Psychiatric Genetics: A Methodologic Critique

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Psychiatric genetics, which is growing in size and influence within psychiatry, employs four major research paradigms: 1) basic genetic epidemiology, 2) advanced genetic epidemiology, 3) gene finding methods, and 4) molecular genetics. Paradigms 1 and 2 study aggregate genetic risk factors inferred from patterns of resemblance in relatives. Paradigms 3 and 4 study individual susceptibility genes localized on the human genome. Paradigms 1, 2, and 3 are statistical in nature, while paradigm 4 is biological. Genetic risk factors reflect the statistical signals from susceptibility genes. Whether it will be possible to identify all the susceptibility genes that underlie genetic risk factors is uncertain. Furthermore, given current research methods, the inability to detect susceptibility genes cannot disconfirm evidence for genetic risk factors. While paradigms 3 and 4 can provide great explanatory power by tracing etiologic pathways back to basic biological mechanisms, genetic epidemiology can also provide important etiologic insights, albeit of a less basic nature. While paradigms 3 and 4 may eventually replace paradigms 1 and 2, this shift is unlikely to occur quickly. Therefore, the field of psychiatric genetics would do best to integrate these four paradigms, stressing their relative strengths and limitations. This integration can be best done within an overall framework of explanatory pluralism that values a range of reductive explanations across varying levels of biological and psychological complexity.

Over the last several decades, as the field of psychiatric genetics has grown in size and influence, several distinct paradigms have emerged that approach from different perspectives the goal of understanding the role of genetic factors in the etiology of psychiatric disorders. In this article, I describe these paradigms, review their strengths and weaknesses, summarize scientific progress made in each area, and then explore the conceptual and philosophical issues posed by these paradigms and their interrelationship.

While psychiatric genetic strategies can be useful in clarifying the action of environmental factors, this essay will focus on genetic effects. We will not review problems of statistical power that are critical for all paradigms.

The Four Paradigms—Explication

Paradigm 1—Basic Genetic Epidemiology

As outlined in Table 1, the goal of basic genetic epidemiology is to quantify the degree to which individual differences in risk (more technically "liability") to illness result from familial effects (as assessed by a family study) or genetic factors (as determined by twin or adoption studies). While family, twin, and adoption studies can each be used to address the issues of basic (and advanced) genetic epidemiology, they differ in approach and emphasis. For the sake of simplicity, I focus here on twin studies; twin studies constitute the area of my own expertise, and these studies have seen the greatest recent growth, driven by the widening availability of twin registries (1) and sophisticated analytic tools (2).

For twin studies, the task of basic genetic epidemiology is to estimate the proportion of liability in a given population due to genetic differences between individuals. This proportion is called heritability. The statistical model that forms the basis of these calculations (the liability-threshold model) (3, 4) assumes a sufficiently large number of individual genetic and environmental risk factors of sufficiently small individual effect that the central limit theorem applies—that is, the resulting distribution of liability in the population approximates normality (5). In this essay, I refer to "genes" identified by genetic epidemiologic methods as genetic risk factors to distinguish them from susceptibility genes, which are identified by paradigms 3 and 4.

Paradigm 2—Advanced Genetic Epidemiology

Given the demonstration of significant heritability, the goal of advanced genetic epidemiology is to explore the nature and mode of action of these genetic risk factors. Potential questions include (6, 7):

1. Are these genetic risk factors specific to a given disorder or shared with other psychiatric or substance use disorders?
2. Do these genetic risk factors affect disease risk similarly in males and females?
3. To what extent are the effects of these genetic risk factors mediated through intermediate phenotypes such as personality or neuropsychological processes?
4. Do these genetic risk factors moderate the effect of environmental risk factors on disease liability (genetic control of sensitivity to the environment) (8)?
5. Do these genetic risk factors affect disease risk through altering the probability of exposure to environmental risk factors (genetic control of exposure to the environment) (8)?
6. Does the action of these risk factors change as a function of the developmental stage of the individual?
7. Do historical experiences moderate the effect of genetic risk factors so that heritability might differ across historical cohorts?
8. For disorders that have multiple stages (e.g., substantial alcohol consumption must precede, but does not always lead to alcohol dependence), what is the relationship between the genetic risk factors for these various stages?
9. Does the level of heritability for a disorder differ across populations?

In both the basic and advanced genetic epidemiologic research paradigms, genetic risk factors are not directly measured. Rather their existence is inferred—by using well-understood statistical methods—from the patterns of resemblance among particular classes of relatives such as monozygotic versus dizygotic twins or biological parents and their adopted-away offspring.

**Paradigm 3—Gene Finding**

The goal of gene finding methods is to determine the locations on the genome of genes (or more technically loci) that have variants that differentially impact on the liability to psychiatric disorders. While molecular methods are used for detecting the genetic variants (or “markers”) that are critical to these analyses, gene finding methods are statistical in nature. By examining the distribution of genetic markers within families or populations, these methods (linkage and/or association) infer the probability that a locus in the genomic region under investigation contributes to disease liability. A further and more refined goal for paradigm 3 is to clarify the history of the pathogenic variant or variants in the susceptibility gene by determining the background pieces of DNA (termed “haplotypes”) on which these variants are found.

**Paradigm 4—Molecular Genetics**

The goal of the molecular genetic paradigm in psychiatric genetics is to trace the biological mechanisms by which the DNA variant identified with gene finding methods contributes to the disorder itself. The first and most critical goal is to identify the change in gene function and/or expression resulting from the identified DNA variant. The more complex goal involves the use of a wide range of methods (e.g., molecular, pharmacological, imaging, neuropsychological) to trace, at a basic biological level, the etiologic pathway(s) from the DNA variant to the abnormal brain/mind functioning that characterizes the disorder.

**The Four Paradigms—Strengths and Limitations**

**Basic Genetic Epidemiology**

Basic genetic epidemiology has the following important strengths:

1. The convincing demonstration of heritability allows for the definitive rejection of the “radical environmentalist” position, which asserts that a clustering of illness within families is ipso facto evidence for the importance of familial-environmental risk factors. For example, it has been argued that the familial clustering of schizophrenia and schizophrenia spectrum traits such as deviant communication patterns indicates that schizophrenia can be “taught” by parents to their children (9). In the psychological, sociological or epidemiologic literature, papers can still be found that assume that parental smoking is a psychosocial risk factor for smoking (10) or that parent-offspring transmission of romantic relationship style (11) can be assumed to be a result solely of social learning.
2. Basic genetic epidemiologic methods assess the aggregate effects of all genetic risk factors regardless of their location on the genome or their individual effect size. These methods therefore provide an overall assessment for a given population of the etiologic importance of genetic variation.
3. Positive results from the basic method—the clear demonstration of genetic risk factors—provide a foundation for further work in which the methods of advanced genetic epidemiology are used.

Basic genetic epidemiologic methods have the following critical limitations:

1. The ultimate goal of science is commonly conceived to be the elucidation of causal processes. By this criterion, the basic genetic epidemiologic paradigm is
unsatisfactory because it is fundamentally descriptive in nature. While this method quantifies the importance of genetic risk factors, it provides no insight into causal or explanatory pathways.

2. Heritability estimates apply to populations and not to individuals. Indeed, the heritability of a disorder in an individual is undefined.

3. In a given population with a particular set of genes, the heritability of a disorder is not immutable and would change by the introduction of new sources of environmental risk. Thus, the magnitude of heritability is not solely a result of gene action. Rather, it is a ratio of the variance in risk in a population due to genetic differences between individuals and the total variance of risk in that population. There is no a priori reason why the heritability of a disorder should be the same across different human populations or historical periods, which likely contain differences in the distribution of both genetic and environmental risk factors. Therefore, contrary to common usage, “heritability” does not designate a characteristic of a disorder or a trait but only of a disorder or trait in a specific population at a specific time.

4. The liability-threshold model that underlies most genetic epidemiologic analyses is biologically non-specific and quite divorced from actual genetic processes. The assumptions of this model (large number of risk loci with very small individual effects) constitute a biological null hypothesis, which is difficult to reject but provides little insight into underlying biological processes.

5. The relationship between heritability and feasibility of gene finding is strong only at one extreme; if heritability is zero, gene finding methods will not succeed. However, given nonzero heritability estimates, the magnitude of these estimates provides little to no information about the ease of gene finding. This is because heritability estimates assess only aggregate genetic effect and are uninformative about the distribution of genetic risk across the genome. It can be easy to find genes for traits with low heritability if most of that genetic risk is concentrated in one genomic location and/or the genetic effects are particularly strong only in some families. It can be very difficult to localize genetic risk for a disorder with high heritability if the disorder is influenced slightly by variation at many loci widely spread throughout the genome. For example, while the heritability of breast cancer is modest (12), researchers have identified two major genes (BRCA1 and BRCA2 [13]) in which mutations can occur that are responsible for a large proportion of familial breast cancers.

6. For the estimate of heritability, twin studies rely critically on excess phenotypic resemblance in monozygotic versus dizygotic twins. Nongenetic processes that cause such excess resemblance will bias heritability estimates. While evidence suggests that such biases are probably not large (6), the observational, nonexperimental nature of genetic epidemiology makes it difficult to rule out such biases definitively.

**Advanced Genetic Epidemiology**

The most important strength of advanced genetic epidemiologic methods is that they move beyond the descriptive approach of paradigm 1 to an exploration of the action of genetic risk factors. Some of these methods, for example, incorporate environmental risk factors or intermediate phenotypes in the analyses. Most important, many of these methods begin to address questions of causal processes (e.g., questions 3–8 listed earlier).

The major limitations of the advanced genetic epidemiologic methods are extensions of the limitations listed earlier for the basic methods—especially points 2, 3, and 6. While such advanced methods can approach causal issues, they are addressed by tracing processes between latent statistically defined genetic risk factors. For example, the latent genetic risk factors for major depression and schizophrenia may act in part by influencing the personality trait of neuroticism (14, 15) and attentional and executive processes (16, 17), respectively. Since neuroticism and attention may be more basic constructs than major depression and schizophrenia, these analyses would constitute a reductive form of explanation—that is explaining a higher-order complex phenomenon as a manifestation of simpler, more basic processes. However, advanced genetic epidemiology offers only partial reductive explanations involving several adjacent levels of a complex causal chain. These causal explanations cannot reach the level of basic genetic/biological processes, such as DNA base-pair variation (18).

**Gene Finding**

Gene finding methods have the following critical strengths:

1. While statistical in nature, these methods have underlying assumptions that are firmly based on the well-characterized biological process of meiosis—that is, genetic recombination and segregation.

2. The results of gene finding methods are more specific, informative, and falsifiable than those from basic genetic epidemiology. By most criteria, these characteristics mean that the results of gene finding methods would have greater scientific value (19).

3. Because these methods are based on sound and well-understood genetic principles, positive results for gene finding methods present a natural basis for further work with the molecular genetic paradigm.

Gene finding methods have the following critical limitations:

1. As with heritability calculations, the statistical methods for gene localization do not solely reflect gene action but rather assess the ratio of genetic to total
variance in liability. The evidence for linkage in a family would vary as a function of the potency and frequency of the environmental risk factors to which its members were exposed.

2. While gene finding methods detect susceptibility genes over small regions of the genome, there is no guarantee that the actual susceptibility gene itself will be easy to determine. Even with relatively large samples, the size of the “high-risk” region detected by linkage analysis can be quite large, containing dozens to hundreds of possible susceptibility genes. In experimental organisms, examples are now emerging of single “signals,” obtained by gene finding methods, that on closer examination, turn out to reflect multiple individual genetic loci.

3. While basic genetic epidemiology performs one test to determine the presence of genetic risk factors, gene finding methods have to perform many individual tests to detect susceptibility genes. Because genetic risk factors have been found for nearly all psychiatric and drug abuse disorders examined to date, the hypothesis tested in paradigm 1 (e.g., genetic risk factors exist for disorder X) has a high a priori probability. By contrast, the hypothesis tested in gene finding methods (that a small region of the genome contains a susceptibility gene for disorder X) is much less likely to be true. Statistical theory predicts that positive results from basic genetic epidemiology studies (one test with high a priori probability) will prove much more reliable than positive results from gene finding methods (many tests with low a priori probabilities). As discussed later in this article, this prediction is well borne out.

**Molecular Genetics**

Molecular genetics has a single overwhelming strength. That is, its methods raise the possibility of reductive biological explanations that would elucidate the causal chain from molecular variation in DNA to the manifestations of psychiatric disorders. Unlike paradigms 1–3, molecular genetics is not fundamentally statistical in nature but rather reflects the biological reductive model of science that has been frequently successful in biomedicine.

Molecular genetics also has one noteworthy weakness: Many practical problems stand in the way of clarifying what may be the extraordinarily complex biological pathways from DNA variation to psychiatric disorders. The individual genetic variants that cause classic genetic disorders are usually easy to detect because they reflect alterations in coding for key amino acids or the destruction of well-defined regulatory sequences. However, the DNA variants that predispose to complex diseases (including psychiatric disorders) may be more subtle in their action and more difficult to detect. Efforts to understand in basic biological terms even the simplest of behaviors in model organisms have met with substantial difficulties.

Molecular genetics also needs to be concerned about how disease risk arises from interactions between genetically controlled biological processes and environmentally induced changes in brain function.

However, the power of molecular biology and neuroscience is also increasing rapidly, so there is reason for guarded optimism that if pathogenic DNA variants are found for psychiatric disorders, it will be ultimately possible to use these variants to gain invaluable insights into the etiology of these disorders.

**The Four Paradigms—Selective Review of Current Status**

In this section my goal is to provide a brief survey of the current status of knowledge in these four paradigm areas so as to inform the following discussion of interrelationships among the paradigms.

**Basic Genetic Epidemiology**

Familial and more specifically genetic risk factors have been found for every psychiatric and drug use disorder that has been the subject of serious study. For most disorders, evidence for genetic risk factors has by now been replicated by using the same research design (most commonly twin studies), and for some disorders (e.g., schizophrenia and alcoholism), the evidence has been replicated across twin and adoption designs. For several disorders (including alcoholism, drug abuse, and depression), twin studies with broadly comparable results have been conducted by using clinical and epidemiologic methods of ascertainment. With only a few exceptions, the consistency of results across studies has been high, and this consistency has been confirmed by the first series of meta-analyses.

As results have accumulated, it has become clear that heritability estimates probably differ meaningfully between disorders, with the highest heritability found for schizophrenia and bipolar illness and the lowest for anxiety disorders. The heritability of alcohol and drug use disorders is at least as high as that found for more traditional psychiatric disorders such as depression and bulimia. Unless there are strong and consistent methodologic biases operating across study designs, this growing body of work indicates that genetic risk factors are of substantial etiologic importance for all major psychiatric and drug use disorders.

**Advanced Genetic Epidemiology**

A wide variety of work has been produced in recent years with this paradigm. This review focuses on six areas. First, a number of adoption and twin studies have provided evidence for genotype-by-environment interaction. Genetic risk factors may frequently influence liability to psychiatric disorders by moderating the pathogenic effect of environmental risk factors. Second, a number of multivariate analyses have indicated that genetic risk factors are often not specific for individual psychiatric or drug use disorders.
abuse diagnoses but rather influence liability for a range of disorders. Sets of genetic risk factors are unlikely to map cleanly onto the nosologic categories of DSM-IV or ICD-10. Third, a number of classic "environmental" risk factors for psychiatric illness, including stressful life events, social support, and the quality of parenting, are moderately influenced by genetic factors. Genetic risk factors may influence susceptibility to psychiatric disorders in part by altering the probability of exposure to certain environmental stressors. Fourth, sex effects may be as important in psychiatric genetics as they have long proven to be in psychiatric epidemiology. The genetic risk factors for several common psychiatric disorders may not be entirely the same in men and women. Fifth, partially distinct genetic risk factors act at the multiple stages in the development of substance abuse and dependence. The genetic risk factors influencing the probability of misusing a substance are only partly correlated with those factors that affect risk for initiation of substance use. Sixth, key transitional events in human development may moderate the effect of genetic risk factors. For example, the genetic risk factors that predispose to anxiety disorders in prepubertal girls may increase the risk for depression after puberty.

**Gene Finding**

A very large number of candidate gene association studies have been reported for numerous psychiatric and drug abuse disorders. The interpretation of these findings remains problematic. Recent reviews have documented what many suspected—that a substantial proportion of positive results in gene association studies for complex disorders do not survive the test of replication (29, 30). Probably only one association finding (variation in aldehyde dehydrogenase activity and risk for alcoholism in Asian populations) is well understood biologically, has been consistently replicated, and has proven to have a substantial effect on risk. A number of other findings have been replicated more frequently than expected by chance and may reflect true positive findings.

Whole genome linkage scans have been reported for many psychiatric and substance use disorders, including schizophrenia, bipolar disorder, alcoholism, autism, attention deficit hyperactivity disorder, bulimia, panic disorder, nicotine dependence, and major depression. A sufficient number of linkage studies of schizophrenia and bipolar illness have been conducted to show that the rate of replication of positive regions across studies has been low. This pattern contrasts strikingly with the high level of consistency seen in the results of basic genetic epidemiologic studies—for example, the results of twin and family studies of schizophrenia (31).

Rigorous meta-analyses of linkage studies of psychiatric disorders are beginning to appear. Particularly noteworthy are two recent studies that utilized raw results of genome linkage scans for schizophrenia and bipolar illness (32, 33). The agreement in regions showing linkage was substantially in excess of chance expectations for schizophrenia, but the results were less clear for bipolar illness.

The last year has seen encouraging advances with a positional candidate gene strategy, in which association methods are applied to genomic regions identified through linkage results. Variants in several genes that appear to affect risk for schizophrenia have been found by using these methods, and replications are appearing for some of them (34). This field is moving quickly and is likely to have changed substantially by the time this article is in print. Increasing efforts have also been made, with some success, to clarify the DNA background (or haplotypes) on which the pathogenic variants in these susceptibility genes occur (e.g., references 35, 36).

**Molecular Genetics**

We have, in the last year, seen the first really viable efforts to trace the biological pathways from potential susceptibility genes to psychiatric phenotypes. For example, mice were developed in which neuregulin 1, one of the recently identified potential susceptibility genes for schizophrenia, was knocked out (rendered nonfunctional) (37). These mice demonstrated reduced expression of N-methyl-D-aspartic acid receptors and abnormalities in prepulse inhibition—a neuropsychological feature found to be, on average, impaired in patients with schizophrenia. Efforts have begun to try to define a common pathway for the molecular effects of identified potential susceptibility genes in deficits that might form part of the pathway from susceptibility genes to the clinical phenotype of schizophrenia (34).

**The Four Paradigms—Interrelationships**

Within the field of psychiatric genetics, how should these paradigms interrelate? Positive results from paradigm 1 lead directly to questions posed in paradigm 2. To confirm the statistical signals of gene finding studies (paradigm 3), it is natural to study the biological changes produced by these genetic variants (paradigm 4). More problematic is the nature of the relationship between paradigms 1 and 2 (hereafter genetic epidemiology) and paradigms 3 and 4 (hereafter gene identification).

The crux of this problem is the relationship between genetic risk factors as defined by genetic epidemiology and susceptibility genes as defined by gene identification methods. (This issue is similar, but not identical to a long-standing debate in the philosophy of biology about the relationship between classic or Mendelian genetics and molecular genetics [see chapters 6 and 7 in reference 38].) Our problem is how to answer a deceptively simple question—are genetic risk factors simply the statistical signals of susceptibility genes? This question can be framed in more philosophical language as, Do genetic risk factors reduce to susceptibility genes?
This central question must be evaluated with great care, because it can be addressed on two different levels with divergent answers. On a theoretical level, the results of twin and adoption studies, if properly conducted, should reflect the distal effects of genetic variation coded in DNA. (No one actively working in psychiatric genetics argues seriously that heritability as assessed in twin or adoption studies emerges from a vitalistic force, although this was advocated in the past in both biological and philosophical circles.) At this theoretical level, therefore, the answer to this question is clear—genetic risk factors are nothing more than signals of susceptibility genes.

However, at a practical level, the answer is more murky in at least two important ways. First, it can be genuinely debated whether it will ever be possible, regardless of technological advances, to trace in a clear and unambiguous fashion a complete set of causal links from DNA base-pair variation to a complex biobehavioral phenomenon such as schizophrenia or major depression. Advocates of these sorts of reductive models argue correctly that the power of emerging technologies to address seemingly intractable scientific questions has more often been underestimated. Furthermore, new analytic methods (such as network theory [39], which could replace unrealistically simplistic linear causal models) may provide an important impetus for further advances. However, the problems of psychiatric illness, involving some of the most complex conceivable questions, including questions of consciousness, self-concept, and reality testing, may involve emergent properties that are not predictable from basic biological phenomena such as DNA variation.

Second, if genetic risk factors are merely manifestations of susceptibility genes, we should be able to use paradigm 3 to confirm the results of paradigm 1. If there is a dispute about whether a twin or adoption study was correct in its conclusion that disorder X is heritable, then we should be able to evaluate these results by linkage and/or association studies. However, while this idea may seem sensible, it is, in practical terms, wrong. If a twin study of disorder X indicated a heritability of 40% and a well-conducted genome scan showed no regions of significant linkage, it would not be sound to argue, on the basis of the linkage result, that the twin study was in error.

The reason for this apparently paradoxical situation is largely the blunt power of gene identification methods combined with the possibility that genetic risk factors may reflect the combined signal of many susceptibility genes of small individual effect. With an infinite sample size, genotyping methods without error, and yet-to-be-designed statistical tools, it might be theoretically possible for gene identification methods to uncover all of the susceptibility genes that form the biological basis for genetic risk factors and to clarify how they combine and interact to produce a specific level of disease liability. Whether such findings will ever be possible is open to debate. If they will be, we are currently a very long way from that goal.

The practical difficulty of moving from paradigms 1 and 2 to paradigms 3 and 4 leaves a gap in the conceptual framework of psychiatric genetics. It is not yet clear whether we can easily get from genetic risk factors to susceptibility genes. Therefore, genetic epidemiologic and gene identification paradigms do not currently relate to one another as do many paradigms in the physical sciences, in which results at a more abstract level can be clearly reduced to more basic methods and definitively confirmed or refuted by the application of these more basic methods.

Competing Paradigms

Some historical periods in science are marked by competing paradigms (40). Such a historical/sociological perspective can be usefully applied to the field of psychiatric genetics, where the two broad camps that have adopted genetic epidemiology or gene identification methods as their main paradigm struggle with each other to attract resources and students. Members of these two groups often attend different scientific meetings. Stereotypes have developed among genetic epidemiologists, who characterize molecular geneticists as “gene jocks.” Gene finders in turn describe genetic epidemiologists as “just interested in statistics—not in real genes.” Over recent years, gene identification methods have gained in prominence, partly at the expense of genetic epidemiologic approaches.

Competition between scientific paradigms most commonly results in one of two outcomes: replacement or integration. In replacement, one paradigm loses, disappearing from the scientific scene. This was the resolution of the competition between the Ptolemaic and Copernican models for planetary motion. In integration, the two paradigms are incorporated into a unified approach. For example, the older paradigm might serve as a useful approximation for the newer paradigm in a limited set of circumstances. While the interpretation is not without controversy (see references 40, 41), many would see the retention of Newtonian mechanics after the introduction of the theory of relativity (because, with commonly encountered speeds and masses, the two systems produce indistinguishable predictions) as an example of integration of scientific paradigms.

Which of these models best applies to the competing paradigms within psychiatric genetics? While the future is uncertain, a time may come when it is easy and cheap to sequence individual genomes and when sufficient statistical tools have been developed that gene identification methods will completely replace genetic epidemiology. Instead of having to infer genetic risk factors from patterns of resemblance across relatives, as is now done in genetic epidemiologic paradigms, it may be possible to measure directly all relevant variants within susceptibility genes and to combine this information with relevant environmental exposures to determine individual liability. These developments would allow a great increase in statistical power be-
cause genetic risk could be determined directly and would not need to be inferred from the risk of illness in relatives.

However, if they are ever achievable, such capabilities will not be available for a substantial period of time. Therefore, the field of psychiatric genetics would be better served currently by working toward a model of integration. Such a model would require an appreciation of the complementary sources of information obtained by genetic epidemiologic and gene identification approaches. The major advantage of genetic epidemiologic methods is that they permit us to assess the magnitude of total genetic influences and then explore how those influences act and interact with various aspects of the internal and external environment. However, most of these questions can also be addressed by using gene identification methods—but only at the level of specific genes or genomic regions. Two examples will illustrate this development. Advanced genetic epidemiology has suggested that the genetic risk factors for the personality trait of neuroticism may be correlated but not identical in men and women (14, 42). A linkage study of neuroticism has recently suggested specific genomic locations for these genes that have different effects in the two sexes (43). A prior twin study suggested that genetic risk factors for major depression in part acted through increasing sensitivity to the depressogenic effects of stressful life events (44). A recent association study has suggested that having a variant in the serotonin transporter gene increases an individual’s risk for developing depression after exposure to high levels of stress (45). These two kinds of knowledge (at the aggregate level for all genetic risk factors and at the level of specific susceptibility genes) are by their nature complementary.

However, there are important questions asked of psychiatric genetics that can be well answered only at the level of aggregate risk. Examples of scenarios involving such questions would include:

1. A large private foundation wants to invest considerable research funds in investigating the etiology of disorder X. In determining how to divide these funds between strategies emphasizing genetic versus environmental risk factors, the foundation representatives turn to psychiatric genetics and ask, “Overall, how important are genetic versus environmental risk factors for disorder X?”

2. A committee for DSM-V is having a hard time determining whether syndromes A and B should be placed in the same or different diagnostic categories. They plan to collect data on several diagnostic validators, such as response to treatment and course. However, given prior evidence that both syndromes are heritable, they are particularly hopeful that genetic studies will provide definitive information to clarify how closely related the genetic risk factors are for these two disorders.

3. A state legislature is considering a large program to reduce youths’ access to alcohol, with the hope that the program will reduce future rates of alcoholism. They know that early onset of alcohol use is associated with later alcoholism but turn to psychiatric genetics to help them evaluate whether that link is causal. Does early onset of alcohol use actually cause future alcoholism, or is the association between early onset of alcohol use and later alcoholism a result of their both being manifestations of an underlying (partly genetic) liability to deviancy?

4. A research team is funded to conduct a large controlled trial of antipsychotic agents in individuals with schizophrenotypal personality disorder. To increase their chances of obtaining positive results, they turn to psychiatric genetics to obtain a definition of this disorder that maximizes its genetic relationship to schizophrenia.

In each of these scenarios, the question cannot be currently answered by using gene identification methods. It requires the ability to assess total genetic risk—currently only possible with genetic epidemiologic methods.

Psychiatric Genetics and Reductive Models for Psychopathology

This review of the relative merits of genetic epidemiologic and gene identification approaches to psychiatric genetics can be productively viewed as part of a broader discussion about the relative value of “hard” reductive models in psychiatry versus “explanatory pluralism” (46). With the remarkable advances in neuroscience and molecular biology, an increasingly common view within psychiatry, and especially biological psychiatry, is that the only valid etiologic models for psychiatric disorders are in basic biological or molecular terms. By contrast, advocates of explanatory pluralism would argue that our ignorance about the underlying causes of psychiatric illness is so profound that we are not in a position to be so selective about the origins of our knowledge. We should not reject, they would argue, partial etiologic explanations, even when they are expressed in nonbiological terms. They would see this kind of patchy reduction to be a much more realistic goal than a complete top-to-bottom hard reductive model (47).

(Advocates of explanatory pluralism are also often skeptical of the claims of hard reductive models that typically assume clear one-to-one relationships between basic biological processes—such as DNA variants in a susceptibility gene—and psychiatric disorders. They would argue that the intervening processes are of such complexity that “many-to-many” relationships are much more likely, because many different susceptibility genes would predispose to one disorder, and variants in one susceptibility gene could, depending on other genes or environmental exposure, predispose to different disorders.)

The question of the relationship between “hard reduction” and explanatory pluralism can be best illustrated by a thought experiment. Imagine there were 15 levels of the...
mind/brain system separating DNA variants and the clinical diagnosis of major depression. (These levels would include processes best conceptualized within a biological framework, such as intracellular signal pathways, cellular organization, local synaptic connections, and neuroanatomical pathways, as well as constructs best understood within a psychological framework, including attachment history, self-esteem, and personality.) Gene identification methods have predominantly focused on trying to directly connect level 1 (DNA variation) to level 15 (major depression).

While complex genetic epidemiology has begun to evaluate reductive models, they differ from those explored by gene identification methods. Consider the evidence that genetic risk factors for the personality trait of neuroticism are closely related to the genetic risk factors for major depression (14). In our thought experiment, this study might be seen as having established a link between level 12 (personality) and level 15 (major depression). Is this study a useful contribution to the psychiatric genetics literature?

Advocates of hard reductive models would argue “no,” probably claiming that all this research does is relate a fuzzy psychiatric disorder to an equally fuzzy psychological construct. For them, a reductive model has to go all the way down to basic biological processes to be valid and useful. By contrast, advocates of explanatory pluralism would argue that this study has produced a useful insight, by making an etiologic connection between two different scientific constructs (personality and psychopathology) at somewhat different levels of abstraction, each having its own literature and set of associated insights.

Conclusions

Psychiatric genetics currently employs a range of research paradigms that can be usefully organized into four groups: basic genetic epidemiology, advanced genetic epidemiology, gene finding methods, and molecular genetics. In this article, I explored the methods employed and the questions asked in each of these paradigms and then briefly reviewed the current status of work in each area. Due to both practical research limitations and the potential theoretical properties of complex systems, a substantial conceptual discontinuity divides the field. It is not clear how easy it will be to get from genetic risk factors, as determined by genetic epidemiologic methods, to susceptibility genes, as determined by molecular genetics.

While genetic epidemiology may eventually be replaced by gene identification methods, this development is sufficiently far in the future that the field of psychiatric genetics will benefit from attempts to integrate these various paradigms, which will require an appreciation of their complementary strengths and limitations. The optimal framework within which to pursue this integration is one of explanatory pluralism, which requires the realization that a restriction to hard reductionist models is counterproductive, given the current immature status of the science. Partial or patchy reductions—for which genetic epidemiologic models are particularly well suited—have an important role to play in future advances in the field.

References


