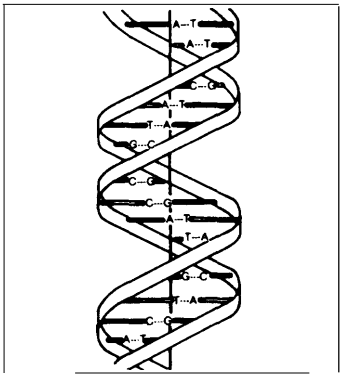
Research Results 2

Discovery of the chromosome location of the Huntington's disease gene more than 10 years ago marked a turning point in genetic research (25). Advances in molecular genetics permitted the extensive search of human chromosomes for specific disease genes. This approach has since dominated the study of genetic diseases, with some stunning results. Locating more than one human gene each day, in the past year alone, researchers have zeroed in on genes linked to Lou Gehrig's disease (amyotrophic lateral sclerosis or ALS), a common form of colon cancer, and others. Upon learning the genetic address of disease genes, not only have diagnostic tests been developed for several conditions (e.g., cystic fibrosis and Huntington's disease), but the very nature of some of the gene defects has been exposed and medical treatment based on gene replacement is under intensive investigation.

Without a doubt, molecular genetics is transforming medicine. The revolution in genetics also has influenced mental disorders research. The search for genes linked to schizophrenia, bipolar disorder (manic-depression), and other mental disorders seemingly found early success, the results of which were highly publicized. But with the exception of Alzheimer's disease, the location of a mental disorder gene has yet to be confirmed.



How should we interpret the current status of mental disorders genetics? Do mental disorders have a genetic component? If so, how big a role do genes play in these conditions and how are they transmitted? Any discussion of the clinical and social implications of mental disorders genetics necessarily begins with an accurate understanding of the scientific data. Discussion at the first day of the workshop sponsored by the Office of Technology Assessment (OTA) and the National Institute of Mental Health

(NIMH) focused on data characterizing the inheritance of Alzheimer's disease, schizophrenia, major mood disorders, panic disorder, and obsessive-compulsive disorder. Following an overview of some basic genetic concepts and research techniques, this chapter summarizes what we know about the inheritance of these mental disorders.[1]

GENETIC RESEARCH PRIMER

Although molecular genetics and the search for specific genes have upstaged other approaches, classical research methods—family studies, twin studies, and adoption studies—are the mainstay of mental disorders genetics (table 2-1) (box 2-l). Characterization of the prevalence and pattern of traits among related individuals helps illuminate their genetic basis, addressing the following questions: Are these traits inherited? What is the relative contribution of genetic versus nongenetic factors? What is the pattern of inheritance? The genetic bottom line—the relative influence of inherited factors-merge from these classical studies.

Classical genetic studies are critical for understanding the inheritance of a trait or disorder; they cannot locate or characterize specific genes. For this reason, as well as technological advances, linkage analysis has become the lodestar of mental disorders genetics. By investigating the distribution of DNA markers and disorders among family members, linkage analysis provides a method for identifying the location of disease genes. Linkage analysis can determine whether a single gene makes a major contribution to a trait and where that gene is located. Based on knowledge of the chromosome location, researchers can narrow in on a gene in a process known as *positional cloning.* Where little knowledge of the underlying cause or molecular mechanism of action in a disorder exists—as is the case in most mental disorders—linkage analysis is especially appealing. However, a variety of factors complicate linkage analysis of many mental disorders, including the likely involvement of multiple causes, their complex patterns of inheritance, and uncertainty as to what is inherited and how (see references 54,64 for detailed discussion). Thus, alternative methods for finding genes associated with mental disorder are of interest.

The sib pair method can be used in the search for genes linked to mental disorders. This approach is based on the premise that if a genetic marker and a trait (a disease or biological marker, for instance) are linked, pairs of siblings (or other affected relative pairs) who share a trait will be more likely to have the same genetic marker than would be expected by chance. The sib pair method offers some significant advantages in mental disorders research: it does not require prior knowledge of how a trait is inherited—which is generally lacking in mental disorders—and it does not require large, multigenerational families with many afflicted members-which are relatively difficult to locate in mental disorders (40,54). The robustness in detecting linkage in the face of ignorance of the genetic mode of transmission comes with a price, however: less sensitivity. That is, it may fail to detect a linked gene. Furthermore, the sib pair method still requires a gene that has a large effect on a condition.

Association studies offer another approach to identifying genes that influence mental disorders. This method examines gene variation and disease in patient samples and controls. Important for behavioral traits in general and perhaps mental disorders specifically, association studies can detect genes playing a minor role in a disorder. Association studies are most useful when candidate genes—genes suspected a priori of playing a role in a condition—are available; systematic search for association throughout the genome is not yet

[1] The chapter offers neither a detailed discussion of methodological issues nor an exhaustive listing of mental disorders linkage studies. The reader is referred to reference number 64 for such information.

TABLE 2-1: Classical Approaches to the Study of Mental Disorder Inheritance

Type of study	Definition	Information that may be derived	Limits of approach
Family studies	Consider whether a trait runs in a family.	Showing that a trait is more prevalent among relatives of an affected individual 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 is consistent with a genetic hypothesis. • The way in which a trait is distributed among family members may also elucidate the mode of inheritance.	• Showing the familial nature of a trait is necessary but not sufficient for proving it is inherited; such data do not conclusively demonstrate the genetic basis of a trait, since family members share not only genes but also their environment.
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 higher 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.	• Raise issues around 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.
Adoption studies	Focus on adopted individuals and their adoptive and biological families. In three commonly used research designs: • the adopted away offspring of affected parents are studied and compared with control adoptees of normal parents; or ▪ the index cases are adopted people who have developed a disorder of interest; the rates of illness are then compared in their biological and adoptive relatives; or ▪ least commonly, the rate of illness in adoptees who have affected biological parents but who were raised by unaffected adoptive parents, are compared with the rates of illness in the offspring of normal parents brought up by adoptive parents who themselves become affected.	• Attempt to disentangle the influence of genes from that of the environment. ▪ Can provide powerful evidence of a genetic effect.	• Generally, do not rule out the effect of nongenetic factors preceding adoption, such as possible prenatal influences.

SOURCES' P. McGuffin, M.J Owen, MC O'Donovan et al., *Seminars in* Psychiatric *Genetics* (London, England: Gaskell, 1994), US Congress, Office of Technology Assessment, The *Biology of Mental Disorders,* OTA-BA-538 (Washington, DC: US. Government Printing Off Ice, September 1992).

BOX 2-1: The Language of Genetics

Candidate gene. A gene whose involvement in a trait or disease is suspected before linkage analysis or other gene-searching techniques are applied.

Chromosome. As seen under a microscope, threadlike structures within the cell. Each chromosome consists of a of linear DNA (deoxyribonucleic acid) molecule.

Chromosome banding pattern. A pattern of alternating dark and light transverse regions (bands) formed on a chromosome by chemical treatment and staining. The different bands along a single chromosome are used to identify different regions of the chromosome.

DNA (deoxyribonucleic acid). A doubled stranded molecule consisting of four deoxyribonucleotide or, more simply, base pairs. Species-specific and individual-specific genetic information is encoded in the order of the base pairs along the chromosomal DNA molecule,

DNA markers. Variations in DNA sequences of known chromosomal location, including restriction-fragment-length polymorphisms (RFLPs) and microsatellite repeat markers. While a DNA marker may not be part of a gene causing a particular disorder, it can be useful in determining a disease gene's location, DNA markers also can be used for genetic testing.

Gene. A length of DNA that specifies the structure of a particular protein product. Genes are arranged along the chromosomes in a linear order, with each having a precise position or /ecus. Alternative forms of a gene that can occupy the same locus are termed *a//e/es.* Each chromosome bears only a single allele at a given locus, though in the population as a whole there may be many alleles, any one of which can occupy that locus.

Genome. The totality of the DNA contained within the chromosome set of a species. The human genome, for example, consists of approximately 6 billion base pairs of DNA distributed among 46 chromosomes.

Molecular genetics. The study of the molecular details of the regulated flow of genetic information among DNA and proteins from generation to generation,

Mutation. Any alteration in the base sequence(s) of the constituent DNA molecule(s) of the genome of an organism.

Positional cloning. Describes a set of techniques by which disease genes are identified through their position in the genome rather than through their function. In its initial stages, this approach can rely upon a systematic search of the genome for linkage, This has been made possible by the availability of systematically constructed linkage maps of the human genome. These consist of DNA markers whose chromosomal positions have been mapped, which are polymorphic and which have been assembled so that they are approximately evenly spaced throughout the genome.

SOURCES P McGuffin, M J Owen, M C O'Donovan, et al , *Seminars Psychiatric Genetics* (London, England: Gaskell, 1994), U S Department of Energy, Los Alamos Science, The *Human Genome Project,* Number 20, 1992.

useful. Unfortunately, few candidate genes exist for mental disorders at the present time.

ALZHEIMER'S DISEASE

Loss of memory for recent events, seemingly benign forgetfulness, marks the beginning of the progressively deteriorating course of Alzheimer's disease (AD). In the six- to 20-year span of the disease, people suffer increasing memory loss, confusion, and disorientation, and may exhibit other symptoms—such as paranoia, irritability, **combativeness, restlessness, fearfulness, and**

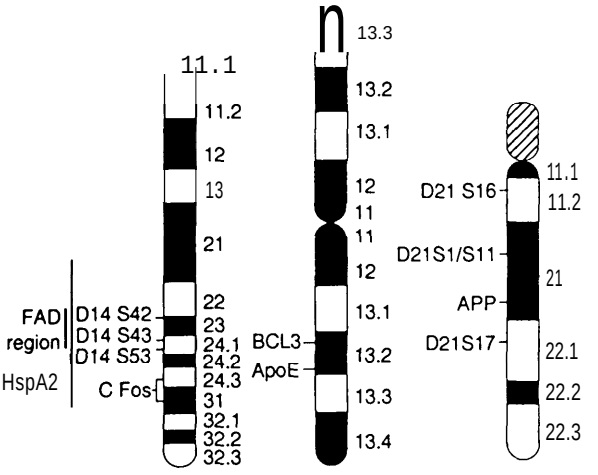
problems with language—until they are incontinent, bedridden, and unable to speak or eat. Usually a disease of elderly people, AD afflicts an estimated 5 percent of people over 65 and approximately 20 percent of those over the age of 80. Much less commonly, AD afflicts people who are younger, in their 40s and 50s.

There is no cure for AD or treatment useful for most patients. The pathology of AD is well characterized: extensive nerve cell loss in some regions of the brain, accumulations of twisted protein filaments inside nerve cells—neurofibrillary tangles—and abnormal clusters of degenerating nerve cell fibers, other brain cells, and a protein called B-amyloid—neuritic plaques. Despite significant research advances in the last 10 years, which increasingly reveal pieces of the etiologic puzzle, the triggers for this neurological catastrophe remain unknown.

Advances in molecular genetics offer important clues about the origins of AD (7,40,57). These advances have not come without difficulty, nor without surprise, as suggested by the genetic epidemiology of the disease. Family studies show a threefold increase of AD among first-degree relatives of afflicted individuals, especially those with an early onset of symptoms. Indeed, data indicate that a few rare forms of AD, mostly with early onset, are produced by a single gene. Of course, most cases of AD do not have an early onset, and the pattern of inheritance is less clear for the more common mid- and late-onset disorder. Part of the problem is determining the family distribution of such a late-onset disease; many family members may succumb to other causes before developing AD. Some hypothesize that what is inherited is not AD per se, but the timing of its onset. Also, both genes and nongenetic factors are thought to play a role.

Two research findings initially propelled molecular genetic research of Alzheimer's disease. First, the gene for a precursor to 13-amyloid, a protein concentrated in the brains of people with AD, was found; the gene mapped to a region of chromosome 21, which is associated with Down's syndrome (figure 2-1). Second, linkage analysis located a gene for AD in the same region. Indeed,

FIGURE 2-1: Location of Alzheimer's Disease Markers and Genes



Chromosomes 14, 19, *and 21 are depicted, with banding patterns identified on the right side of each chromosome. The locations of markers and genes that have been reported to be linked to AJzheimer's disease are on the left. FAD region indicates the region on chromosome* 14 *containing the AD locus.*

KEY: HspA2 = heat shock protein A2, Apo E = apolipoproteln E: APP = 13-amyloid precursor protein

SOURCE: R.F. Clark and A.M. Goate, "Molecular Genetics of Alzhelmer's Disease, " Archives of Neurology 501164-1172, 1993

researchers were long aware of the link between AD and Down's syndrome: all people with Down's syndrome ultimately show brain changes typical of AD.

The intensive investigation that ensued unfortunately turned out mostly negative or at least confusing data. A role for the 13-amyloid precursor protein gene in AD was supported by data from some linkage studies, and specific mutations in the gene have since been found. One study linked a mutation in this gene to an inherited form of cerebral hemorrhage. But many studies did not replicate the linkage between AD and the 13-amyloid precursor protein gene. Ultimately, researchers agreed that while the 13-amyloid precursor protein

gene is associated with AD, it accounts for only a very small proportion of the early-onset cases. Most AD is caused by something else. That should not diminish the importance of this result. This discovery has implications for our basic understanding of AD. First, the data from molecular genetics suggest that 13-amyloid protein may be more than just a correlated factor with AD; it may cause AD, a hypothesis under intensive investigation. Second, mutations to this gene lead to AD *and* recurrent stroke, evidence that these two clinical conditions are not distinct, but rather different results of the same gene defect.

Nonetheless, the vast majority of AD cases are not explained by mutation of the 13-amyloid protein precursor gene located on chromosome 21. A genomewide search thus ensued for other genes linked to early-onset AD. Evidence for such a gene on chromosome 14 soon emerged. With quick replication, even among some families where the chromosome 21 site had been implicated previously, it became clear that a gene on chromosome 14 is responsible for a majority of (but not all) early-onset AD cases. Currently, researchers worldwide are pursuing intensively the chromosome 14 AD gene.

As noted, evidence points to etiologic heterogeneity—the involvement of more than one gene as well as nongenetic factors—in late-onset AD. But recent and surprising discoveries point to the important action of a gene on chromosome 19 in late-onset AD. Replicated data link a particular version of a chromosome 19 gene coding for apolipoprotein E—the e4 allele—to AD. How this protein may lead to AD is not known: studies show that apolipoprotein E plays a role in fat metabolism, cell injury repair, and cell growth, and is a constituent of amyloid plaques and neurofibrillary tangles in AD. Nor does apolipoprotein E appear to play a role in all late-onset AD; by current estimates, approximately 50 percent of all cases do not possess the e4 allele.

Despite the obstacles-difficulties in performing family studies among an elderly population and the likely interplay of a variety of causative and modulating factors—researchers have learned a great deal about the molecular genetics of AD. The discovery of some of the genes that may be involved in AD suggests brain mechanisms that underlie this disease. These findings also offer clues about how AD relates to other illnesses. These data offer considerable promise that we will understand the cause of AD, will be better able to diagnosis it, and perhaps can develop treatments for and ultimately preventive interventions against its devastating effects.

SCHIZOPHRENIA

For many, the term *schizophrenia* is synonymous with severe mental illness. It assails an individual thought processes, perceptions, emotions, and behavior. Thought and perceptual disturbances are the hallmark of schizophrenia. Components of thought may become dissociated or fragmented and the flow of thought interrupted. The ability to concentrate and focus attention is impaired. Individuals with schizophrenia commonly experience delusions and hallucinations. Nearly one in every 100 American adults will develop schizophrenia during the course of his or her lifetime. The disease's symptoms typically emerge during the late teens and 20s, with the majority of individuals suffering an intermittent but lifelong course. Currently, there is no way to prevent or cure schizophrenia; although, medications are available that can control some symptoms for many patients.

For nearly a century, researchers have explored the role of genes in schizophrenia (reviewed in 20,21,30,40,64). Though questioned because of several methodological weaknesses (e.g., knowledge of the diagnostic status of family members could have made researchers less objective, diagnoses often were based on hospital records or third-party interview rather than direct observation, and the criteria for diagnosis were not clearly enumerated), early family studies demonstrated that schizophrenia runs in families, and twin studies support the role of genes. Using more stringent protocols and procedures, more recent family, twin, and adoption studies confirm these earlier results.

Undoubtedly, schizophrenia runs in families. Of the more than 40 systematic family and twin

TABLE 2-2: Schizophrenia Among Identical and Fraternal Twins[a]

Study	Identical twins		Fraternal twins	
	Number of pairs	Concordance rate (percent)	Pairs	Concordance rate (percent)
Finland 1963, 1971	17	35%	20	13%
Norway, 1967	55	45	90	15
Denmark, 1973	21	56	41	27
United Kingdom, 1968, 1987	22	58	33	15
Norway, 1991	31	48	28	4
United States, 1969, 1983	164	31	268	6
Pooled concordance				
Median	310	46	480	14
Weighted mean		39		10

[a]Data from newer twin studies, using probanwise concordance rates.

SOURCE. I I Gottesman, *Schizophrenia Genesis; The Origins Madness (New* York, NY: W H. Freeman, 1991), I I Gottesman, "Schizophreia,"*Seminars* in *Psychiatric Genetics,* P, McGuffin, M.J. Owen, M.C O'Donovan, et al. (eds.) (London, England Gaskell, 1994)

studies, all show increased rates of schizophrenia among family members versus rates in the general public. First-degree relatives of an individual with schizophrenia have approximately 10 times the general risk of developing the disorder.

Of course, just because a trait runs in families does not necessarily implicate genes as the cause. Data from twin and adoption studies, however, do strongly support a role for inherited factors in schizophrenia. Although estimates vary, depending on the statistical method used and the sample population, data consistently show that a person whose identical twin has schizophrenia is at higher risk for this condition than a person whose fraternal twin has the disorder (table 2-2). To be precise, six modem studies in the literature and a seventh ongoing in Nagasaki, Japan, show increased concordance among identical versus fraternal twins (22). Similarly, replicated data from adoption studies indicate that schizophrenia runs in biological but not adoptive families (58). Data recently reported from a nationwide study in Denmark expand on this observation: schizophrenia was found exclusively among biological relatives, with a ten times greater prevalence than in the biological relatives of controls (31,37).

The discussion thus far yields too simplistic a view of the genetics of schizophrenia. Even as data from nearly a century of research consistently point to genetic factors in schizophrenia, its complexity is also an undeviating observation. The very presentation of the disorder is complicated. Symptoms vary widely among individuals, combining in different ways, and changing over time. This variability has raised questions about how to conceptualize schizophrenia: Is it a single disorder? A group of disorders? A conglomerate of several disease processes? What is its relationship to other mental disorders?

The clinical presentation of schizophrenia has raised questions for geneticists. What in fact would a schizophrenia gene or genes result in? Hypotheses include: schizophrenia alone; schizophrenia and mood disorders; schizophrenia and any mental or substance abuse disorder; schizophrenia and some types of abnormal personality traits and disorders; psychosis; or other traits such as problems with eye movements. More work is

needed to definitively prove any of these hypotheses (62).

Not only is schizophrenia's relationship to other disorders and traits complex and somewhat obscure, but data concerning its inheritance are equally confounding. The way inherited factors may express themselves within families remains unknown. The distribution of schizophrenia within families is not consistent with any simple pattern of inheritance. Studies generally rule out the action of a single gene without determining whether a couple of genes, or many, are important in producing schizophrenia.

While classic genetic studies support a role for genes in schizophrenia, they also circumscribe how big a role inherited factors might play. Because an identical twin of someone with schizophrenia exhibits the disorder approximately 30 to 60 percent of the time, nongenetic factors must also be important (61). Such discordance among identical twins does not necessarily mean, however, that nongenetic factors are the cause of schizophrenia in the affected twin. The unaffected twin simply may not express the genetic factors that both twins have. Evidence for this interpretation emerges from a followup and expansion on a Danish twin study (23). The researchers found that the risk of schizophrenia to the children of unaffected twins equaled that of the affected twins' offspring.

Researchers recently applied the tools of molecular genetics and linkage analysis to probe the inheritance of schizophrenia. A report that an uncle and nephew with schizophrenia shared a chromosome defect—an extra copy of part of chromosome 5—prompted linkage analysis using markers on this chromosome (4). Support for such linkage soon emerged from a study of seven British and Icelandic families (56). However, a simultaneously reported study in a separate extended family in Sweden ruled out this linkage (36). Subsequent studies have since rejected a link between genes on chromosome 5 and schizophrenia (30, 64).

Crow and colleagues (12) have proposed that the pseudo-autosomal region of the X and Y chromosomes contains a schizophrenia gene. The pseudoautosomal region is a small portion of the X and Y chromosomes. When genes located in this region are inherited from the paternal side, affected offspring will be the same sex more often than expected by chance. Such a pattern of inheritance does occur in schizophrenia. Furthermore, data from a sib pair analysis offers support for this hypothesis (9), although other data are not consistent with linkage to this region of the X and Y chromosomes (3,47). More recent work suggests linkage to a gene on the X and Y chromosomes outside of the pseudoautosomal region (13,16).

Another series of recent linkage studies implicate a gene on chromosome 22. Pulver and colleagues (51) reported a potential linkage to this chromosome. The finding was not statistically significant but might have indicated a gene that accounted for only a small proportion of the cases of schizophrenia. Two other groups found evidence consistent with this finding (10,49). However, a second sample reported by Pulver and colleagues (50) excluded linkage to a site on chromosome 22.

Unlike AD, the complexities of diagnosis and family aggregation, as well as its relationship to other traits and disorders and the multiplicity of causative factors likely involved, have made schizophrenia elusive prey for the molecular geneticist. That schizophrenia runs in families and that genes play a role are strongly supported by many sources of data. The nature of the genetic contribution is far from clear. Furthermore, although some studies hint at "genetic" forms of schizophrenia, to date nothing sets apart a subgroup of schizophrenia as obviously produced by a single gene (15). Finally, although there have been occasional reports of linkage between schizophrenia and various chromosome markers—including protein-based markers such as blood proteins, DNA markers, and various candidate genes—researchers have yet to confirm the location or identity of a schizophrenia gene. A leading genetic researcher recently commented on these difficulties, contemplating the implications for future research (62):

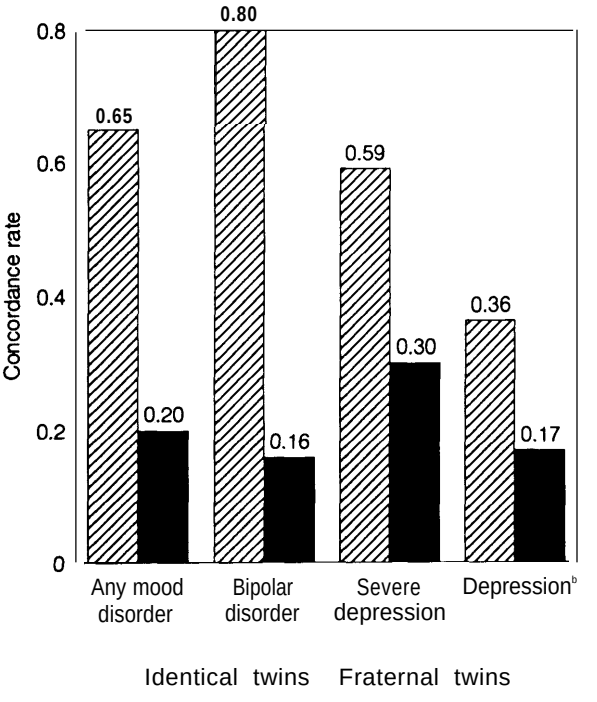
Why has the genetic epidemiologic trail for schizophrenia not led to a clear genetic mechanism? It may be that our initial expectations were too high. Unlike familial Alzheimer's disease, schizophrenia does not show a clear mechanism of transmission. Nor does it have an unambiguous pathophysiological signature. It is tempting to appeal to genetic heterogeneity, but heterogeneity has not stymied research in Alzheimer's disease. Unless schizophrenia is extremely heterogeneous, why is it so difficult to find schizophrenia genes? Some see a multifactorial explanation that posits the accumulation of many genetic and environmental risk factors as the cause of schizophrenia. This hypothesis has much merit but presages a long journey along the epidemiologic trail if "many" turns out to be a large number.

MAJOR MOOD DISORDERS

Data from a recent, large epidemiologic study show that in a given year nearly 5 percent of American adults—including twice as many women as men—will experience an episode of major depression (65). Interest or pleasure in activities will dissipate, sleep and appetite are affected, and sense of worth and the ability to concentrate typically decline. Suicide stands as a very real threat. Nearly 1 percent of the population will cycle between such bouts of depression and manic illness, with its extremely elevated mood and self-esteem, reduced need for sleep, abounding energy, racing thoughts, unrestrained activity and talk, and even psychosis. Although treatments effective for many people with major depression or manic-depressive illness (also called bipolar disorder) are available, **no cure exists.**

The concentration of mood disorders in families has long been recognized (19,35,40,41,63, 64,65). Data consistently show that the parents, siblings, and children of people with bipolar disorder or major depression are at a much greater risk than the general population. Twin studies corroborate this observation, pointing to a role for inherited factors. 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 (figure 2-2).

FIGURE 2-2: Mood Disorders Among Twins



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

a Three or more epsodes of depression

[b] Less than three episodes of depression

SOURCE: Adapted from A. Bertelsen, B Harvald, and M. Hauge, "A Danish TwinStudy of Manic-Depresswe Disorders, " *British Journal of Psychiatry* 130.330-351, 1977

Similar replicated results can be found in 11 independent twin studies of mood disorders (22).

Family and twin studies provide strong and consistent evidence that genes contribute to major mood disorders. But as is the case with AD and schizophrenia, details from the research tell a complicated story: concordance rates for bipolar disorder and major depression among twins vary considerably between studies reflecting among other things the use of different diagnostic categories and methods. Although data from adoption studies generally support a role for genetics, they are not completely consistent. Research focused on milder forms of depression, and not bipolar

disorder, provides even more ambiguous results concerning the role of inheritance. And studies of how major mood disorders are distributed within families do not divulge the kind of genetic mechanisms that may be involved (e.g., a single gene).

The relationship between bipolar disorder and the spectrum of depressive illnesses, as well as other disorders and personality traits, presents further uncertainty. Considerable evidence from studies evaluating family history, clinical symptoms and course, response to pharmacological treatment, and other factors distinguishes bipolar disorder from major depression. But the separation is not complete. Family and twin studies suggest at least a partial genetic connection between major depression and bipolar disorder. For example, identical twins who both have a mood disorder not infrequently have different forms. Similarly, first-degree relatives of a person with bipolar disorder are at greater risk of developing any mood disorder than the general population.

Questions about the nature of depression are even more difficult to answer. Is depression a single disorder or a class of disorders? How are less severe episodes of depression and other mental disorders related to major depression? Because depression varies considerably in its course, symptoms, severity, and association with other disorders, some believe that depressive disorders may differ in kind as well as degree-that depression is heterogeneous. However, other data from family histories and longitudinal studies provide evidence that depression may constitute a continuum from "the blues" to severe depression. The heritability of depression appears to be correlated with the severity of the condition. Recurring bouts of depression appear to be more heritable than a single episode. Also, major depression that has an earlier age of onset maybe more heritable. A variety of data point to a genetic relationship between depression and other conditions as well. Certainly there is high comorbidity between depression and substance abuse and anxiety disorders (2,32,33, 60,67,69). For example, a recent large study of twins found that various personality traits-emotional instability, vulnerability to stress, and anxiety-proneness-appear to be connected to depression, largely as the result of genetic factors according to the study's authors (33).

Many studies have attempted to locate specific genes that lead to mood disorders, with initial reports of positive findings on the X chromosome and chromosome 11 receiving the most publicity. More recently, data suggest that a gene on chromosome 18 is linked to susceptibility to mood disorders (5). However, none of these results, nor any other, have been consistently confirmed. As the first modem linkage study for a mental disorder receiving intense publicity but later being retracted, the search for a mood disorder gene on chromosome 11 bears retelling.

The scientific and popular press heralded a report linking mood disorders to chromosome 11 among a group of Amish families in Pennsylvania (18). 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. 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 (17,27). 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 two years later disputed the original findings (29). 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 gene on chromosome 11 as the cause of all cases of mood disorders in the Amish families.

How can we summarize the current status of research into the genetics of mood disorders? As with schizophrenia, data converge on the conclusion that genes play a role in mood disorders, especially bipolar disorder and more severe forms of depression. But the nature of this inheritance is

TABLE 2-3: Family Studies on Panic Disorder

Proband diagnosis	Lifetime prevalence rates of panic disorder in first-degree relatives (percent)	
	Panic disorder	Control
Direct interview studies		
Harris et al., 1983	20.5%	4.2%
Crowe et al., 1983	17,3	1.8
Noyes et al., 1986	14.9	3.5
Weissman et al., 1993	14.2	0.8
Mendlewicz et al., in press	13.2	0.9
Maier et al., 1993	7,7	1.5
Family history studies		
Moran and Andrews, 1985	12.5	
Hopper et al., 1987	11.6	

SOURCE: M M Weissman, "Family Genetic Studies of Panic Disorder," *Joumal of Psychiatric* Research, (Suppl.) 27:69-78, 1993.

obscured by sometimes diverse research results, an uncertain mode of transmission, and the high prevalence of depressive disorders. Furthermore, the application of molecular genetics to mood disorders has yet to yield a confined, positive result.

PANIC DISORDER

The hallmark symptom of panic disorder is a sudden, inexplicable attack of intense fear that is associated with powerful physical symptoms (44,64,68). In just a few minutes, an extreme sense of fear overtakes an individual, his or her heart begins racing, he or she starts to perspire—sometimes profusely—and he or she has trouble breathing. A single attack is shortlived, lasting about 10 minutes. These symptoms often leave a patient believing that he or she is suffering from a heart attack or is losing his or her mind. Some patients go to the emergency room in the belief that they are about to die from a heart attack. In fact, many individuals with panic disorder seek general medical professional care at an increased rate.

Panic attacks occur about two times a week, although the frequency varies considerably among individuals. One person's panic attacks may be rare, having little effect on his or her functioning, while another's panic attacks and accompanying anxiety may be so intense that he or she remains completely sequestered at home, a condition known as agoraphobia. Although not completely effective, treatment of panic disorder with medication or psychotherapy, or both, often appears helpful. Data show that approximately one to two persons in 100 will develop panic disorder during their lifetime, with women being twice as likely to develop it as men. Another 3.6 percent of the population suffer repeated panic attacks, without meeting the criteria for full-blown panic disorder.

A major shift in the categorization of panic disorder occurred in 1980. It was distinguished from general forms of anxiety (34,38,40,66,70). While research data generally support this distinction, it means that few studies preceding the reclassification address the inheritance of panic disorder specifically. At least eight family studies have been completed using the modern definition of panic disorder (table 2-3). Even these modem studies are not uniform in their methodology, diagnostic classification, or estimates. But all point to higher rates of panic disorder among first-degree rela-

tives of individuals with this condition when compared with the general population or control groups. Furthermore, data from one of the family studies (46) show a familial link between panic disorder and agoraphobia. Family studies subjected to statistical analyses have not demonstrated the way in which panic disorder might be inherited: a single gene with incomplete penetrance could explain the pattern of disorder seen in families, or several genes plus nongenetic factors may be at play. The family studies do suggest that more severe forms of the condition aggregate in families.

No adoption studies focus on panic disorder; however, data from three twin studies shed light on this condition. All of the twin studies point to a relatively modest role for genes in panic disorder. One small study found only a 31 percent concordance rate among the 13 pairs of identical twins and no concordance among the 16 pairs of fraternal twins examined, a rate lower than family studies predict (60). In 446 pairs of twins, concordance rates for panic disorder were not significantly different among identical and fraternal twins (l). A substantial increase in concordance rates among the identical twins emerged when all anxiety disorders were included in the estimate, leading the authors to hypothesize that genes relate to a general risk of anxiety. Another large twin study found only a modest increase in panic disorder among identical versus fraternal twins (34). The study's authors concluded, in concert with data from the other twin and family studies, that genes appear to play a smaller role in less severe cases.

The data from genetic studies of panic disorder, although more limited than the other mental disorders discussed so far in this chapter, reveal similar trends: panic disorder runs in families and genes seem to play some role; however, there are fewer data, which are much less consistent. Linkage studies of panic disorder are currently in progress, but no evidence at yet links this condition to the action of a major gene.

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) is characterized by recurrent and persistent thoughts, images, or ideas-obsessions-and stereotypic, repetitive, and purposeful actions-compulsions (64). Individuals with OCD cannot resist these persistent ideas or impulses, although they view them as irrational and unwanted. One common manifestation of this disorder is the obsessive feeling of being dirty or contaminated, which leads to the compulsion of repeated hand-washing. Hand-washing may be so frequent that the skin is rubbed raw. Another common obsession is excessive doubt, which leads to compulsive checking. Although long thought to be resistant to treatment, research has led to medications and psychotherapy that offer considerable therapeutic benefit.

Recent epidemiologic data indicate that OCD, once thought to be quite rare, afflicts approximately 2.6 percent of the U.S. population at some time during their lives. Men and women appear to be afflicted equally, although OCD may be slightly more common among women. The symptoms begin in childhood or adolescence in one-third to one-half of the individuals who develop the disorder. The average age of onset is 20.

Few family and twin studies using modem diagnostic criteria and methodologies have assessed the distribution of OCD in families and the role of genetic factors in this condition. There are no published adoption studies. What do we know from existing data? Although fraught with methodological shortcomings, including unclear methods for diagnosing OCD, no direct interviews conducted to make diagnosis, and no control groups, most studies conducted before 1970 found that symptoms of OCD tend to run in families (2,52). Several recent family studies have used standard diagnostic criteria and direct structured interviews of subjects and their family members and most evidenced a familial basis for OCD.

These recent family studies are not unproblematic, however. Several of the studies lacked control groups. Not all of them reported increased OCD among family members of those afflicted by OCD. The rates of OCD among family members varied considerably. There are two other family studies of OCD and Tourette's syndrome, which implicate a link between these conditions, at least in some families (24,48).

Data from existing twin studies also paint a complicated picture. In 1986, Rasmussen and Tsuang published a review of previous twin studies of OCD (53). They calculated an overall concordance rate of 63 percent for identical twins. This high concordance rate must be interpreted conservatively since most of the included data were from single-case reports with no control groups or fraternal twin estimates. Other twin studies with data on OCD focused on a variety of symptoms in anxiety disorders (1,6,8,59). In general, these studies did not find much higher rates of OCD in identical versus fraternal twins. Rather, most of these studies signal a genetic component underlying nonspecific symptoms of anxiety.

In summary, existing data do not unambiguously support a significant role for genetic factors in OCD. Further study, using sound methods, is needed to resolve any role that genes play in OCD. Attention to the spectrum of possible disorders that may be inherited, including OCD, symptoms of other anxiety disorders, and Tourette's syndrome, is also warranted.

SUMMARY AND CONCLUSIONS

Studies have characterized the familial nature of the disorders considered in this chapter. Data consistently point to the role of inherited factors in Alzheimer's disease, schizophrenia, and major mood disorders. Furthermore, researchers have located and in some cases identified specific genes involved in Alzheimer's disease. No replicated positive findings have yet emerged from efforts to locate individual genes associated with any other mental disorder considered in this chapter. And data also show that nongenetic factors contribute to these conditions.

The immediate clinical implications of genetic research of mental disorders are quite limited. Genetic tests to improve diagnosis are not yet available, nor are new treatment approaches. In general, there are enough data to give family members some information about empirical risk—the probability of developing a related condition. The important caveat here is that such information is not specific to a particular individual or family and thus may be difficult to interpret (see chapter 3).

The limited clinical application of data from genetic studies of mental disorders by no means impugns the relevance of this research. Indeed, in AD the research advances have been quite remarkable. The complexity of major mental disorders and genetics predicts a slow accumulation of knowledge (box 2-2), as noted by one workshop participant (55):

> We don't fully understand the genetics of the disorders. We don't have very strong evidence beforehand about how many genes are involved, or how difficult the problem is going to be. It's hard to say to the public what the answer is going to be because we really don't know ourselves. It's something we're going to have to live with, I think, for a number of years until it all gets sorted out.

Several factors justify continued research into the genetics of mental disorders: inherited factors contribute to at least a subset of major mental disorders. Rapid advances in molecular genetics make this a powerful technology. For many conditions, genetic approaches offer the most important lead for understanding their biological underpinnings. Ultimately, information about the molecular genetics of mental disorders may lead to improved diagnosis and treatment. Finding causative or contributing genes may be the key to rational design of new drugs and therapeutic advances. Alzheimer's disease provides an encouraging example, with the location of genetic culprits being found even in the late-onset form of the disorder, which is common and complex like the other mental disorders considered in this report.

BOX 2-2: Quest for the Huntington's Disease Gene: Lessons for Mental Disorders

In terms of genetics, Huntington's disease (HD) could not be more different from the mental disorders discussed in this chapter. The pattern of HD inheritance is simple: every individual who receives a single copy of the HD gene will develop HD, Despite the apparent straightforward genetics, quest for the HD gene proved unexpectedly prolonged and torturous, evincing the unpredictable path of research as well as the many mysteries of genetics that remain. Herein lies a lesson for mental disorders genetics.

Our story begins with an incredible stroke of good fortune. Using the nascent technology of linkage analysis with RFLPs, the HD gene was located on chromosome 4 in 1983, As the first disease gene located using this approach, the finding launched an era of disease gene searches, including genes linked to mental disorders. It also inspired near elation among individuals with HD and their families. Despite knowledge of the pattern of inheritance and the brain degeneration involved in HD, there was no cure for this terrible disease, no way to prevent it, nor even an effective treatment. Manifesting in midlife, body movement and mental functions are profoundly affected in HD. Over the course of 10 to 20 years, individuals with HD suffer the progressive loss of muscular control, resulting in terrible jerking of limbs, abnormal posture and speech, impulsiveness, psychosis, wild mood swings, and ultimately complete incapacitation, immobility, and death.

Knowledge of the HD gene location had a near-immediate clinical impact. A genetic test for the disease was developed. But it was the prospects for actually isolating the gene, understanding its structure, and the protein for which it coded that spurred an intensive research effort. With a historic collaboration in place, researchers probed the tail end of chromosome 4, isolating various markers for the region, mapping intimate details of its physical and chemical structure, assessing subtle changes in chromosome structure among individuals with HD and their families, and testing the potential role of genes known to be located at this site. But year after year passed without the successful isolation of the HD gene. It took a decade and the efforts of many scientists for this goal to be realized.

It turns out that the genetic mechanism involved in HD-this so-called simple and straightforward genetic disease-was new to researchers. Instead of some static alteration in the DNA code that is passed unchanged from generation to generation, the HD mutation involves an unstable DNA sequence, repeated many times, the number of copies changing as it is transmitted from parent to offspring. This novel mechanism, eluding researchers for so long, explained characteristics of HD that previously had not made sense. Clinicians and scientists had observed rare cases of HD emerging in childhood and adolescence; almost always such juvenile onset resulted from paternal inheritance, We now know that a large increase in the number of copies of the DNA sequence involved in HD correlates to a younger age of onset. The longest repeats result from male transmission.

The type of mutation underlying HD has been found in a number of genetic disorders, including Fragile X syndrome, spinobulbar muscular atrophy, and myotonic dystrophy. In fact, a variety of new genetic mechanisms that are linked to disease are being uncovered, Thus, we are only beginning to understand the human genome and genetic mechanisms involved in disease. For the study of mental disorders, this humbling realization urges patience and steadfastness. Researchers not only have to contend with the many uncertainties and complexities of mental disorders, but also the limits of our knowledge of human genetics.

SOURCES J F. Gusella, M.E. MacDonald, C.M. Ambrose, et al., "Molecular Genetics of Huntington's Disease, ''Archives of Neurology 501157-1153, 1993; J.F. Gusella, NS. Wexler, P.M. Conneally, et al., "APolymorphic DNA Marker Genetically Linked to Huntington's Disease, " *Nature* 308:234-238, 1983; The Huntington's Disease Collaborative Research Group, "A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes," Cc// 72:971-983, 1993.

With research being an imperative for achieving a better understanding of these conditions, the question becomes: what kind of research? Unfortunately, there is no single or simple answer to this question. For conditions in which a major gene appears to be at the root, such as early-onset AD, the application of molecular genetics, including **linkage analysis and positional cloning, has and continues to offer great promise. For conditions in which the contribution of inherited factors is not clear, such as in OCD, continued probing of the role of genetics, using family and twin studies, is necessary. For most mental disorders, the relative investment indifferent research approaches represents a judgment call, for which there are varying views. In one publication, genetic epidemiologists summarized the options for schizophrenia research in the following way (30):**

> The best analogy might be that of a stock portfolio. Family, twin, and adoption studies are low-risk, slow-growth, dependable investments that will continue, at a modest speed, to provide increasing knowledge about the genetics of schizophrenia. Linkage studies are hot, new high-risk investments that might produce great break-throughs but also might stall or even go bust. Individual investors will hold different views as to the optimal balance of these alternative strategies, depending on their objective assessment of the relative chances of success or failure and the rewards associated with each strategy, as well as on their personal comfort level in dealing with varying levels of uncertainty. Most investment counselors would suggest that a portfolio should include at least some of both kinds of investments. As a field, we would do well to follow such advice.

Many participants at the OTA-NIMH workshop conveyed the sense that while the search for mental disorder genes has been turbulent to date, continued application of linkage analysis—with an eye toward strengthened methodologies-offers considerable promise because major genes may contribute to the disorders. One workshop participant supported continued linkage analysis for at least three reasons: 1) advances in molecular genetics permit the comprehensive search for genes, 2) verification of a positive finding can be obtained quickly, and 3) finding a gene relevant in only a few large families will teach us something about the biology of a condition (11). Kendler and Diehl offer the following rationale for schizophrenia, which may well apply to other mental disorders (30):

> [I]t is critical that we avoid premature disillusionment with linkage studies of schizophrenia. The human brain is very complex and quite difficult to access, and schizophrenia is a common and crippling condition. For a complex disorder such as schizophrenia, this approach would most likely begin with gene mapping by linkage analysis. The aggregate results from twin and adoption studies allow us to conclude with some confidence that genes that influence liability to schizophrenia exist somewhere in the human genome. The crucial questions to which we do not have answers are (1) How many such genes are there? (2) How common are they? and (3) How large are their individual effects? If there are any relatively common genes of moderate to large effect, we have a very good probability of detecting them reliably in most study populations if we persevere in our study of large samples and maximize our statistical power to detect linkage under complex modes of inheritance. If there are very many genes, none of which has any more than a small effect on 1 iability, current methods and projected sample sizes are almost certainly inadequate and will yield negative or unreplicated results. . . To carry out a truly credible execution of the linkage strategy for a disease as complex and heterogeneous as schizophrenia, large numbers of carefully diagnosed families and highly informative markers are required. These resources are just now beginning to be brought into action. While definitely not offering a guaranteed success, this approach, if allowed sufficient time to mature, could yield truly unprecedented insights into the etiology of this disorder.

While some enthusiastically endorse linkage analysis of major mental disorders, and most do not rule it out as a reasonable approach, no one disagrees that further attention is needed to better characterize the inherited trait and familial risk

presented by these conditions by using family and twin studies. Furthermore, other methods for finding culprit genes, the sib pair method and association studies, offer important alternatives for the study of mental disorders.

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