Chapter 5

The Genetics of Mental Disorders

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Few theories in biology provoke as heated a debate as the notion that human behavior in general, and mental disorders in particular, have a genetic basis. While there could be no more potent evidence of a biological basis than the identification of causative genes, none has yet been found. On the other hand, opponents of this theory characterize it as deterministic, casting behavioral genetics as the enemy of free will. Furthermore, discriminatory social policies, linked to genetic theories of behavior and mental disorders in the past, are an ever present specter in this field.

On this stage of invective and praise, the search for genes linked to mental disorders continues, propelled by one of the all-time largest research projects in the history of biology—the Human Genome Project-and supported by the primary funding agency for research into mental disorders, the National Institute of Mental Health (NIMH) (table 5-l). This gene hunt has resulted in claims of success in finding genes for bipolar disorder and schizophrenia, only to be followed by contradictory data and withdrawal of claims.

Despite the polemics and clashing research findings, there remains powerful evidence from multiple sources that many mental disorders, including the ones considered in this report, have a genetic component. The only evidence to date that mental disorders are *caused,* at least in part, by biological factors comes from genetic studies, However, the inheritance of mental disorders is far from simple, and nongenetic factors also play a role. This chapter summarizes what is known about the inheritance of schizophrenia, major mood disorders, and anxiety disorders. A technical section explains why specific genes are so difficult to find. Finally, the chapter considers some of the implications of what is known about the inheritance of these conditions. First, the basis of inheritance is reviewed.

BASIC GENETIC CONCEPTS

In nearly every cell of the body, instructions for making protein—the chemicals required for the function and structure of cells-are encoded in genes, the fundamental units of heredity. Humans have 50,000 to 100,000 genes, as many as half of which function primarily in the brain. The existence of these now famous substrates of inheritance was predicted long before modern chemistry or microscopy could resolve the minute structure of the cell. By crossbreeding pea plants and meticulously observing the resulting colors and shapes, the Augustinian monk Gregor Mendel (1822-1884) hypothesized that offspring receive discrete elements of inheritance from their parents.

Genes are made up of deoxyribonucleic acid (DNA), a double-stranded molecule that twists into a helix (figure 5-l). Complementary chemical subunits, called base pairs, tether the two strands of the helix: guanine with cytosine and adenine with thymine. The linear sequence of bases in each strand of DNA forms the genetic code. It is this sequence of bases in genes that determines the structure of proteins and regulates cell activity. In all, an estimated 3.3 billion base pairs constitute the human genome, of which only a small fraction-l to 3 percent—is believed to code for proteins.

Genes, along with intervening regions of DNA that do not appear to code for proteins, are folded into rod-shaped bodies, or chromosomes. Each human cell except gametes (eggs and sperm) contains 23 pairs of chromosomes: 22 pairs of autosomes and 1 pair of sex chromosomes, either two

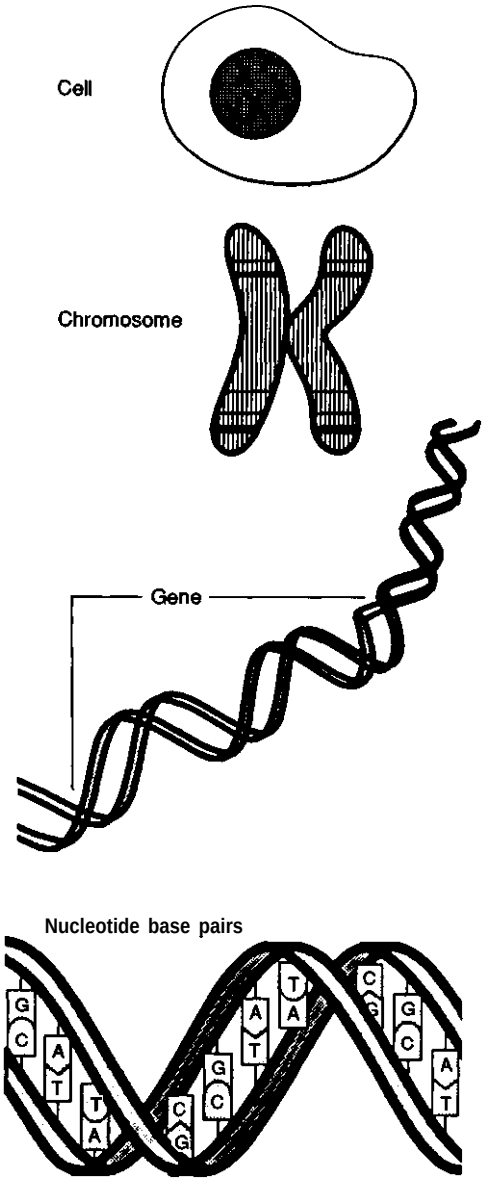
Table 5-1—NIMH Genetic Research Investment, Fiscal Year 1991[a]

	Total costs of genetic research	Number of grants	Genetics as a percent of budget
Division of Clinical Research	$25,629,833[b]	88	15%
Division of Basic Brain and Behavioral Sciences	$13,351,201	55	10.9Y0
NIMH total	$38,981,043	143	8.7%

[a]These figures represent funding for research where the primary focus is human genetics of mental disorders.
b$2,0go,812, or 8.14 percent, of the Division of Clinical Research's genetics budget, is devoted to Diagnostic Centers Cooperative Agreement.

SOURCE: National Institute of Mental Health, 1992.

Figure 5-l—Substrates of Inheritance

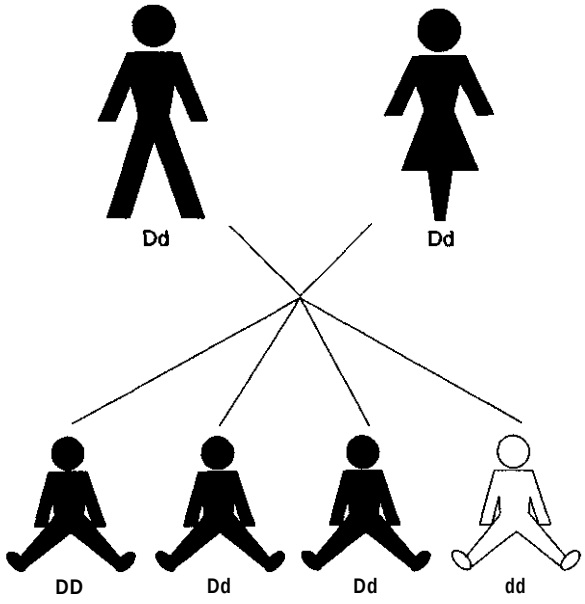


Series of thousands to millions of base pairs form genes, the substrates of inheritance. Genes, which are strewn along chromosomes in the cell nucleus, code for specific proteins.
SOURCE: Office of Technology Assessment, 1992.

X chromosomes, in women, or an X and a Y chromosome, in men. Each gene has a specific address, or locus, on the chromosomes, with two versions, or alleles, of each gene inherited from each parent. If the two alleles at a particular locus are identical, the individual is said to be homozygous; when the two alleles differ, heterozygous. Some alleles are dominant, requiring only one copy to cause expression of a trait, or phenotype (figure 5-2). In such cases, an individual expresses the dominant phenotype regardless of whether the hereditary information for a trait, or genotype, is homozygous or heterozygous. Other alleles are recessive and require two copies of the allele for expression of the trait. In other words, the individual must be homozygous for the gene, with two recessive alleles, in order to express the recessive phenotype. Of course, the inheritance of traits can be much more complex. Many traits reflect the action of several genes as well as the environment. Or a gene may not be expressed, even when present. These complexities have important implications for the study of mental disorders.

Eggs and sperm have only 23 chromosomes (22 autosomes and one sex chromosome), and these form the genetic contribution from our parents-that is, we receive one set of chromosomes from each. During the production of gametes, the 23 pairs of chromosomes are duplicated in the parent cell, endowing it with four copies of each chromosome (figure 5-3). The parent cell divides twice, producing

Figure 5-2—A Simple Pattern of Inheritance



The father and mother both have a dominant version, or allele, of a gene (D) and a recessive version (d). Both express the dominant trait, indicated by shading. Each offspring has a 75 percent chance of receiving either one or two copies of the dominant allele and therefore expressing the dominant trait. One out of four times an offspring will receive two recessive versions of the gene and exhibit the recessive trait, shown in white.
SOURCE: Office of Technology Assessment, 1992.

four gametes, each with a single copy of the 23 chromosomes. However, the production of gametes does not simply involve the separation of chromosome pairs-considerable genetic reshuffling also occurs. The pairs of chromosomes lineup near each other before their final departure to separate gametes. As the pairs of chromosomes draw near one another, they actually exchange segments. This segment exchanger recombination-has important implications for linkage analysis, a technique used to map genes.

STUDYING THE INHERITANCE OF MENTAL DISORDERS

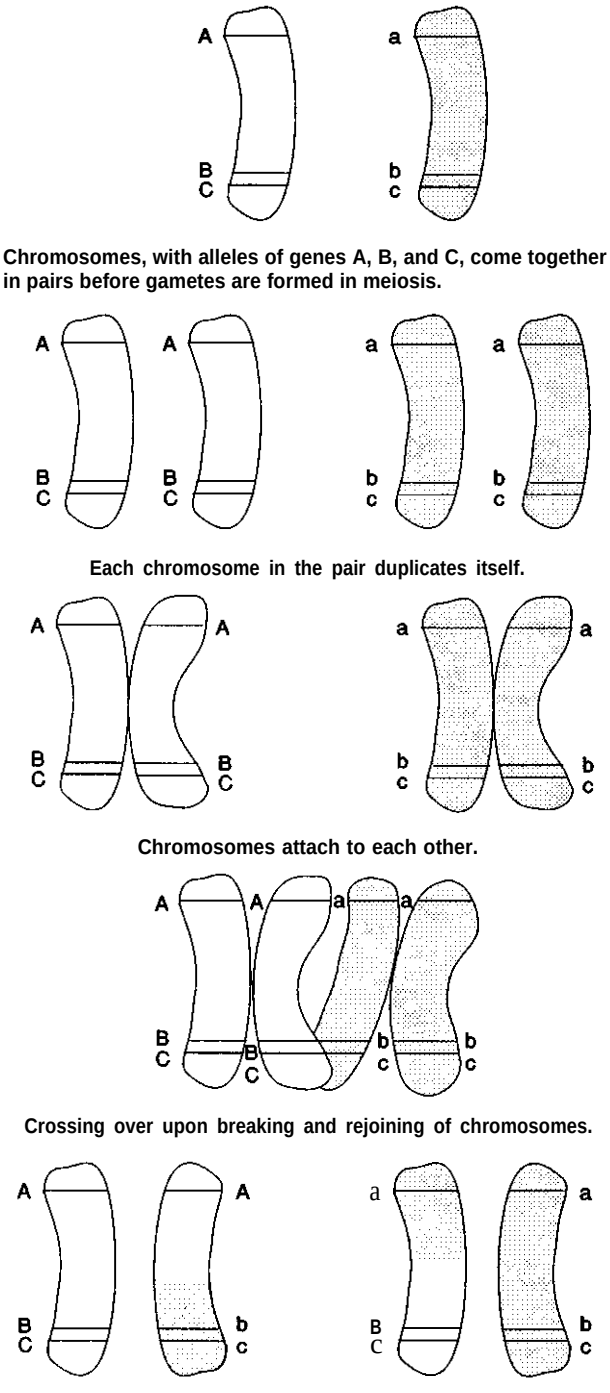
Observers have long noticed that behavioral traits, such as mental disorders, tend to run in families, suggesting the involvement of genetic factors. However, the genetics of human behavioral traits is more difficult to study than other phenotypes. Aside from the ethical impossibility of human breeding experiments and the relatively long time between generations, the phenotype itself is complex.

> Behavior . . . is not just another phenotype. Because behavior involves the functioning of the whole organism rather than the action of a single molecule, a single cell, or a single organ, behavior is the most complex phenomenon that can be studied genetically . . . (83).

Despite these difficulties, methods have been developed to take advantage of "natural" breeding studies. Observing the prevalence and pattern of behavioral traits among related individuals helps illuminate their genetic basis. Charles Darwin's cousin, Francis Galton (1822-1911), launched this approach to the study of the genetics of human behavior. The prodigious Galton explored the inheritance of intelligence, developed new statistical methods for analyzing such traits, and introduced the study of twins (85). Unfortunately, his work also ushered in the ugly era of eugenics in this century (box 5-A).

Classic investigations into human inheritance include adoption, twin, and family studies. These approaches seek to answer the following questions: Are these traits inherited? What is the relative contribution of genetic versus nongenetic factors?[1] What is the pattern of inheritance? Is the trait

Figure 5-3-The Chromosome Swap in Meiosis



SOURCE: Office of Technology Assessment, 1992.

[1] Nongenetic, or so-called environmental, factors may include biological, psychological, or social components. Thus, the now passé nature versus nurture debate does not necessarily boil down to biological versus psychosocial factors.

Box 5-A—Eugenics and Mental Disorders

In Nazi Germany **and the** United States during the earlier part of this century, people with mental disorders were among the initial targets of eugenic policies. People with mental disorders were subjected to immigration restrictions, involuntary sterilization, and extermination. While modems deny that such practices could be repeated, the record of eugenics and its historical link to mental disorders raise uncomfortable questions: Is the new age of genetics a harbinger of a new age of eugenics? Are people with mental disorders especially vulnerable?

Eugenics enjoys along, well-bred intellectual pedigree, with the cousin of Charles Darwin, Sir Francis Galton, as its modem forefather. Galton coined the term "eugenics" in 1883, christening the scientific pursuit of improved inborn human qualities through judicious matings: positive eugenics. Prior to Galton, eugenic notions can be traced back as far as Plato's Republic, wherein the philosopher also proposes positive eugenic practices. Of course, the human genetic pool can be distilled by other means. Negative eugenics refers to the systematic attempt to minimize the passing of deleterious genes by reducing or preventing the reproduction of individuals carrying such genes.

A number of scientific discoveries planted the seeds of eugenic policies in the 19th and 20th centuries. Galton himself observed that many accomplished men of his day were linked by blind lines, which led to his belief that proper matings could produce a race with enhanced intellectual, behavioral, and physical characteristics. In addition, Galton, as well as others, developed statistical techniques that permitted the quantitative analysis of inherited traits.

While these and other scientific advances were the seeds of eugenics, they were not solely responsible for such policies in the United States. Social, political, and economic factors of the late 19th and early 20th centuries fertilized the growth of the eugenics movement. National attention was increasingly focused on social issues of unemployment, criminality, prostitution, and chronic alcoholism. Also, concerns arose that increased immigration from southern and eastern Europe was drawing the United States away from its "Anglo-Saxon superiority. "

At the Federal level, eugenic policies took the form of increasingly restrictive immigration laws, Eugenicists, asserting the simple inheritance of such traits as lunacy, epilepsy, alcoholism, pauperism, criminality, and feeblemindedness, proffered scientific rationales for excluding individuals from entry to the United States. It is important to note that while authentic advances in genetics seeded the eugenics movement, they provided no evidence for the simple inheritance of the traits mentioned above.

Eugenic considerations also prompted States to enact laws regarding compulsory sterilization. In 1907, Indiana passed the first law legalizing the compulsory sterilization of inmates at the State reformatory; by 1931,30 States had passed compulsory sterilization laws applying to individuals categorized as feebleminded, alcoholic, epileptic, sexually deviant, or mentally ill. Individuals with mental disorders made up half of the 64,000 persons in this country sterilized for eugenic reasons between 1907 and 1964, When eugenic sterilization laws were challenged in 1927, the Supreme Court ruled the practice was constitutional.

What is the current status of eugenic policies in the United States? While immigration laws still restrict the entry of people with mental disorders, denial of entry is not based on eugenic principles, but rather on concerns about whether behavior associated with a disorder poses a threat. State sterilization laws still stand, as does the 1927 Supreme Court ruling upholding them. As of 1987, compulsory sterilization laws remained on the books in 22 States; however, these laws are rarely invoked.

The current application of immigration and compulsory sterilization laws suggests that eugenics is not a major concern at this time. Furthermore, the understanding that mental disorders do not have a simple genetic basis and that nongenetic factors play an important role would seem to limit the potential of eugenic policies. Perhaps most important, American repulsion by the Nazi legacy and the emphasis in this country on individual reproductive rights also make State-determined eugenic policies unlikely. But indirect pressure not to have children may well come to bear on individuals seen to have a greater genetic risk of mental disorders; society may brand them irresponsible or immoral for transmitting disorders to their children. Given the financial strain posed by mental disorders today and the stigma attached to them, in conjunction with scientific advances, it is possible that these factors could unlock what some call a backdoor to eugenics.

SOURCES: T. Duster, Backdoor to *Eugenics (New* **York, NY: Routledge,** 1990); K.L. Gamer and B. Gamer, "Eugenics: Past, present, and Future, " *American Journal of Human Genetics 49:1109-1118,* 1991; 1.1. Gottesman, *Schizophrenia Genesis: The Origins of Madness (New* York, NY: W.H. Freeman, 1991); D.J. Kevles, *In the Name of Eugenics (New York, NY: Knopf, 1985);* D. Suzuki and P. Knudtson, *Genethics: The Clash Between the New Genetics* and *Human Values* (Cambridge, MA: Harvard University press, 1989); N.A. Holtzman, *Proceed with Caution: Predicting Genetic Risks in the Recombinant DNA Era* (Baltimore, MD: The Johns Hopkins University Press, 1989).

dominant? Recessive? Determined by more than one gene?

Adoption studies, though variable in design, compare the presence of a trait among biological versus adoptive family members or other control groups. They attempt to disentangle the influence of genes from that of the environment and can provide powerful evidence of a genetic effect. Generally, they do not rule out the effect of nongenetic factors that preceded adoption, such as possible prenatal influences. While few adoption studies have evaluated the genetics of anxiety disorders, they provide evidence about the inheritance of mood disorders and schizophrenia.

Twin studies compare how often identical twins, who are genetically identical, and fraternal twins, who have the genetic similarity of nontwin siblings, are similar, or concordant, for a trait. A high concordance rate for a trait among identical twins versus fraternal twins usually demonstrates a genetic basis for the trait. The absence of 100 percent concordance among identical twins shows that nongenetic factors also play a role in producing the trait.

Twin studies raise several issues, including the certainty with which identical twins versus fraternal twins are identified; the way in which twins are sampled; the assumption that identical and fraternal twins experience the environment identically; the definition of concordance; and the statistical methods for measuring concordance (39,85). All of these factors must be weighed when evaluating data from twin studies.

Of all the traditional approaches to studying genetics, family studies have been used most frequently to evaluate mental disorders. Such studies consider whether a trait runs in families. The familial nature of a trait is essential for proving it is inherited; however, such data do not conclusively demonstrate the genetic basis of a trait, since family members share not only genes but also their environment.

Showing that a trait is more prevalent within a family than in a control population suggests the importance of genetic factors. The observation that a trait is more common among first-degree relatives—parents, siblings, and offspring-than more distant ones strengthens the genetic hypothesis. The way in which a trait is distributed among family members may also elucidate the mode of inheritance. For example, if a trait is never passed from father to son, an X-linked gene is implicated. More complicated quantitative techniques may reveal other aspects of the mode of inheritance. While family studies provide part of the foundation for the genetic theory of mental disorders, they have not resolved how these disorders are inherited.

Classic genetic studies are quite useful. And data from these studies form the sole existing support for the genetic basis of mental disorders. This research produces the bottom line of genetic influence, that is, distinguishing the relative influence of heredity from that of the environment (84). But there is a limit to what classic genetic studies can reveal. They cannot identify a specific gene defect. Because of this limitation, researchers have been eager to apply the new, powerful tools of modem genetics to the study of mental disorders.

The search for the molecular genetic underpinnings of mental disorders in the last several years has involved mostly the technique of linkage analysis. Linkage analysis can determine whether a single gene makes a major contribution to a trait and where that gene is located. A positive finding of linkage shows that a nearby gene plays an important role in the inheritance of the investigated trait. It maps the gene to a location on the chromosomes; it does not isolate the specific gene or reveal its function.

Linkage analysis takes advantage of the fact that although alleles for genes of most traits are inherited independently-since they lie on different chromosomes or are so far apart on a single chromosome that they are separated during the chromosome segment exchange that occurs during meiosis—those lying close together on the same chromosome are usually inherited together. Their loci, or chromosomal positions, are linked (see figure 5-3). The actual distance between two loci can be estimated by determining how frequently the alleles at those sites are inherited together. If the alleles for two traits are passed on together 90 percent of the time (and 10 percent of the time they are not), they are said to have a 10 percent recombination fraction, which corresponds to roughly 1 million base pairs. A recombination fraction of 50 percent indicates that the alleles for two genes are not linked; they are far removed from each other on a single chromosome or on separate chromosomes.

Linkage analysis uses genetic markers-traits or DNA sequences—with known chromosomal ad-

dresses. In the past, traits such as color blindness or blood type served as markers; however, they were quite limited in their usefulness. There were not very many of them, and they lacked variability, an important feature in a genetic marker. The surge in popularity of linkage analysis in the last decade reflects the discovery of new breeds of genetic markers, including restriction fragment length polymorphisms, or RFLPs (pronounced rif' lips), and, more recently, microsatellite repeat markers (7,1 1). These markers derive from variation in the very DNA sequence, revealed by the techniques of molecular genetics. And because these markers span the entire genome, they enable investigators to search for linked genes, regardless of their location.

Linkage analysis is used to distinguish two questions: Given the way a trait is distributed within a family under investigation, does the responsible gene lie within a short and specified distance from the genetic marker? Or is it so far away from the marker that the gene was inherited independently? That is to say, are the two loci (for the gene of interest and the genetic marker) likely to be linked or not in this family? The probability that either of the questions is true is expressed in the form of an odds ratio. Traditionally, an odds ratio of 1,000 to 1 has been taken as proof of linkage (75): It is 1,000 times more likely that the gene loci are linked than not. An odds ratio of less than 1 to 100 has been regarded as proof against linkage. Odds ratios are typically transformed into LOD scores, their base 10 logarithm. Therefore a LOD score of 3 ($\log_{10}$ 1,000/1) or greater is considered evidence of linkage; linkage is rejected with a LOD score of-2 ($\log_{10}$ 1/100) or less.

Upon finding a LOD score of nearly 7—placing the likelihood of linkage at 10 million to l—a researcher would seem to have near absolute proof of linkage. In fact, such a finding has been reported for schizophrenia (96). But, as with all statistical tests, certain assumptions must hold true if the results are to be meaningful. And there is always a chance that a positive finding is spurious, a random occurrence. For example, with a LOD score of 3, there is a 1 in 20 chance that the finding of linkage is spurious. The confusion and controversy that surround the gene search in mental disorders stem from the fact that these conditions violate the rules and assumptions of linkage analysis. The problems associated with this method are considered in a subsequent section, but first, the available evidence that these conditions have a genetic basis is summarized.

GENETICS OF SCHIZOPHRENIA

Classic genetic studies show that schizophrenia has a genetic component (for review, see 38,39,49,54, 102). Data from family studies lead to estimates that first-degree relatives of an individual with schizophrenia have approximately 10 times the general risk of developing the disorder. Twin and adoption studies also implicate genetic factors. Although estimates vary, data consistently show that a person whose identical twin has schizophrenia is at higher risk for schizophrenia than a person whose fraternal twin has the disorder (table 5-2). Adoption studies indicate that schizophrenia runs in biological but not adoptive families (53). These data also point to a genetic relationship between schizophrenia and other disorders, such as schizotypal personality disorder (50).

Clearly, schizophrenia has a genetic component. But genetics is not the whole picture. Twin studies indicate that genetic factors do not entirely account for the development of schizophrenia; an identical twin of someone with schizophrenia exhibits the disorder approximately 30 to 50 percent of the time. Thus, nongenetic factors must also be important. Furthermore, important questions about genetics persist. Even though having a family member with schizophrenia increases the likelihood of developing the disorder, many family members do not develop schizophrenia, and 80 to 90 percent of individuals with schizophrenia have no first-degree relative with the disorder (38). The distribution of schizophrenia within families is not consistent with any simple pattern of inheritance. Studies generally rule out the

Table 5-2—Relatives' Risk of Schizophrenia

Relationship	Risk (%)
First degree	
Parents	5.6
Siblings	10.1
Children	12.8
Children of two parents with schizophrenia	46.3
Second degree	
Half siblings	4.2
Uncles/aunts	2.4
Nephews/nieces	3.0
Grandchildren	3.7

SOURCE: Adapted from I.I. Gottesman, Schizophrenia *and* Genetic *Risks* (Arlington, VA: National Alliance for the Mentally Ill, 1984).

action of a single gene without determining whether a couple of genes, or many genes, are important in producing schizophrenia.

A report that an uncle and nephew with schizophrenia shared a chromosome defect—an extra copy of part of chromosome 5—impelled the search for a schizophrenia gene on this chromosome (8,31,51, 62,95). Linkage to chromosome 5 was asserted soon thereafter in a study of seven British and Icelandic families (96). A simultaneously reported study in a separate kindred in Sweden ruled this linkage out (52). Subsequent studies have since rejected a link between chromosome 5 and schizophrenia (2,26,41, 47,63,77,93).

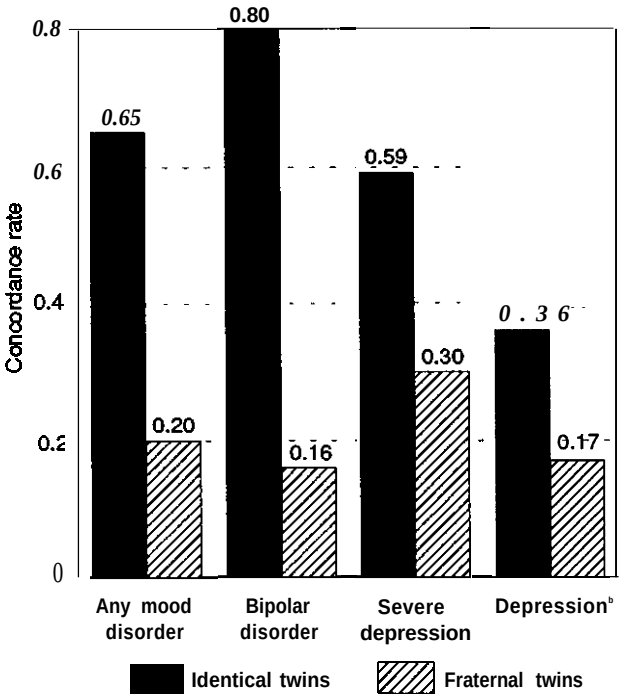
Studies have evaluated the linkage of schizophrenia to the classic genetic marker, the HLA (human-leukocyte-associated) antigen system on chromosome 6. The HLA antigen system is a collection of genes important for immune function. An early study provided only weak evidence of linkage to the HLA system (106), and four subsequent studies ruled out linkage to the HLA system and a wide variety of other classical markers (1,14,36,60). While schizophrenia has not been linked to a region of the X chromosome thought to play a role in bipolar disorder (23; see later discussion), preliminary data support linkage to a region that lies at the ends of the X and Y chromosomes (18).

GENETICS OF MOOD DISORDERS

What do classic genetic studies indicate about the inheritance of mood disorders? Identical twins share mood disorders more frequently than do fraternal twins (for review, see 32,61,74,103,105). For example, data show that the identical twin of an individual with bipolar disorder would exhibit that disorder three times more often than would a fraternal twin (32) (figure 5-4). Parents, siblings, and children of individuals with bipolar disorder or major depression more commonly develop these disorders, although the estimated incidence among family members varies among studies. Only a few adoption studies have evaluated the inheritance of mood disorders. Data from these studies generally support the role of inheritance in mood disorders (for review, see 32,74).

The heritability of mood disorders appears to be correlated with the severity of the condition. Bipolar disorder has the largest genetic component of all mood disorders, and recurring bouts of depression

Figure 5-4—Mood Disorders Among Twins



Graphically depicted data were derived from evaluation of 110 pairs of twins. Identical twins shared mood disorders, especially bipolar disorder, more frequently than fraternal twins.

[a]Three or more episodes of depression.
[b]Less than three episodes of depression.

SOURCE: Adapted from A. Bertelsen, B. Harvald, and M. Hauge, "A Danish Twin Study of Manic-Depressive Disorders," ***British Journal of Psychiatry 130:330-351, 1977.***

appear to be more directly heritable than a single episode. Also, major depression that has an earlier age of onset maybe more heritable. Family and twin studies suggest a genetic link between depression and bipolar disorder. For example, identical twins, who often share the same mood disorder, not infrequently have different forms (10). Similarly, first-degree relatives of a person with bipolar disorder are at greater risk of developing *any* mood disorder than the general population (32). But the genetic overlap between major depression and bipolar disorder is not complete (1 10). For example, while rates of major depression are greatly increased among the relatives of an individual with bipolar disorder, the opposite is not true: The relatives of an individual with major depression are not at a much higher risk for developing bipolar disorder.

Family and twin studies demonstrate the importance of genetic factors in both bipolar disorder and major depression. However, studies do not reveal a simple pattern of inheritance, nor do they implicate

the action of a single gene. The genetic relationships between major depression and bipolar disorders, between schizoaffective disorder and mood disorders, as well as among various subtypes of depression are not clear (see ch. 3). And since identical twins are not always concordant for mood disorders, nongenetic factors must also play a role.

Many studies have attempted to locate specific genes that lead to mood disorders. So far, they have focused on the X chromosome and chromosomes 11 and 6.

Since the first reports in 1969 that, in some families, fathers do not transmit mood disorders to their sons (87,117), many studies have described attempts to find a gene for mood disorders on the X chromosome (6,24,30,34,35,57,66-7 1). Although a few of the studies report significant evidence of linkage-a LOD score over 3—the results are not unanimous. Some provide only equivocal support for X linkage, and others, according to their LOD scores, completely rule out linkage to the X chromosome.

What explains these conflicting data? The use of a specific marker, the Xg blood group, accounts for some of the inconsistencies. Studies using the Xg blood group, which is located far from the other markers used to date, have never shown linkage. The remaining discrepancies may result from genetic heterogeneity: Genetic factors leading to mood disorders may vary among families.

The finding of X linkage in more than one study supports the hypothesis that a gene on that chromosome leads to mood disorders in some families. Nonetheless, doubts about the X linkage of mood disorders persist. The report of linkage to one marker, the F9 marker, does not easily square with positive findings for other, somewhat distant markers. Another study of 10 families without male-to-male transmission failed to map mood disorders to the X chromosome, despite the prediction that many such families would display this linkage (9,92). And while there has been disagreement about the pedigrees used in this study refuting X linkage (3,29,42,116), the results question how frequently a gene on the X chromosome accounts for inherited cases of mood disorders, even in families without father-to-son transmission.

The scientific and popular press heralded a report linking mood disorders to chromosome 11 among a group of Amish families in Pennsylvania (27). The Amish are an ideal population for studying the genetics of all kinds of disorders, especially mental disorders. They are the progeny of a small group of people who emigrated from Europe in the early 18th century (27). Since they seldom marry outside their own community, they have preserved a relatively homogeneous genetic heritage. Also, due to their religious convictions, they forswear the use of drugs and alcohol, abuse of which may confound the diagnosis of mood disorders.

The results of the Amish study conflicted with two reports on non-Amish families published about the same time (25,43). These studies ruled out linkage of mood disorders to chromosome 11 in nine families. Furthermore, results from a followup study of the same Amish families 2 years later disputed the original findings (48). The reanalysis, which included new family members and a change of diagnosis in two individuals due to the subsequent onset of mood disorders, also excluded the possibility that mood disorders are linked to a gene on chromosome 11.

Several studies have evaluated the possible linkage of mood disorders to the HLA system on chromosome 6(12,36,46,55 ,56,97-101,108,109,114, 115). Four produced evidence of linkage, with one reporting odds of approximately 10^8 to 1 (109). However, there are questions concerning the methods used in some of these studies. Gershon (33), for example, points out that the remaining studies produced no evidence of linkage. Therefore, no strong evidence fixes a gene for mood disorders on chromosome 6. Other studies, not described here, provide equivocal evidence, at best, for linkage of mood disorders to other chromosome markers (105).

GENETICS OF ANXIETY DISORDERS

Panic disorder and obsessive-compulsive disorder (OCD) appear to have a genetic component, although inheritance of these disorders has undergone less experimental scrutiny than that of schizophrenia and mood disorders. While several family studies have been conducted, only a few twin studies and no adoption studies have analyzed the inheritance of these anxiety disorders. Further studies are necessary to discern the role of genetics in these disorders.

Several family studies have found higher rates of panic disorder among frost-degree relatives of a person with panic disorder than among control populations (79,112). Also, there appears to be a greater frequency of agoraphobia—the fear of being in public places—with panic disorder among family members (21). These family studies have also distinguished between panic disorder and other disorders. For example, data indicate that panic disorder is distinct from generalized anxiety disorder (112) but that families of individuals with both panic disorder and depression are at increased risk of depression, panic disorder, and other conditions (20). Thus, the data indicate that panic disorder does run in families. Information from the few twin studies performed to date suggests that panic attacks, if not panic disorders, have a heritable component (21,104). No adoption studies of panic disorder have been conducted (104).

Based on the observed pattern of panic disorder in families, researchers have begun the search for genetic linkage. A recent linkage study provides preliminary evidence that a gene found on chromosome 16 might influence panic disorder (20-22); other linkage studies are underway (111).

Investigators of the genetics of OCD have used both family and twin studies; there are no adoptive studies (107). Data from family studies suggest that OCD has a genetic component (13,81,86,107), as do data from twin studies (13,81). They also suggest a link between OCD and Tourette's syndrome (80,82). No data from linkage studies of OCD have been reported to date.

THE CHALLENGE OF MAPPING GENES FOR MENTAL DISORDERS

Although evidence from multiples sources indicates that schizophrenia, bipolar disorder, and major depression, as well as panic disorder and OCD, have a genetic component, linkage studies have not succeeded in locating specific genes for these disorders. Attempts to pin mental disorders to specific chromosomes have produced acclaimed reports of linkage and subsequent contradiction of findings (89). These conflicting results have been analyzed in a series of papers (5,33,59,72,89,91). Two basic, unanswered questions confound linkage analysis of mental disorders: What accounts for the complex genetics of mental disorders? And what is inherited?

What Accounts for Complex Genetics?

Linkage analysis has achieved spectacular success in mapping diseases with a simple genetic basis, such as Huntington's disease and cystic fibrosis. Such diseases are rare in the general population, and a single gene can easily account for their occurrence. Mental disorders, like many cancers, Alzheimer's disease, and diabetes mellitus, present a much more complicated picture of inheritance. Although they also tend to run in families, they are common in the general population and no single gene can account for all cases.

Several factors may contribute to the complex pattern of inheritance of mental disorders, thus confounding linkage analysis:

- Distinct factors, genetic or nongenetic, may lead independently to a disorder.
- A gene that sometimes produces a particular disorder may not always do so.
- Several genes acting in concert may be necessary to produce a disorder.
- Nongenetic factors contribute to the development of a disorder.

The most optimistic explanation for inconsistent linkage results is genetic heterogeneity-that is, one gene leads to a disorder in some families, while a different gene operates in others. With this explanation, reports mapping a mental disorder to a specific chromosome in some families but refuting linkage in others can both be correct.

Several types of evidence may implicate genetic heterogeneity. Reports of linkage to different chromosomes may support this hypothesis. Distinct clinical profiles, symptoms, patterns of inheritance, and other biological measures among families may also indicate the action of separate genes (89). Given the complex characteristics of schizophrenia and mood disorders, it would be surprising if they did not have a heterogeneous basis. Some data suggest subtypes of these disorders; e.g., major depression seems to be more concentrated in families when it has an early age of onset (113). In general, however, clinical subsets of these disorders are not firmly established, and linkage studies (as well as diagnostic classification systems) have not incorporated them. On the contrary, many linkage studies have included a wide spectrum of mental disorders.

Experts caution against interpreting conflicting linkage results alone as proof of genetic heterogeneity. Only replication of a finding of linkage provides strong evidence that a nearby gene leads to the disorder (5,32,89). Furthermore, evidence of linkage to more than one gene is required to prove that a disorder is genetically heterogeneous.

Separate genes operating among and even within families make the search for linkage more difficult. One strategy is to study large families with many members who are afflicted with mental disorders (5). A single, large family, especially one that is relatively isolated, is more likely to be genetically homogeneous. The presence of a disorder in many family members also predicts, but does not prove, that a single gene is the culprit.

This approach has some disadvantages. Large families with many members showing a mental disorder are relatively rare. Also, a single gene that produces schizophrenia or mood disorders in certain families may only rarely do so in the general population. In this event, the finding of linkage will not lead to a genetic test that is generally useful. Of course, mapping a mental disorder to a specific gene, even in a few families, may lead to improved understanding of the disorder.

So far, this discussion has focused on the possible genetic heterogeneity of mental disorders. Various nongenetic factors may also be responsible. That is, a disorder maybe produced by genetic or nongenetic factors. In fact, nongenetic factors can produce a phenocopy of a disorder—that is, symptoms that mirror the genetically derived disorder. For example, depression produced by genetic factors may be symptomatically indistinguishable from depression provoked by external factors. While diagnostic criteria ferret out conditions obviously caused by a known and distinct factor, such as chemically induced symptoms, it is currently impossible to identify some phenocopies.

Sometimes a trait is not expressed even though the gene coding for it is present. In other words, only a fraction of persons carrying a particular gene actually display the trait. This is called incomplete penetrance. The causes of incomplete penetrance are unknown, although it is believed that modifying genes or other factors may thwart gene expression. Akin to incomplete penetrance is variable expressivity, where expression of a disorder varies in individuals with the gene from very severe symptoms to nearly none at all. The complex pattern of inheritance of mental disorders is commonly attributed, at least in part, to this phenomenon.

There are other unexplained aspects of the genetics of mental disorders. For example, if a single gene causes a disorder, is it dominant or recessive? How many alleles are there? While incomplete penetrance and these other unknown factors complicate linkage analysis, they need not preclude it (16,19,37). Linkage studies commonly consider a range of estimates for these variables and factor in such considerations as age of onset, cohort effect, and nonrandom mating, which often occurs in mental disorders (see ch. 3) (5). Accounting for all of these variables and unknowns does, however, require statistical adjustments, since they violate the assumptions of LOD score analysis (15,90).

Given the unknown parameters of inheritance, the sib-pair method of analysis offers some advantages in the search for genes linked to mental disorders (89). This method is based on the fact that, if a marker and a trait are linked, pairs of siblings who share a trait will be more likely to have the same genetic marker than could be expected by chance. The sib-pair method does not require prior knowledge of the mode of inheritance, as does the LOD score method. Furthermore, this approach does not require extended pedigrees, which may be difficult to find.

Although the problems discussed thus far complicate linkage analysis, they do not rule it out as a reasonable research approach. However, successful linkage analysis relies on a single gene making a major contribution to a disorder. While research has not resolved the number of genes involved in producing mood disorders or schizophrenia, data do suggest that a single gene is unlikely to make a major contribution inmost cases of schizophrenia or mood disorders (89,105).

Why, then, does linkage analysis remain a serious research endeavor? First, a major-gene effect, at least in some families, has not been ruled out in major mood disorders and schizophrenia. A large, systematic linkage study, though expensive, is the only available method likely to answer the question, Is a single gene linked to these mental disorders? Such an approach could then locate a major gene if it exists in the families studied or rule out the presence of such a gene. Also, new techniques and methods of analysis are being advanced all the time,

possibly resulting in new ways of searching for genes. Another rationale for continued linkage analysis is that a gene may contribute in a large way to these mental disorders in a few families. Single genes have been linked to a fraction of cases of other complex disorders, such as Alzheimer's disease (94). Unfortunately, studies have not identified families where prior evidence suggests that a single gene produces a mental disorder (89).

What if, as suspected by some observers, many genes, each with a very small effect, underlie these disorders? There is little likelihood that linkage analysis could locate one of many minor genes. Other techniques would be required (e.g., see 58).

The absence of 100 percent concordance for schizophrenia and mood disorders between identical twins implicates the importance of nongenetic factors in the genesis of these disorders (4). Other types of studies also point out that genetic factors and the environment, nature *and* nurture so to speak, produce mental disorders (95). Nongenetic factors may range from exposure to a chemical or virus to social interactions. Research has not identified these factors precisely (58,88); however, mapping a major gene that leads to increased susceptibility to a mental disorder may facilitate research into nongenetic factors (4,28,78,95).

What Is Inherited?

In order to map a gene, it is crucial to identify correctly the inherited trait, or phenotype. While the problems mentioned above are common to all complex disorders, uncertainty about what is inherited plagues mental disorders especially.

How well does the current classification of mental disorders define the inherited phenotype? Researchers disagree. Some are confident that rigorous use of the available diagnostic classifications will serve genetic research well. Others are uncomfortable that these diagnostic classes have not been validated and have no biological marker. It is perhaps ironic that while psychiatry looks hopefully to genetic research for help in refining systems of disorder classification (95), questions in the current classification system may impede genetic research.

When performing a linkage study, this question emerges: Are some disorders genetically related? For example, should a study attempting to map the gene for schizophrenia include only individuals with schizophrenia? Or should it include individuals with other forms of psychosis too? Individuals with any mental disorder?

Family studies provide some clues about the genetic relationship among disorders. For example, data suggest that bipolar disorder is genetically related to depression (32). Schizophrenia appears to run in families with schizotypal personality disorder and possibly other types of psychotic disorders (17,49). Agoraphobia and panic disorder appear to be genetically related (76), as do OCD and Tourette's syndrome (80,82). Further studies are needed to establish which disorders appear together in families and thus may be genetically related.

In practice, linkage studies have generally taken the approach of doing multiple analyses of different sets of mental disorders, ranging from core diagnoses to a broad spectrum of disorders. Two points warrant consideration. First, statistical accommodation is necessary for multiple analyses. Second, decisions concerning which diagnoses to include in each analysis must precede the study.

Instead of using an entire diagnostic class for linkage analysis, such as depression, some subset of the class may more accurately reflect the inherited trait, for example, recurrent bouts of depression or depression with an early age of onset. Although the identification of such ''phenotype markers' is in its infancy, there are several potentially useful biological and psychological markers for specific subsets of disorders. Response to drug treatment is one such possibility, and it forms the basis of pharmacogenetics (64). Similar responsiveness to the same drugs may identify individuals with genetically related disorders. Tsuang and Faraone (105) review data supporting the conclusion that individuals who respond well to certain antidepressant agents tend to have relatives who respond well to these agents. In general, linkage analysis has not yet incorporated such markers.

Another possible answer to the question, What is inherited? is illustrated by research into abnormal eye movements and schizophrenia (44,45). Individuals with schizophrenia sometimes have a problem with smooth-pursuit eye movements (SPEM); that is, they may have difficulty maintaining a focus on moving objects. Approximately 65 percent of individuals with schizophrenia, versus 8 percent of the general population, have problems with SPEM. Furthermore, data suggest a genetic link between

schizophrenia and these eye-movement abnormalities. Forty-five percent of the parents and siblings of individuals with schizophrenia exhibit SPEM abnormalities. Both identical twins exhibit schizophrenia or problems with SPEM, or both, 80 percent of the time. On this basis, researchers are looking for a gene that accounts for either schizophrenia or abnormal eye movement (51,65).

Ultimately, clues about what is inherited may suggest specific genes that underlie mental disorders. Identifying such candidate genes will enable researchers to target their search for linkage. One candidate gene was the gene that codes for the D_2 receptor. This receptor binds the brain chemical dopamine. Antipsychotic agents, which are used to treat schizophrenia, also bind to the D_2 receptor (see ch. 4). However, studies aimed at mapping schizophrenia to the gene for the D_2 receptor failed to establish linkage (51,73). One of several other candidate gene approaches sought to link bipolar disorder to a receptor for another brain chemical, serotonin (41); it also failed to establish linkage. The absence of a known etiology for mental disorders has thwarted the candidate gene approach to linkage analysis so far. However, continued advances in molecular biology and neuroscience will undoubtedly provide information on new possible targets for candidate gene searches.

IMPACT OF GENETIC RESEARCH

optimism generally surrounds today's genetic research into mental disorders. The modern-day sleuth-the molecular genetics researcher-is on the trail of perhaps the most enigmatic of all human afflictions. High hopes for an improved understanding of mental disorders and better, more rational treatments are pinned to this research.

This typically American enthusiasm for scientific progress may benefit from some temperance. Undoubtedly, genetic research will advance our understanding of at least some mental disorders, but rapid achievement of this goal is not likely. Researchers caution that identifying the location of relevant genes may require several years. And mapping a gene is only the first step in understanding the etiology of a mental disorder. The next step involves identifying the specific gene, which can take years. For example, the location of the gene for Huntington's disease was found in 1983 (40), but the gene has yet to be identified. Understanding how a gene's action is translated into something as complex as a mental disorder will probably demand a great deal of further research.

But genetic research has already had some important effects. One has been on the general perception of mental disorders (see ch. 7). Our overwhelming acceptance of the hereditary basis for mental disorders is astonishing. Only two decades ago, the idea that psychosocial factors produced schizophrenia dominated scientific thought, leading, for example, to the pervasive and brutally stigmatizing stereotype of the ''schizophrenogenic' mother (see ch. 7).

Family, adoption, and twin studies in the 1960s and 1970s established a solid theoretical basis for the role of genetics in mental disorders. These data, coupled with the revolution in genetics, fueled the emphasis on genetic research and focused the public spotlight on it. The frequent newspaper headlines and increasing number of books for the layperson evidence the spreading perception that mental disorders are inherited.

What is the impact of this perception that mental disorders are inherited? Perhaps more than any other type of research, genetics identifies mental disorders as biological. Thus, proponents of the biological-medical model of mental disorders generally support and commend this research. In a review article on genetics and mental disorders, leaders in the psychiatric community state that "wider recognition of the biological basis for mental illnesses (derived from genetic research) may allow these illnesses, finally, to be seen as similar to other medical problems" (78).

Spurious interpretation of the fact that genetic factors contribute to mental disorders can result in the belief that genes are destiny. This interpretation is founded on the false assumptions that human behavior is simply programmed by genes and that no useful intervention-barring a eugenic approach—can be developed. In fact, an environmental intervention can be successful in treating a genetic condition, as exemplified by phenylketonuria, or PKU. PKU is a single-gene defect that, if untreated, leads to mental retardation. This result can be prevented if a diet low in a particular amino acid (phenylalanine) is provided during the early years of life.

A few voices caution against the overemphasis on genetic factors in mental disorders, noting that

genetics does not completely account for these disorders and that a single-gene cause is unlikely to be found (58,83). What danger is there in overemphasizing the role of genetics? Although considered unlikely today, past enthusiasm for genetics led to atrocious abuses, such as the sterilization of individuals with mental disorders (see box 5-A). In this era of tight competition for research support, funding for genetic research may supplant support for other types of research. Some fear that unfulfilled expectations of quickly finding a particular gene or a new treatment may lead to impatience, disappointment, perhaps even a backlash against genetic research.

Since there is an increasing appreciation of the genetic component of mental disorders, it is not surprising that patients and family members would seek advice on the inheritance of these disorders. What information can genetic counseling provide on mental disorders (box 5-B)? At this point, one cannot unequivocally predict whether an individual will or will not develop a disorder (table 5-3). Genetic counseling can only provide a general estimate of risk for a disorder. While relatives are at increased risk of a mental disorder, estimates of risk are not easily adapted to individuals. They vary among studies (105) and are not specific-an individual's risk may exceed or fall short of average estimates. One important message of genetic counseling is that family members do not usually face a large threat of developing a disorder. For example, on average only 10 to 15 percent of individuals with schizophrenia or mood disorders, on average, will have a child with the disorder. Given that family members face a relatively low risk of developing a mental disorder, genetic counseling is often in the position of putting patients and family members—who may have overestimated their risk of a severe disorder-at ease (95).

Individuals could receive much more specific information during genetic counseling once genetic tests for mental disorders have been developed. Genetic tests are typically the frost spin-off from the successful mapping of a gene for a disorder, preceding treatment advances by many years. While no such tests are available now, and it may be somewhat premature to raise concerns about genetic testing for mental disorders, data point to the importance of genetic factors. Therefore, tests for a genetic predisposition to some mental disorders may be technically feasible in the future. Our current understanding of the genetics of mental disorders makes a single, highly predictive genetic test that is useful across the general population unlikely. Data from genetic studies predict that such genetic tests could possibly take the following forms:

- A major gene found in a subset of families with a disorder could lead to the development of a genetic test. It would be highly predictive of mental disorders within a few families but not useful in other families.
- Discovery of a gene that contributes to the development of a disorder, but alone cannot produce the disorder, may lead to a genetic test for increased susceptibility. This scenario is commonly envisioned for many disorders that are produced by genetic and nongenetic factors, such as diabetes, some cancers, coronary heart disease, and hypertension. Not everyone testing positive for the gene will develop the disorder. On a far more positive note, such individuals may be able to control their destiny by avoiding known risk factors.

SUMMARY AND CONCLUSIONS

Advances in genetics have bequeathed an increasing understanding of how simple traits are inherited, what the cellular and molecular substrates of inheritance are, and, more recently, the identity of genes in human disease. Interest in probing the inheritance of human behavior has paralleled our increasing knowledge of genetics. However, the study of human

Table 5-3—Risk of Mental Disorders (In percent)

	Schizophrenia	Bipolar disorder	Major depression	Obsessive-compulsive disorder	Panic disorder
To general population	1.0	0.8	4.9	2.6	1.6
To first-degree relative (parent, child, or sibling)	9.0-13.0[a]	4.0-9.0	5.9-18.4	25.0	15.0-24.7

[a]46 percent when both parents affected.

SOURCE: K. Berg and D.G.Kirch, National Institute of Mental Health, 1992.

Box 5-B-Genetic Counseling for Mental Disorders

According to researchers and other experts, individuals with mental disorders and their families have become increasingly interested in knowing the risk of inheriting these conditions. Such information is relayed in the context of genetic counseling, a clinical service that provides an individual and sometimes his or her family with information about heritable conditions. Unfortunately, empirical data on mental disorders and genetic counseling are sorely lacking.

Genetic counseling for mental disorders apparently occurs quite rarely. Who does seek it? Some individuals in the early stages of their disorder seek genetic counseling on the impact the disorder is likely to have on a potential spouse or children. The majority of genetic counseling requests come from relatives of affected individuals concerned about incipient or potential mental disorders in another family member or reproductive issues. Prospective spouses may also request information regarding both their partner and their potential offspring.

The accepted aim of genetic counseling is to provide information. It is generally held that genetic counseling should be nondirective and show the highest respect for the requester's autonomy. While it is no simple task to relay complicated concepts of risk it is perhaps even more difficult to do so in a nondirective manner. Furthermore, individuals request genetic information for a reason: to make reproductive decisions, to seek comfort or assuage fears. Genetic counseling in general is concerned with the psychological effects of receiving frightening information; given the psychopathology in mental disorders, this concern will most likely be amplified. For this reason, some people believe that psychiatrists should provide genetic counseling. However, many physicians have less-than-adequate knowledge of genetics. And no professional organization (e.g., American Psychiatric Association) or government institution (e.g., the National Institute of Mental Health) has put forth guidelines on the practice of genetic counseling for mental disorders.

A common concern of individuals seeking genetic counseling for mental disorders is reproductive decisions: Should we have children? Various factors may come to bear on such a decision, including the perceived risks and burdens of a mental disorder among offspring. Current risk estimates are not specific and generally are not very high. Thus, as stated by one genetic researcher, "Avoiding childbearing is not necessary, even from the most hardheaded primary prevention viewpoint."

One measure of the burden of a disorder arises from its clinical profile: age of onset, associated morbidity, available treatment, and cost of treatment. From this standpoint, mental disorders pose a considerable burden. They usually emerge in early adulthood and are often chronic. Although there is no cure, treatments that control the symptoms of mental disorders are available. Genetic counseling should deliver information regarding possible treatment, course, and community resources. This becomes crucial for the decisionmaking process insofar as awareness, early diagnosis, and provision of the correct treatment can limit the burden of the disorder,

There is also a subjective component to estimating the burden of a disorder in offspring. First, the desire for children can be strong. Furthermore, patients and their families assess the burden quite differently. In one study of schizophrenia, 92 percent of well family members versus 25 percent of affected individuals viewed schizophrenia

behavior and mental disorders has always proved difficult.

Methods traditionally used to examine the genetics of mental disorders include adoption, twin, and family studies. Data from these approaches indicate that mental disorders are at least in part inherited. Adoption, twin, and family studies reveal that schizophrenia has a genetic component. Twin and family studies, in particular, point to the importance of genetic factors in bipolar disorder and major depression. The heritability of these mood disorders seems to correlate with severity; bipolar disorder appears to have the clearest genetic component, followed by recurring bouts of major depression. The inheritance of panic disorder and of OCD has undergone less scrutiny; however, based on data largely from family studies, it appears that genetic factors are involved. Data also indicate that nongenetic factors play a role in all of the mental disorders examined in this report. Questions concerning the inheritance of these disorders remain: specifically, the precise definition of what is inherited and the number of genes involved.

Spectacular advances in molecular genetics have enabled researchers to locate specific genes for diseases caused by a major gene. However, despite early claims of success and evidence from multiple sources that schizophrenia, bipolar disorder, and

as a severe, debilitating disorder entailing extreme burden. With regard to childbearing decisions, 29 percent of parents versus 66 percent of affected individuals reported that they would have children (either in hindsight or in the future), given their present understanding of schizophrenia,

Another concern sometimes voiced when considering the burden of a mental disorder, especially bipolar disorder, relates to its possible link with creativity. Historical analysis and some systematic studies increasingly support this link. The concern is whether the creative output balances the burden of a severe mental disorder. The link between mental disorders and creativity raises the question, What is the value of a human being with a mental disorder? Does it lie in his or her creative output or contribution to society? Or does it emerge from the simple fact that he or she is a human being? While the creative output of individuals with mental disorders can be a source of pride, this consideration may pit the interests of society against those of the individual.

Prominent psychiatric geneticists generally reject directive counseling on reproductive decisions, emphasizing the benefit of genetic information for the individual, the rather low risk of inheriting these disorders, and their treatability. Exceptions to the prohibition against directive counseling are generally supported when severely affected individuals are involved or both spouses are afflicted. Risk to offspring greatly increases when both parents are affected. Also, pregnancy may severely exacerbate the symptoms of a mental disorder. Research concerning pregnancy, childbirth, and childrearing in persons with mental disorders, while limited reveals possible complicating factors for both mother and offspring, including birth complications, potential teratogenic and other negative effects of psychotropic drugs on offspring, and the effect of pregnancy and the postpartum period on the mother's mental disorder, such as increased symptoms or heightened severity of symptoms.

Given the reluctance to counsel against childbearing, the question arises, How is information about the genetics of mental disorders useful to affected individuals and their families? As previously mentioned, it may relieve excessive fears of passing on the disorder to offspring. It also enhances the likelihood of early intervention. Being alert to early symptoms of a disorder will permit early treatment, perhaps forestalling the most debilitating symptoms, Unfortunately, knowledge about genetic risk does not open the door to prevention. No known interventions can prevent the development of severe mood disorders or schizophrenia. This potential scenario underscores the need for research into the prevention of mental disorders.

SOURCES: E.S. Gershon, "Genetics," ***Manic-Depressive Illness***, F.K. Goodwin and K.R. Jamison (eds.) (New York, NY: Oxford University Press, 1990); E.S. Gershon, National Institute of Mental Health, personal communication, 1991; I.I. Gottesman, ***Schizophrenia Genesis: The Origins of Madness*** (New York, NY: W.H. Freeman, 1991); K.K. Kidd, Yale University, personal communication, 1991; M. Lappe and J.A. Brody, "Genetic Counseling: A Psychotherapeutic Approach to Autonomy in Decision Making," M.A. Sperber and L.F. Jarvik (eds.), ***Psychiatry and Genetics: Psychological, Ethical, and Legal Considerations (New*** York, NY: Basic Books, 1976); J. Marks, Sarah Lawrence College personal communication, 1991; P.M. Schulz, "Patient and Family Attitudes About Schizophrenia: Implications for Genetic Counseling," ***Schizophrenia Bulletin*** 8:504-513, *1982;* S.D. Targum and E.S. Gershon, "pregnancy, Genetic Counseling, and the Major Psychiatric Disorders," ***Genetic Diseases in Psychiatry, Maternal Effects and Fetal Outcome*** J.D. Schuluan and J.L. Simpson (eds.) (New York, NY: Academic Press, 1981); M.T. Tsuang, "Genetic Counseling for Psychiatric Patients and Their Families," ***American Journal of Psychiatry*** 135:1465-1475, 1978; U.S. Congress, Office of Technology Assessment, ***Genetic Monitoring and Screening in the Workplace***, OTA-BA-455 (Washington DC: U.S. Government Printing Office, 1990).

major depression have a genetic component, linkage studies have failed so far to find specific genes for these disorders. Gene searches are difficult because these mental disorders probably are caused by more than one gene, both genetic and nongenetic factors contribute to them in an unknown way, and identification of the phenotype is difficult.

The complexity of the genetics of mental disorders and past failures to locate specific genes should not promote a pessimistic view of this research. Rather, our knowledge to date points out the need for various types of studies and can serve as a guide for future research endeavors. Furthermore, we can look to continued advances in molecular genetics and analytical techniques to help discern the specifics about the genetics of mental disorders. A wise investment of research dollars would support a broad effort, including continued family, twin, and adoption studies, the development of analytical methods for complex genetics, the search for major and minor genes using various approaches, and the investigation of nongenetic factors.

What is the impact of all this excitement in the field of genetics? Commentators have noted that the public increasingly views mental disorders as inherited, in sharp contrast to only a couple of decades

ago. There is also an air of expectation that genetics will improve our understanding and treatment of these disorders. It is important that such hopes be tempered with realism. A long-term investment in this research is necessary, given the complexity of these disorders. At this point, the clinical implications of these data are limited; therefore, only limited information about the risk of inheritance can be provided to persons with mental disorders and their families. Finally, past abuses of genetic knowledge and the potential for a genetic test for mental disorders remind us of the necessity for great care in the use of genetic information and underscore the need to consider the social, ethical, and legal implications of this research.

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