercourse has increased. After World War II, Norway based access to higher education on merit rather than family finances. At least for males, this change was associated with a substantial increase in the heritability of educational attainment. Similar results were found in Sweden.

Other studies outlined in Table 2 have examined variation in marital, family, and school characteristics. In each study, heritability was greater in less restrictive environments. More research will be needed before we can conclude whether, as predicted, this is a general pattern. These results have most obvious implications for the genetics of drug use disorders where heritability would be predicted to increase with increasing availability.

Table 2 focuses on studies in which twins differed in broad aspects of their environmental experiences. Another approach to the assessment of genotype-environment interaction is to examine exposure to discrete environmental stressors. For example, we examined differences in rates of onset of MD in groups at various levels of genetic risk. These differences were much greater in the presence of than in the
absence of highly stressful life events. For this study, the paradigm might be that genetic variation that is phenotypically silent in the baseline state can be elicited by specific environmental exposures. Two further examples from the medical literature might clarify this type of genotype-environment interaction. In addition to increasing the risk for Alzheimer disease,43 the APOE e4 allele increases deposition of amyloid in the brain after head injury.44 When boxers were divided into those at low and high exposure to traumatic brain injury, those with low exposure had mild symptoms of organic brain damage that was unrelated to the apolipoprotein E genotype.45 Those with a high level of exposure to brain trauma had higher mean levels of brain damage and the level of brain injury was significantly greater in those with the APOE e4 allele. In the baseline state, genetic variation in metabolic/detoxification enzymes is unrelated to cancer risk.46 However, given industrial exposure to polycyclic aromatic hydrocarbons, the same genetic variants substantially affect risk for lung, bladder, and breast cancer. In these 2 examples, genetic variation that was silent with respect to a specific phenotype in the baseline state (brain damage or cancer) was “elicited” by environmental exposures (to brain trauma and carcinogens, respectively).

Although heritability estimates from twin studies for schizophrenia, MD, and alcoholism appear stable across times and place, our review of genotype-environment interactions makes it clear that these results could have been otherwise. The heritability for many traits of psychiatric relevance may be modifiable by environmental exposure (eg, stressful life events).47,48 For schizophrenia, MD, and alcoholism, heritability might be altered if populations were exposed to environmental conditions outside the range of those studied to date.

To reiterate, traits or disorders do not have a true heritability. Rather, all heritability estimates are specific to a population with its range of environmental exposures. Whether any heritability estimate can be extrapolated to other populations or similar populations with different environments is an empirical question.

**FAMILY ENVIRONMENT**

For more than a century, a strong tradition within psychiatry has suggested that the family environment to which children are exposed is important in determining their risk for adult psychiatric disorders. More recently, a range of empirical studies49-52 has supported this position. However, nearly all twin studies of psychotic, affective, and anxiety disorders detect little or no etiologic role for the family environment. Two major methodologic issues may explain this apparent discrepancy.

First, genetic epidemiology defines family environment (the terms common or shared are also sometimes used) in a particular way that refers only to those shared experiences that influence liability to a disorder similarly in both members of the twin pair. Examples might include a strict religious upbringing with strong beliefs that drug use is sinful or marked parental discord ending in a bitter divorce that was traumatic for all the children in the family. However, many things occur in families that do not similarly affect both members of a twin pair. Imagine a twin family in which a stepfather sexually abuses one member of a twin pair, an experience that predisposes the twin to later psychopathology.50 Since this happened “in the family,” common sense would suggest that it represents a family environmental risk. However, from the perspective of twin studies, it would be seen as an individual-specific environmental risk because it was not shared by both members of the pair and tended to make the twins less rather than more similar.

A more subtle but equally realistic scenario would be when 2 twins respond differently to the same “objective” event. For example, because of prior differences in parent-child relationships (eg, one twin is closer to the mother and one to the father), a parental divorce could prove more pathogenic to one twin than to another. Because the source of information for twin modeling comes solely from patterns of twin resemblance, this difference in their responses, even though to a classic “family” event such as divorce, would be reflected in twin studies as individual-specific environment.

Second, twin studies have limited statistical power. If genetic factors substantially contribute to twin resemblance, a moderate further impact of the family environment on twin similarity would go undetected in all but the very largest studies. For example, if we examine a disorder with a population prevalence of 10% and heritability of 40%, and assume a P value of .05, we would need approximately 4000 and 10000 twin pairs to detect, 80% of the time, a family environment that contributed 30% and 20%, respectively, of the variance in liability.51

What proportion of variance in liability to psychiatric illness might be due to components of the shared family environment? We recently addressed this question for parenting behavior.52 Using the Parental Bonding Instrument,53 and combining scores from the twin, cotwin, and parent, we showed a moderate relationship among 3 major dimensions of parenting and lifetime risk for 8 common psychiatric and substance use disorders. For example, a 1-SD increase in parental coldness was associated with a 38% and 56% increased risk for MD and drug dependence, respectively.

Because we knew both the strength of the association between parenting and later psychopathologic conditions and the similarity in parenting experienced by members of a twin pair, we could estimate that the proportion of variance in liability to these disorders in siblings due to their shared experiences of being parented was between 1.3% and 3.4%.54 Environmental features of families that are shared by siblings significantly affect risk for psychiatric illness. However, the magnitude of the impact is modest and accounts for too small a proportion of overall liability to be detectable by standard twin modeling.

Recently, Reiss and colleagues55 proposed an intriguing hypothesis about the role of family environment in the etiology of psychiatric disorders. In a novel longitudinal study
of 720 families with same-sex adolescent siblings of varying-sex adolescent sibling pair relationships (from monozygotic twins to unrelated step-siblings), these investigators found robust correlations between measures of family functioning and adolescent adjustment, but also found strong genetic effects on both measurement domains. Three plausible models would explain these findings. First, family functioning and adolescent adjustment may be causally unrelated to one another but both may be due to correlated sets of genetic risk factors. Second, genes may influence adolescent adjustment, which in turn affects family functioning. Third, genes may affect family functioning—perhaps through early childhood temperament—that then influences adolescent adjustment. Reiss and colleagues, based on preliminary data, favor the third hypothesis. For example, they suggest that an irritable child might elicit paternal hostility, which in turn further encourages the development of antisocial behavior. They suggest that families play a major role in modulating the expression of the genetic factors that influence adolescent adjustment and psychopathology. Much further work is needed to evaluate this idea. It is my guess that the second model—in which family dysfunction occurs in response to genetically influenced adolescent psychopathology—is also a common causal pathway linking genes, adolescent behavior, and family functioning.

TWIN STUDIES OF ANXIETY AND EATING DISORDERS AND DRUG USE AND ABUSE

Traditionally, twin studies of adult psychiatric disorders have focused preponderantly on the psychotic and affective syndromes. Of note, therefore, is the recent report61 on broadly defined panic and generalized anxiety disorder from the large, population-based Vietnam Era Twin Registry. The heritability estimates reported (43% and 37%, respectively) were reassuringly similar to the prior population-based studies on these disorders from Virginia and Sweden.56-58

Even more progress has been made on twin studies of bulimia and associated disordered eating behaviors.59 From the initial report60 on bulimia in females from the Virginia Twin Registry, a follow-up study,61 which controlled for errors of measurement by combining data from 2 interview waves, produced substantially higher heritability estimates. Using diverse measures of disordered eating characteristics of bulimia, obtained from 3 waves of assessment in the Australian Twin Registry, Wade et al.62 also found evidence for substantial heritability. In an intriguing study of 11- and 17-year-old female twin pairs from the population-based Minnesota Twin Registry, Klump63 examined body dissatisfaction, binge eating, compensatory behavior, and weight preoccupation. For several of these dimensions, shared family environment was important in the 11-year-olds. However, in the 17-year-olds, twin resemblance was solely due to genetic factors with levels of heritability (35%-60%) similar to that seen in the previous studies of adults. Initial concerns that heritability estimates for bulimia might be inflated by greater environmental similarity in monozygotic vs dizygotic twins54 has not been supported by further studies.59,65

Although the use and abuse of illicit drugs runs strongly in families,66-68 except for the important adoption studies of Cadoret and colleagues69,70 and 3 small sample twin studies,71-73 we have, until recently, known little about the causes of this familial resemblance. The first major population-based twin study to address this question was conducted by Tsuang and colleagues74 in the Vietnam Era Twin Registry. In their 2 major reports74,75 on abuse of 3 drug classes (marijuana, stimulants, sedatives, opiates, and psychedelics), they found that twin resemblance was due to both genetic factors (with most heritabilities ranging from 30% to 50%) and family environment (which in one of their analyses ranged, across substances, from 13% to 29%).75

The second major population-based twin study of illicit substance use and misuse was conducted in the Virginia Twin Registry, first in female-female76-78 and more recently in male-male pairs.79 The analysis of cannabis, cocaine, and stimulants in the female-female pairs76-78 revealed a similar pattern. For all 3 substances, twin resemblance for use was about equally due to genetic and familial-environmental factors. However, twin resemblance for abuse and dependence was solely due to genetic factors with high heritability (ie, >0.60). In females, a similar pattern was seen for cannabis.79 Again, heritability estimates for nearly all substance abuse and dependence exceeded 0.60.

Two points of consistency across these twin studies are noteworthy. First, both large-scale studies agreed that genetic factors substantially influence risk to substance use and misuse. The concept that individual differences in the vulnerability to illicit drug abuse is solely due to social factors is difficult to sustain in light of these and previous data. Second, both studies found that family environment makes an important contribution to twin resemblance for drug use and abuse. By examining multiple levels of use, abuse, and dependence, the Virginia studies suggest that the impact of family environment is usually strongest at the first step—initial drug use. These results are also similar to those recently reported on drug use and abuse from a treated sample of US twins.80 As with the Virginia study, more evidence was found for familial-environmental effects on use of illicit substances than on their misuse. Although there was some variability, especially in females, most of the heritability estimates for abuse and dependence were in the range of 0.50 to 0.80.80

Prior twin studies of psychotic, affective, and anxiety disorders suggest that family environment plays little etiologic role. However, for drug use and possibly misuse, the family environment appears to be an important source of individual differences. This contrast may arise because the decision to use illicit drugs is strongly influenced by religious and social attitudes, which themselves are strongly influenced by the family of origin. Furthermore, much, but not all, of the transmission of these attitudes within families appears to be due to environmental processes such
Heritability of initiation, for example, equals $a^2$, which is equal to the square of the connecting path. This vulnerability to substance misuse derives from 2 sources: (1) risk factors shared between initiation and misuse, reflected in path b, and (2) risk factors that influence misuse that are independent of the liability to initiation. These are also subdivided into additive genetic ($A_a$), common environmental ($C_m$), and individual-specific environmental ($E_m$) components, where the subscript M indicates that they are specific for misuse. Path coefficients, indicated by lowercase letters (a, c, and e), reflect standardized partial regression coefficients. Therefore, the proportion of variance in the observed dependent variables accounted for by the latent independent variable is equal to the square of the connecting path. Heritability of initiation, for example, equals $a^2$. The total heritable influences on drug misuse can be subdivided into those that are shared with initiation, which equals $a^2 \times b^2$, and those that are specific to misuse, $e^2$.

Figure 1. A bivariate twin model for substance initiation and subsequent substance misuse. Observed variables are depicted in boxes and latent variables in circles and ellipses. The model begins with the risk factors for initiation (indicated by the subscript I), which are divided into additive genetic ($A_i$), common environmental ($C_i$), and individual-specific environmental ($E_i$) components. For individuals above the threshold on this dimension, initiation occurs and they become susceptible to misuse. The proportion of variance in the observed dependent variables accounted for by the latent independent variable is equal to the square of the connecting path. Heritability of initiation, for example, equals $a^2$. The total heritable influences on drug misuse can be subdivided into those that are shared with initiation, which equals $a^2 \times b^2$, and those that are specific to misuse, $e^2$.

Figure 2. A, The traditional view of genes and environment in which genetic expression takes place solely in a physiological internal milieu (ie, inside the skin), whereas the environment exists outside the skin. Both genes and environment can affect disease susceptibility. In this traditional model, the causal relationship between the organism and the environment flows in only one direction: from environment to organism. B, A revisionist view of genes and environment in which genetic factors, by influencing behavior, affect the external (outside-the-skin) milieu. This process has been termed genotype-environment correlation or genetic control of exposure to the environment. C, A combined model of genes and environment that posits 2 pathways through which genes can affect disease susceptibility: the traditional, physiological, inside-the-skin pathway and revisionist, outside-the-skin pathway by influencing exposure to environmental risk factors.

This hypothesis predicts that family environmental effects should not contribute to twin resemblance for use or misuse of a psychoactive substance that is socially acceptable and universally available. There is one such substance in our society: caffeine. Indeed, we found no contribution of family environment to twin resemblance for the level of caffeine use, heavy use, toxic effects, tolerance, or withdrawal.

A further development in the genetic epidemiology of drug use and abuse stems from the realization that key features of the development of drug abuse were not captured by the standard twin model. Most important, drug abuse is a conditional process. Key risk factors for drug abuse can only be expressed in those who have initiated use. Initial attempts to model this multistage process were undertaken by Heath and Martin. We developed what may be a more parsimonious approach to the problem, using a causal, contingent, common pathway model (Figure 1). The model is causal in that it assumes a direct path (b) from the liability to substance initiation to the liability to substance misuse. The model is contingent in that misuse can be assessed only in those twins who have initiated use. It is a common pathway model in that genetic and environmental effects on initiation can influence misuse only by acting through the phenotype of initiation.

Most important, this model separates genetic and environmental influences on initiation (subscript I in Figure 1) from those that affect misuse (subscript M). A “thought experiment” about marijuana might illustrate the model. Assume one set of genetic factors influence the probability of experimentation through personality traits such as sensation seeking. These “initiation genes” would be specified in the model as $A_i$. Another set of specific genes (eg, variation in cannabinoid receptors) influence risk for developing marijuana abuse by affecting the drug’s hedonic effects. In the absence of exposure to cannabis, such genes are “silent” and would not affect risk for marijuana initiation. Such misuse-specific genes, in our model, are reflected by $A_m$.

This model, when applied to the initiation and abuse/dependence of any illicit substance, and cannabis and stimulants specifically in female twins, indicated that familial-environmental factors only affected the risk for initiation, not the risk for abuse/dependence. This confirms the hypothesis based on the earlier modeling that families impact on drug abuse largely by influencing risk for initiation. Furthermore, evidence was consistently seen for both initiation and misuse-specific genes. Two separable genetic factors affect the final stage of drug abuse—those that influence risk for initiation and those that influence the probability, given initiation, of progression to abuse. Similar results were obtained when this model was applied to data on smoking initiation and nicotine dependence.

In the traditional view of gene action (Figure 2A), genetic expression takes place in a physiological internal milieu—inside the skin. The environment, by contrast, exists outside the skin. Both genes and environment can impact on disease susceptibility. In this model, the causal...
relationship between the organism and the environment flows only from environment to organism.

When considering behavior, however, a revised view of gene action is indicated. By influencing behavior, genes can also affect the external milieu (Figure 2B). In humans, this effect is clearly seen in the psychosocial environment, in particular stressful life events, social support, and parent-child relationships.

STRESSFUL LIFE EVENTS

Individuals do not experience stressful life events at random because stable individual differences are seen in event proneness. Part of these individual differences are due to genetic factors that influence exposure to a range of recent stressful life events in children and adults and specific event, such as combat trauma and divorce. In most studies, heritability of event exposure is modest, usually approximately 20% to 30%, with family and individual-specific environmental factors accounting for the large bulk of individual differences. Moreover, evidence for heritability is largely restricted to events influenced by an individual’s behavior (eg, relationship breakup) and is not consistently seen for fateful events (eg, death of mother).

A longitudinal twin study of stressful life events addressed a critical question—what is the contribution of genetic factors to the stability of event proneness? For personal events, 55% of the variance was consistent across domains. For stressful life events, social support has been conceptualized “as an individual difference variable as well as an environmental provision.” This view is supported by data that show that perceived social support is correlated with personality and is moderately stable over time, even when the social environment changes completely.

Two twin studies have examined the contribution of genetic and environmental factors to individual differences in the dimensions of social support. The Swedish Adoptive Twin Study of Aging assessed 2 dimensions: quantity of relationships and perceived support. Whereas genetic factors made no contribution to the size of the social network, the heritability of quality of social relations was estimated at 30%. Six dimensions of social support were assessed at personal interview in 2 waves in female-female twin pairs from the Virginia Twin Registry. Heritability estimates for the stable component of these 6 dimensions ranged from 43% (friend support) to 66% (confidants).

PARENTING

In psychiatry, parenting is often viewed as the quintessential environmental variable. Because parenting involves parent and child, genetic factors in the parent can affect the provision of parenting, whereas genetic factors in the child can influence its elicitation. Studies in which twins are in the offspring generation consistently suggest genetic influences on the elicitation of parenting (or related family environment measures). Particularly convincing have been correlations of 0.30 to 0.40 for retrospectively rated measures of family environment from 2 samples of monozygotic twins reared apart. Two studies examined the provision of parenting by investigating twins as parents. Both found substantial genetic influences. In most studies, heritable factors were more important for measures that reflect parental warmth than parental control.

However, these studies relied on self-report measures, retrospectively over many years. Perhaps genetic factors act only on the recall and interpretation of parenting experiences. However, videotaped parent-child interactions in siblings of varying genetic relationships have now been examined. Genetic effects were seen across a wide array of behavior of the adolescents toward their parents, including warmth, involvement, anger, and conflict. The average heritability across domains was 23%.

An adoption study has recently examined genetic contributions to the elicitation of parenting with particular elegance. The parenting behavior of adoptive parents was significantly influenced by the psychiatric diagnosis of the biological parent. This effect was largely mediated by the adoptee’s hostile and antisocial behavior. That is, children at genetic risk for psychopathology tended to be more hostile and antisocial as children, which elicited harsher behavior and less nurturance from their adoptive parents.

GENE-ENVIRONMENT CORRELATION AS A MECHANISM OF GENE IMPACT ON LIABILITY

For behavioral traits, gene action in humans is not limited to the internal milieu but instead influences important aspects of an individual’s social environment. This has direct relevance for psychiatry practice because it suggests an additional pathway through which genes can influence liability to illness. As depicted in Figure 2C, genes may act on the brain to produce behavior that causes environmental stress (or reduces environmental reserves) in a way that feeds back to increase disease susceptibility. This outside-the-skin pathway may supplement the more traditional within-the-skin pathway when we consider genetic effects on illness risk.

Our longitudinal study of female-female twin pairs from the Virginia Registry provides evidence for the importance of this outside-the-skin pathway of gene action for MD. The genetic liability to MD increases the risk for interpersonal and occupational stressful life events and reduces the average level of relative and spouse support. In an in-
tensive path model for the etiology of MD, genetic risk factors increased the probability of experiencing both lifetime traumas and recent stressful life events, which in turn increased the risk for MD. Of the total genetic effect on liability to MD, approximately 16% flowed through these 2 environmental risk factors. That is, about one sixth of the total genetic effect on MD flowed outside the skin, increasing the risk for major environmental adversities, which in turn increased the risk for depressive episodes.

**FUTURE DIRECTIONS FOR TWIN RESEARCH**

Five areas of development for twin studies are likely to be particularly fruitful in the coming years. First, longitudinal twin studies provide great power at clarifying the developmental pathways through which genes and environment contribute to risk for psychiatric and drug abuse disorders. Several such studies, focusing on childhood and adolescence, are already under way. Longitudinal twin studies of senescence would help clarify the determinants of successful aging.

Second, because of unique relationship patterns (a monozygotic twin is the genetic parent but cultural aunt of her co-twin’s children), studies of twins and their offspring will likely prove invaluable in dissecting out the causes of the transmission of the vulnerability to psychiatric illness from parent to child.

Third, most large-scale twin studies have relied on phenotypes assessed via human introspection about current and past mood states and experiences. Such self-report information is important and well-known limitations. An increasing number of putative endophenotypes for psychiatric disorders are becoming available from many fields, including neuropsychology, affective and cognitive neuroscience, and neuroimaging. (By endophenotype, I mean that given an etiologic susceptibility to a complex phenotype, the endophenotype robustly reflects processes in that cascade more proximal to gene expression than the clinical phenotype itself.) Many of these elegant endophenotypes can only be evaluated in controlled laboratory environments and are expensive. However, an increasing number of such measures are now portable (eg, on laptop computers) and robust enough to be collectable in the home. The next generations of large-scale twin studies may be incorporating several such carefully chosen measures.

Fourth, research in twin studies specifically, and genetic epidemiology more broadly, will continue to be stimulated by developments in statistical methods. Our current tools for addressing a number of key issues remain suboptimal.

Finally, we will see increased interactions between twin and gene-finding approaches. This will take several forms. Twin studies will continue to help refine phenotypes for gene-finding efforts and clarify which endophenotypes will prove helpful. Identified genes can be incorporated directly into standard twin designs, allowing us to explore, for example, interactions between the specified and other “background” genes. Most important, for psychiatric and drug abuse disorders, the explanatory power of any individual susceptibility locus is likely to be modest. Realistic etiologic models will therefore need to include multiple genes, multiple environmental risk factors, and the interactions through time both within and across these domains. Twin research is among our best available methods for providing this essential scientific context within which the results of gene-finding studies will need to be interpreted.

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