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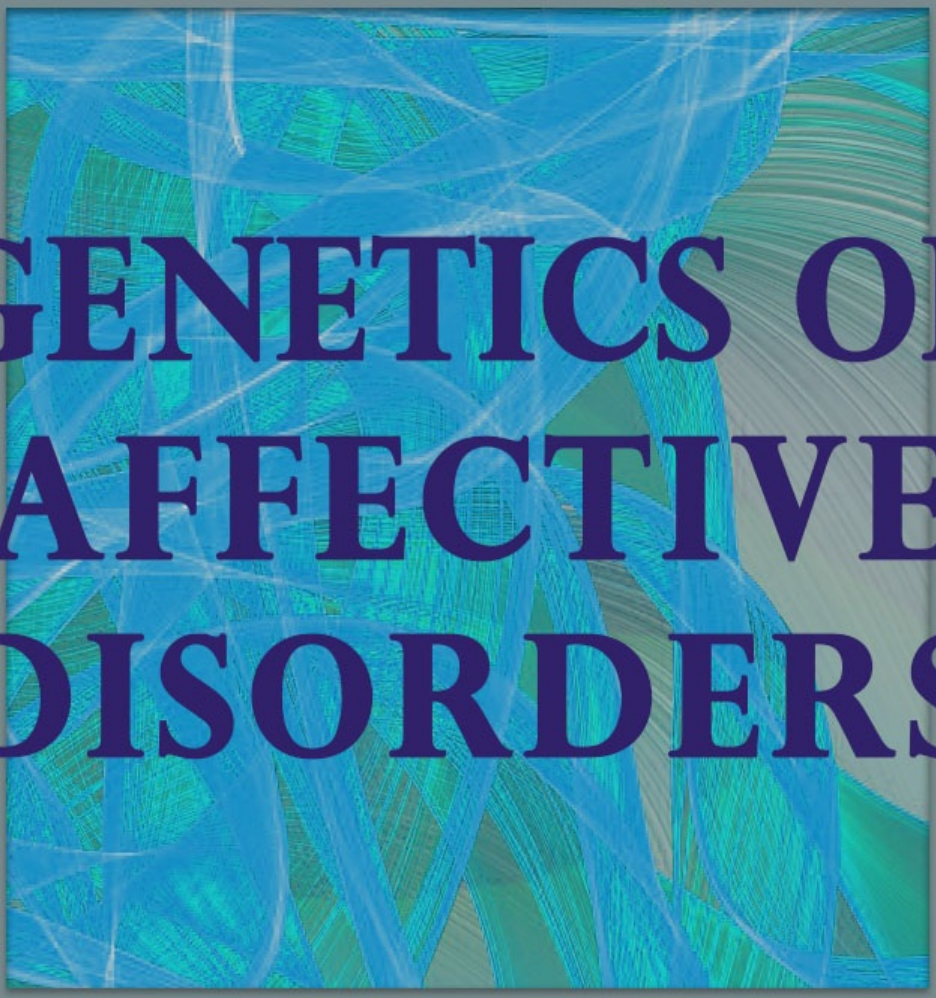

GENETICS OF AFFECTIVE DISORDERS

Depressive Disorders

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Table of Contents

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A regular finding in the study of affective disorders is that persons with these illnesses often cluster within families. All major psychiatric disorders appear to result at least partially from an inherited predisposition and in that manner are not unlike other medical disorders such as diabetes or coronary artery disease. The theory that affective disorders and other medical disorders share common genetic modes of transmission can be a difficult concept to follow, if one assumes that mental disorders are purely abnormal psychological reactions to environmental events. This is not to say that the environment plays no role in the development and course of these disorders. In fact, the environment probably plays a large role in the development and course of mental disorders and other medical disorders as well.

For example, it is quite clear that coronary artery disease runs in families (Wolinsky, 1979); having a first-degree relative with the disorder is considered to be a risk factor. It is also hypothesized that the environment may influence the course of coronary artery disease. Smoking, obesity, lack of exercise, and high dietary fat content are all environmentally controlled factors that may influence the course of the illness (Messerli, 1986). A person with a genetic predisposition to coronary artery disease will have different physiological reactions to these

environmental factors that one who does not possess that predisposition. The heart and blood vessels are then the substrate for the environment to act upon. The physical and metabolic abnormalities that are the product of the genetic diathesis (congenital predisposition) will interact with the environment to produce the usual features of coronary artery disease (i.e., atheromas, reduced coronary blood flow, and angina). Removing or minimizing the environmental factors in coronary artery disease may stall the onset of the disorder, produce clinically insignificant changes, or entirely prevent the development of any manifestation of the disorder. The underlying congenital predisposition, however, remains constant.

The interaction between the environment and genetic factors may be played out similarly in the affective disorders. Certain environmental or biological events in genetically susceptible persons possibly may lead to episodes of affective illness. The combination of environmental and biological genetic factors is the liability that a given individual will develop an affective disorder.

The genetics of any mental disorder can be researched in a variety of ways. In this chapter we will discuss four major research paradigms—twin studies, adoption studies, family studies, and genetic marker studies.

TWIN STUDIES

Twin studies compare the concordance rates for monozygotic and dizygotic twin pairs. Monozygotic twins possess identical sets of genes. Dizygotic twins share only 50 percent of the genes they inherited from their parents and in that manner are exactly the same as other sibling pairs. If a disorder is genetically transmitted, then monozygotic twins should show a higher concordance rate than dizygotic twins because of their identical genetic material. A major assumption in these studies is that environmental factors are controlled, since twins raised by their biological parents share identical environments. Although environmental influences may be important, studies of psychological traits in twins indicate that monozygotic twins who have highly similar environments do not on average show any greater concordance for personality traits or IQ than monozygotic twins with less environmental similarity (Loehlin & Nicholas, 1976).

Five twin studies of affective illness are shown in Table 6.1. The hypothesis of a genetic component for affective disorders is supported by the repeated finding of a higher concordance in monozygotic than in dizygotic pairs. Pooling the data from all studies, an overall concordance rate of 63.8 percent is observed for monozygotic and 14 percent for dizygotic pairs. In a large study using the Danish twin register, Bertelsen and colleagues identified 110 same-sex twin pairs in which at least one had affective disorder (Bertelsen, 1979). Twins were personally interviewed and zygocity was established using serologic markers or, if both twins

were not alive, anthropometric methods. Of 55 monozygotic twin pairs, 58.3 percent were concordant for affective disorder whereas only 17.3 percent of the 52 dizygotic pairs were concordant.

In a study of 12 monozygotic twin pairs reared apart, using data gleaned from published series, 67 percent were concordant for affective disorder, a figure strikingly similar to the pooled figure of 63.8 percent (Price, 1968).

*TABLE 6.1. Concordance Rates for Affective Illness in Monozygotic and Dizygotic Twins**

Study	Monozygotic Twins		Dizygotic Twins	
	Concordant Pairs/ Total Pairs	Concordance (%)	Concordant Pairs/ Total Pairs	Concordance (%)
Slater (1953)	4/7	57.1	4/17	23.5
Kallman (1954)	25/27	92.6	13/55	23.6
Harvald & Hauge (1965)	10/15	66.7	2/40	5.0
Allen, Cohen, Pollin, & Greenspan (1974)	5/15	33.3	0/34	0.0

Bertelsen (1979)	32/55	58.3	9/52	17.3
Totals	76/119	63.8	28/198	14.1

*Data not corrected for age. Diagnoses include both bipolar and unipolar illness.

Source: Adapted from: Numberger, J. I., Goldin, L. R., & Gershorv, E. S. (1986). Genetics of psychiatric disorders. In G. Winokur & P. Clayton (Eds.), *The medical basis of psychiatry* (pp. 486-521). Philadelphia: Saunders.

ADOPTION STUDIES

Adoption studies attempt to separate genetic susceptibility from environmental factors. A demonstration that offspring reared away from their biological parents have higher than expected rates of illness would be a persuasive argument for inheritance.

Adoption studies can be carried out in a number of ways. The simplest method is to identify a group of adopted affected individuals and compare them to a control group of unaffected adoptees. The adoptive and biological parents of both groups would be studied for the presence of illness. If the biological parents of ill adoptees show higher rates of illness than the biological parents of control adoptees and both sets of adoptive parents, then a genetic factor can be said to be present. An adoption study can also be done by identifying ill parents who adopt away their children. These offspring can be compared to adopted-away children born to unaffected parents. A complicated adoption study, the cross-fostering study, compares children of affected biological parents reared by well adoptive parents to children of well biological parents reared by ill adoptive parents.

Adoption studies do not provide information about the mode of transmission. They have been criticized because unknown and unquantifiable factors such as demographics and selection practices among adoption agencies may place children in environments where nongenetic risk factors are prevalent.

The families of adult bipolar adoptees and three control groups were studied by Mendlewicz and Rainer (1977). In addition to the adoptive and biological parents of 29 bipolar adoptees, the study included the biological parents of 31 bipolar nonadoptees, the adoptive and biological parents of 22 unaffected adoptees, and the biological parents of 20 individuals who developed polio. The polio group was added to control for the effect of raising a disabled child. Interviews were conducted blind to the clinical status of the adoptees.

Table 6.2 shows the diagnoses of the adoptive and biological parents. The biological parents of the bipolar adoptees and nonadoptees showed similar rates of affective disorder (31 percent vs 26 percent). These same parents showed higher rates of affective illness than either the adoptive or biological parents of normal adoptees, and higher rates than the parents of polio patients. Three major points can be made from this study. First, the hypothesis of a genetic contribution to bipolar affective disorder is supported by these data. Second, the excess amount of unipolar disorder seen in the biological parents of all bipolar patients supports the notion that unipolar illness in some cases stems from the same genetic abnormality as bipolar illness. Lastly, the data show that unipolar illness is more common in the adoptive parents than bipolar disorder. In fact, only one case of bipolar disorder was found in the adoptive parents.

TABLE 6.2. Affective Illness in Parents of Bipolar Adoptees and Controls

Group	Diagnosis of	Adoptive	Percent	Biological	Percent

	Parent	Parents	Ill	Parents	Ill
Bipolar adoptees N=29	Bipolar	1		4	
	Unipolar	6	12%	12	31%
	Other affective disorder	0		2	
Bipolar nonadoptees N=31	Bipolar	—	—	2	
	Unipolar	—	—	11	26%
	Other affective disorder	—	—	3	
Normal adoptees N=22	Bipolar	0		0	
	Unipolar	3	10%	1	2%
	Other affective disorder	1		0	
Poliomyelitis N=20	Bipolar	—	—	0	
	Unipolar	—	—	4	10%

Other affective disorder	—	—	0

Data from "Adoption Studies Supporting Genetic Transmission in Manic-Depressive Illness" by J. Mendlewicz and J. Rainer, 1977. *Nature*, 268, 326-329.

This suggests that unipolar disorder is probably a heterogeneous group of illnesses, with some being related to bipolar illness and others perhaps not genetically mediated at all.

Wender, Kety, and Rosenthal (1986) studied the biological and adoptive families of 71 adoptees with affective disorders and 71 matched control adoptees with no illness. Biological relatives of ill adoptees had significantly higher rates of affective disorder (bipolar and unipolar) compared to the biological relatives of controls. Alcohol abuse and dependence was also seen in greater frequency among the biological relatives of ill adoptees, supporting earlier findings that in some cases affective disorders and alcoholism may be genetically related. The most significant finding was a striking increase in completed suicide in the biological relatives of ill adoptees, compared to those of controls.

In a study by Cadoret, 83 adoptees were selected from adoption records showing evidence that their biological parents had mental disorders (Cadoret, 1978). Forty-three matched controls were also obtained. All adoptees and at least one adoptive parent were interviewed. All data were collected blind to the

diagnosis of the biological parents. Eight adoptees were found to have one biological parent with an affective disorder. Three of these adoptees were diagnosed as having an affective disorder, all of which were unipolar illnesses (38 percent). The remaining 75 adoptees in the experimental group and the 43 controls had four (5 percent) and four (9 percent) cases of unipolar depression respectively. The differences in the observed rates of affective illness in the adoptees of biological parents with affective disorder compared to those without such a disorder are significant.

In a large study of 2,966 adoptees born in Sweden and adopted out prior to age three, Von Knorring and colleagues identified 56 adoptees with affective disorders and 59 with substance abuse (Von Knorring, Cloninger, Bohman, & Sigvardsson, 1983). Each affected adoptee was matched to one of 115 control adoptees with no mental illness. Adoptees with affective disorder showed no higher rates of affective disorder in either the biological or adoptive parents when compared to parents of matched controls. There was, however, a trend for nonpsychotic depressed adoptees to have more mothers with affective disorders than normal controls. Adoptees with affective disorder did show a significant increase in biological mothers with substance abuse compared to mothers of adoptees with no illness. No general concordance of any specific psychiatric diagnosis was observed between adoptees and biological parents.

It should be pointed out that all subjects in this study were diagnosed by

medical records only. Subjects identified as having no psychiatric illness could have, in fact, had episodes of illness that were treated but not recorded, misdiagnosed, or not treated at all. In support of this, not one of the eight parents of adoptees with psychotic depression was diagnosed as having affective disorder. Although this is possible and is similar to the rate found in the controls, it is much lower than the rate observed in studies where relatives are directly examined. Despite its shortcomings, the study does suggest that some cases of unipolar depression may not be genetically transmitted.

FAMILY STUDIES

Family studies are easily applied to the research of the genetics of affective disorders and have been its cornerstone. Studies such as these usually begin with an affected individual (proband) and study all available relatives. Two basic types of family research are recognized. The family history method involves obtaining all pedigree information from the proband only. Studies of this nature have been criticized because other affected family members may conceal their illnesses or may have milder forms of illness that would go unnoticed by others (Andreasen, Endicott, Spitzer, & Winokur, 1977). In general, family history studies are biased by underreporting. The second, more complete type of family study involves the direct examination of all available relatives.

Family studies are useful in delineating the range of disorders that may be associated with a single genetic vulnerability. For example, Winokur demonstrated through a series of family studies that unipolar depression, alcoholism, and sociopathy cluster in certain kindreds, suggesting that all three stem from the same genetic abnormality (Winokur, 1972). When two or more disorders appear to be genetically related, they are referred to as a spectrum.

A family study attempts to identify all affected persons. In order to show that an illness is familial, the rates of illness in the relatives of probands must be higher than the rates of the same illness in controls. The statistic used to compare families of probands to controls is called the morbid risk—the ratio of the number

of ill relatives divided by the total number of relatives at risk for the disorder. The calculation of the number at risk for the disorder must take into account variable age of onset. In order to do this, the number of relatives who are in a particular decade is multiplied by the percentage of affected persons who first become ill by that decade of their lives. This product is called the Bezugziffer (BZ). For each decade, BZs are summed and the total number is used in the calculation of the morbid risk (Nurnberger, Goldin, & Gershon, 1986).

The familial concentration of affective disorders has been clearly demonstrated in numerous family studies. Table 6.3 shows the lifetime prevalence of affective disorders in first-degree relatives of patients and controls. Of the eight studies listed, eight identified bipolar probands, six identified unipolar probands, and two utilized unaffected controls. Bipolar and unipolar probands had more relatives ill with either disorder than did normal control probands. The most common affective disorder seen in the relatives of either unipolar or bipolar probands was unipolar disorder. This suggests that at least in some families bipolar and unipolar illnesses are different phenotypic expressions of the same genetic illness.

TABLE 6.3. Morbid Risk for Bipolar and Unipolar Disorders in First-Degree Relatives of Patients and Controls

	Number at Risk	Morbid Risk (%)

		Bipolar	Unipolar
Bipolar probands:			
Angst (1966)	161	4.3	13.0
Perris (1966)	627	10.2	0.5
Winokur & Clayton (1967b)	167	10.2	20.4
Helzer & Winokur (1974)	151	4.6	10.6
Gershon, Baron, & Leckman (1975)	341	3.8	6.8
Smeraldi, Negri, & Melica (1977)	172	5.8	7.1
Taylor, Abrams, & Hayman (1980)	601	4.8	4.2
Gershon, Goldin, Weissman, & Nurnberger (1981)	598(572)*	8.0	14.9
Unipolar probands:			
Angst (1966)	811	0.3	5.1

Perris (1966)	684	0.3	6.4
Gershon, Baron, & Leckman (1975)	96	2.1	11.5
Smeraldi, Negri, & Melica (1977)	185	0.6	8.0
Taylor, Abrams, & Hayman (1980)	96	4.1	8.3
Gershon, Goldin, Weissman, & Nurnberger (1981)	138(133)	2.9	16.6
Normal probands:			
Gershon, Baron, & Leckman (1975)	518(411)	0.2	0.7
Gershon, Goldin, Weissman, & Nurnberger (1981)	217(208)	0.5	5.8

*Total number at risk for bipolar illness appears first. The number in parentheses represents the number at risk for unipolar disorder when known.

Source: Adapted from: Gershon, E. S., Hamovit, J., Guroff, J. J., Dibble, E., Leckman, J. F., Sceery, W., Targum, S. D., Nurnberger, J. I., Goldin, L. R., & Bunney, W. E. (1982). A family study of schizo affective, bipolar I, bipolar II, unipolar and normal control probands. *Archives of General Psychiatry*, 39, 1157-1167.

As seen from Table 6.3, morbid risk figures vary widely among studies.

There are many reasons for these observed variations. Diagnostic criteria employed, method of data collection, and cultural factors all vary and may be responsible for the differences observed. Studies utilizing a family history method tend to underestimate prevalences, whereas direct examination of all available relatives tends to produce a higher figure that may be a more correct estimate of the true prevalence.

Although each study has its own flaws with respect to methodology and cannot be directly compared to the others, each shows a clear increase in affective disorder among first-degree relatives of ill probands. Taken together, family studies support the genetic hypothesis in the transmission of affective disorders.

Family, twin, and adoption studies, regardless of methodological flaws, all support the hypothesis of a genetic component for affective disorder. Just how affective disorder is transmitted is not known. Segregation analysis of family study data has failed to show the exact mode of transmission for any affective disorder (Gershon, Bunney, Leckman, Van Eerdewegh, & De Bauche, 1976). There are likely to be several reasons for this, but in order to proceed with this discussion two definitions are needed: *Genotype* is the actual inherited genetic material, and *phenotype* is the observed effect of the genotype.

Genotype and Phenotype

Since the environment may play a role in the development of the disorder,

the absence of critical environmental factors may obscure the mode of transmission: Certain individuals with a genetic predisposition (affected genotype) and no environmental input may not show the disease (affected phenotype) at all. The finding that monozygotic twins fail to show 100 percent concordance for affective disorders suggests that the disease may not manifest itself in all persons who possess the gene. Reduced penetrance, the term applied to this phenomenon, may play a role in many mental disorders—schizophrenia and anxiety disorders, as well as affective disorders. Any genetic illness with low penetrance would clinically appear to be uncommon even though the actual frequency of the disease gene may be high. The possibility that many individuals could be carriers without overt illness would make it nearly impossible to determine the mode of transmission from family study data alone. Reduced penetrance implies that the disease gene does not manifest itself at any time in a carrier's lifetime, assuming that the carrier has lived through the entire age of risk for the disorder. The accepted ages of risk for bipolar and unipolar disorder are 20-50 years and 20-70 years respectively (Paykel, 1982). Since affective disorders have a variable age of onset, the penetrance of a disease gene may be age-dependent. In any family study there will be a large number of individuals who may be gene carriers but who have not yet reached the age where the illness manifests itself. The ideal family for segregation analysis would be a large kindred with the youngest generation well into the age of risk and with a clear unilateral source of illness. Since family studies examine pedigrees only at one point in time,

many younger family members who may be carrier would be classified as unaffected, thereby obscuring the path of transmission.

Until now it has been assumed that a single disease gene leads to a defined single phenotype. This assumption may not be valid for clinical psychiatry; there is evidence that phenotypes may vary from person to person even though they may contain the same genetic material. Winokur described a clinical spectrum of disorders termed *depression spectrum disease,* which includes sociopathy, unipolar depression, and alcoholism (Winokur, 1972). This clustering appeared to breed true, and a closer look at the families studied showed that the cases of depression were commonly seen in women under the age of 40 who had unstable personalities; alcoholism and sociopathy were more commonly seen in males. Winokur's work suggested that the three disorders may stem from a single genetic abnormality that manifests itself differently due to sex effect and/or perhaps other undetermined environmental or biological factors. Other clinical studies have shown affective disorder to cluster with eating disorders and panic disorder in certain families (Cantwell, Sturzenberger, Burrows, Salkin, & Green, 1977; Leckman, Weissman, Merikangas, Pauls, & Prusoff, 1983). Even among affective disorders, the wide range of possible phenotypes includes bipolar I, bipolar II, unipolar, cyclothymia, dysthymia, and schizoaffective disorder. Whether all these disorders stem from the same genetic diathesis is a matter for debate, but the fact that many kindreds do show more than one type of disorder suggests that, for at least some families, single genetic abnormalities produce a variety of phenotypes.

Since affective disorders are not determined from laboratory or other biological/physical exams, the diagnosis is made purely from the description of the disorder made by the patient and sometimes by a knowledgeable informant. The absence of objective tests for diagnosis means that other disorders with a different pathophysiology may mimic an affective illness. Examples include hypothyroidism, reactive depression, Cushing's disease, and bereavement. Cases such as these, called phenocopies, may be clinically indistinguishable from primary affective disorders. Phenocopies are probably common in studies of unipolar depression (depending upon the diagnostic criteria used) and would certainly obscure efforts to find the mode of transmission in the families involved.

Heterogeneity

The last and perhaps most difficult obstacle to uncovering the mode of transmission for any affective disorder is heterogeneity. Genetic heterogeneity is a factor in many diseases. For example, diabetes in its variety of forms may stem from several different genetic abnormalities. Early onset (insulin-dependent) and late onset (non-insulin-dependent) have different pathophysiologies and it has been demonstrated that non-insulin-dependent diabetes is familial but the insulin-dependent form is not (Unger & Foster, 1985). In a study of a heterogeneous illness, detecting the mode of transmission would be nearly impossible. A variety of genetic mechanisms would be in play and each would have its own mode of transmission. In an attempt to limit the heterogeneity factor,

families showing X-linked inheritance have been singled out for analysis. In these cases there is a father-to-son transmission because fathers can pass only a Y chromosome on to their sons. It is assumed in these cases that the genetic abnormality is limited to the X chromosome, thereby excluding all of the autosomes. In X-linked dominant transmission, females would be affected more often because they possess two X chromosomes and therefore have twice the risk of getting a disease gene. Winokur and colleagues observed both an excess of ill females and a lack of male-to-male transmission in a study of 62 bipolar probands (Winokur, Clayton, & Reich, 1969). They postulated an X-linked dominant mode of transmission for bipolar illness in these selected kindreds. These data and others, however, have been reanalyzed, and neither an X-linked or an autosomal single-major-locus model of transmission could explain totally the cases of bipolar illness observed in these families (Bucher et al., 1981; Bucher & Elston, 1982). X-linked dominant transmission was also postulated by Mendlewicz and Fleiss in a series of bipolar probands but a reanalysis of these data found that the X-chromosome single-major-locus model did not fit their data (Mendlewicz & Fleiss, 1974; Van Eerdewegh, Gershon, & Van Eerdewegh, 1980). Data from families suggesting X linkage remain conflicting and the results obtained vary, based on assumptions made and statistical methods used. The hypothesis of an X-linked form of affective disorder is likely to be viable but probably accounts for only a minority of cases.

As mentioned earlier, variable phenotype may hinder segregation analysis studies and thereby obscure the mode of transmission. This issue has been taken

up by a number of researchers in the analysis of family study data. Gershon and colleagues have hypothesized that unipolar, bipolar I, bipolar II, and schizoaffective disorders are all part of a continuum stemming from a common genetic background with multiple thresholds (Gershon et al., 1982). Their family study data are in support of that model. Further support for the concept of variable expressivity comes from work by Winokur. In one study (Winokur, 1984), the morbid risks for affective disorder in first-degree relatives of bipolar and unipolar probands were nearly identical. In another study (Winokur, Kadrmas, & Crowe, 1986), first-degree relatives of schizoaffective bipolars were found to have morbid risks for affective disorder similar to those of first-degree relatives of other bipolar probands. Smeraldi, Fiammetta, Heimbuch, and Kidd (1981) found that the probands' polarity did not predict illness in relatives.

Sex differences in the transmission of affective disorders have been demonstrated. Winokur and Clayton found that ill mothers more often transmitted their illness to daughters than to sons whereas ill fathers transmitted their illness with equal frequency to both sons and daughters (Winokur and Clayton, 1967a). Angst, Frey, Lohmeyer, and Zerbin-Rudin (1980) demonstrated that first-degree female relatives of female probands had higher morbidity risks than other relatives. At this point it is clear that the mode of transmission for affective disorders is not known and is likely to be complex, even though the familial clustering of these illnesses is easily demonstrated.

GENETIC MARKER STUDIES

Genetic markers pose a new method to uncover the inheritability of affective disorders. It is possible that genetic markers may uncover subtypes of illness that are linked to a particular marker, thereby directly addressing the problems of heterogeneity and variable expressivity.

The search for genetic markers linked to mental disorders has included studies of color blindness, blood group polymorphisms, HLA (human leukocyte antigen) types, and DNA (deoxyribonucleic acid) markers. The methodology used in these studies is called linkage analysis. This method determines the probability that a genetic marker and a disease trait are inherited together, suggesting that they are physically close to one another on the same chromosome. Marker loci must be polymorphic; that is, they must have at least two forms so that one form can be demonstrated to be linked to a particular disease. Additionally, the mode of inheritance for the marker locus must be known. If linkage can be demonstrated between marker locus and disease locus, it is convincing evidence for the presence of a genetic component, since it is unlikely that environmental influences would cause such an association.

Linkage

To demonstrate linkage, it is necessary to employ mathematical models to estimate the likelihood of linkage. The lod (log of the odds ratio) score method of

Morton tests the hypothesis of linkage between two loci (marker and disease) when the mode of transmission of each locus is known (Morton, 1955). This method assumes that the gene frequency and penetrance for the disease and marker loci are known. It is also assumed that there is no population association between the marker and disease loci and that random mating occurs. The pattern of segregation seen between the marker and disease loci is compared to the probability of observing the same pattern if the two loci are not linked (random assortment). The probability of linkage is expressed in terms of the recombination fraction called theta. On a given chromosome, genes can recombine at the time of meiosis. Genes that lie far apart will recombine more frequently than genes that are close together. If a marker locus and disease locus are tightly linked, then they should recombine infrequently. Theta takes on a value between zero and one half. A recombination fraction of one half means that the loci are expected to recombine 50 percent of the time; that is, they segregate independently and are not linked. At the other extreme, a recombination fraction of zero means that the loci are expected never to recombine and always to segregate together. Using these recombination fractions a lod score is defined as:

$$\text{LOD Score} = \log_{10} \frac{\text{probability of observing a family for } \theta < 1/2}{\text{probability of observing a family for } \theta - 1/2}$$

A lod score of 1.0 indicates that linkage is 10 times more likely than no linkage.

LOD scores are calculated for several values of theta because there is no way of directly determining its exact value. The recombination fraction that gives the highest score is considered to be the best estimate of theta. By convention, a lod score of 3.0 is required to establish linkage. A score of -2.0 excludes linkage. Intermediate scores indicate that not enough information is available to make a conclusion on linkage and more families would need to be studied in order to confirm or exclude linkage. LOD scores can be summed across families so that several families, each giving a small positive or negative lod score, can be taken together to provide evidence confirming or excluding linkage. Statistical software packages are available that will compute lod scores on personal computers.

The lod score method has certain disadvantages when applied to the genetics of mental disorders. First, the method requires that the mode of inheritance for both the marker locus and disease locus be known. In most cases the mode of inheritance for the marker locus is known but very little is known about the mode of transmission for the disease locus. As mentioned earlier, the exact mode of inheritance for *any* mental disorder is unknown at this time. Most genetic marker studies using the lod score method for psychiatric disorders assume that the trait is transmitted in an autosomal-dominant fashion, with reduced penetrance. This assumption may not be valid.

The lod score method works best with diseases that show complete penetrance. Although newer versions of statistical packages that compute lod

scores include functions to account for age-dependent and incomplete penetrance, the fact that psychiatric disorders do not show complete penetrance reduces the value of the lod score method for these types of disorders. Genetic marker studies using the lod score method have had to make estimates of disease penetrance, and these estimates have varied widely. At this time there is no way of estimating the true penetrance for any mental disorder (Kennedy et al., 1988). This is unfortunate because the penetrance function is highly sensitive to minor changes and it has been demonstrated that lod scores can vary widely, depending on what value of penetrance is used for the disease gene. Another disadvantage of the lod score method is that it is most powerful for large, multigenerational families, which are difficult to come by in clinical psychiatry. The lod score method can be easily applied to small, nuclear families, but obtaining the large number required to calculate a meaningful lod score can be difficult.

The sib-pair method of Penrose was developed to study linkage of various diseases to HLA loci but can be applied to other genetic markers as well (Penrose, 1953). In this method, affected sib-pairs are compared for the presence of a specific marker. If the affected pairs share the marker together more often than can be expected to result from chance alone, then a case can be made for an association between the marker and the disease. This method requires fewer assumptions than the lod score method. It does not require complete pedigrees, or that the mode of inheritance be known, or that the gene frequency and penetrance of the disease and marker loci be known. For these reasons, the sib-pair method is

useful for diseases thought to have low penetrance. A specific disadvantage of the sib-pair method is that, to be informative, it requires highly polymorphic loci. Other, less polymorphic loci can be used in a sib-pair analysis but very large sample sizes are required to obtain adequate results.

Both the lod score method and the sib-pair method calculate probabilities of linkage. Both can be applied to specific clinical situations and each has its own distinct advantages and disadvantages. A major problem for both of these methods, however, is that neither can adequately address the issue of genetic heterogeneity. Both methods assume that the disease in question is caused by the same genetic locus in each person. If genetic heterogeneity is present, then pooling families or sib-pairs would lead to erroneous results.

Color blindness, XG blood group marker, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are three X chromosome markers that have been studied for linkage to bipolar illness. Interest in the possibility of a genetic locus for bipolar illness on the X chromosome started after Winokur presented a family in which X-linked color blindness segregated with manic-depressive illness in a large kindred (Winokur, Clayton, & Reich, 1969). Shortly thereafter, Mendlewicz reported evidence of linkage of bipolar illness to the red cell XG locus, which is on the opposite arm of the X chromosome as color blindness (Mendlewicz, Fleiss, & Fieve, 1975). Mendlewicz reported linkage between bipolar illness and G6PD deficiency in a single large pedigree (Mendlewicz, Linkowski, &

Wilmotte, 1980). Alternatively, Gershon found no evidence of linkage to either color blindness or XG blood group in a series of families (Gershon, 1980). It is clear that research on the X chromosome has yielded conflicting results, with some pedigrees showing evidence for linkage to color blindness, XG blood group, and G6PD deficiency, and others showing no evidence of linkage. These conflicting results may be due in part to methodological uncertainties, but the presence of genetic heterogeneity may also be a factor. In a recent study of genetic linkage of bipolar illness to G6PD deficiency and color blindness, Baron reported a maximum lod score of 7.52 assuming homogeneity and 9.17 assuming heterogeneity for the disorder (Baron et al., 1987). His results provide confirmation that a major psychiatric disorder can be caused by a single genetic trait. It appears from these data that the existence of an X-linked locus is involved in the etiology of some cases of bipolar disorder.

The HLA locus on chromosome 6 has been a source of some interest. In one of the early studies of HLA and affective disorder, Shapiro reported an increased frequency of HLA BW16 in patients (Shapiro, Block, Rafaelson, Ryder, & Srejgaard, 1976). Smeraldi reported that affected sib-pairs shared HLA haplotypes more often than would be expected from chance alone (Smeraldi, Negri, Melica, & Scorza-Smeraldi, 1978). Other studies have failed to show a significant association of HLA haplotypes in affective disorder (Goldin, Clerget-Darpoux, & Gershon, 1982). Weitkamp, reporting data from a sib-pair study of HLA haplotypes, found that the frequency of haplotype sharing did not deviate from random (Weitkamp,

Stancer, Persad, Flood, & Guttormsen, 1981). Other studies have also failed to demonstrate any relationships between HLA and affective disorder. In summary, studies of association between HLA haplotypes and affective disorder have yielded inconsistent results.

Several other autosomal markers have been tested for linkage to affective disorders. Depending on the method of diagnosis used and the statistical analysis employed, weak evidence of linkage to several autosomal markers has been demonstrated. An overview of selected recent studies of linkage between affective disorders and autosomal markers is presented in Table 6.4. Depression spectrum disease had shown weak linkage to haptoglobin and compliment factor 3 in two studies (Tanna, Winokur, Elston, & Go, 1976a; Tanna, Go, Winokur, & Elston, 1979). Provisional evidence of linkage has also been reported for PGM1 and GC in two separate studies of familial pure depressive disease families (Tanna, Winokur, Elston, & Go, 1976b; Tanna, Go, Winokur, & Elston, 1977). Three studies that took bipolar and unipolar illness together as a single illness found provisional evidence of linkage to PEPA in one study, to MNS blood group marker in another, and to GC blood group marker in a third (Fieve, Go, Dunner, & Elston, 1984; Goldin, Gershon, Targum, Sparkes, & McGinniss, 1983; Johnson, Hunt, Robertson, & Doran, 1981). In a recent study by Hill, Wilson, Elston, and Winokur (1988), indications of linkage between familial pure depressive disease and MNS blood group marker and between depression spectrum disease and orosomucoid on chromosome 9 were found to support previously reported findings. All of these protein

polymorphism studies share methodological flaws with other genetic studies. The differences in methods used may, in part, explain the differences observed.

TABLE 6.4. Linkage Studies of Affective Disorders and Protein Polymorphisms

Study	Diagnostic System	Statistical Analysis	Significant Results
Tanna, Winokur, Elston, & Go (1976)	DSD[a]	Sib-pair	Provisional linkage to C3 and HP
	FPDD[b]	Sib-pair	Provisional linkage to GC, PCM 1
Tanna, Go, Winokur, & Elston (1977)	FPDD	LOD Score	Provisional linkage to GC
Tanna, Go, Winokur, & Elston (1979)	DSD	LOD Score	Provisional linkage to HP
Johnson, Hunt, Robertson, & Doran (1981)	BP + UP[c]	LOD Score	Provisional evidence for GC; excluded ABO, RH, HP
Goldin & Gershon (1983)	BP + UP	LOD Scores	Provisional evidence for MNS
Fieve, Go, Dunner, & Elston (1984)	BP + UP	Sib-pair	Provisional linkage to PEPA

Hill, Wilson, Elston, & Winokur (1988)	DSD & FPDD	Sib-pair	Provisional linkage to MNS for FPDD & ORM for DSD

[a]DSD – Depression Spectrum Disease

[b]FPDD–Familial Pure Depressive Disease

[c] BP + UP – Bipolar and Unipolar Disorders

DNA Marker Studies

Advancement in molecular biological techniques has allowed geneticists to study specific DNA markers and their relationships to specific disease loci. These advances have led to the chromosomal localization of genes responsible for several diseases, including Huntington's chorea, Duchenne's dystrophy, and cystic fibrosis. The discovery of polymorphic DNA probes has provided a new method to test genetic hypotheses using probes that are specific for a particular marker. Investigators can see whether a particular disease is linked to a marker detected by a DNA probe. Polymorphic DNA probes can recognize specific nucleic acid and sequences that have been cut with restriction enzymes derived from bacteria. These specific nucleic acid sequences are referred to as restriction fragments and each is a characteristic length. Each individual's DNA contains restriction sites that are inherited in a Mendelian fashion. When a specific DNA probe binds to a fragment that has been cleaved by a restriction enzyme, the combination is

referred to as a restriction fragment length polymorphism (RFLP). RFLPs can be examined in families evidencing affective illness to see which RFLPs may cosegregate with the illness. RFLPs that always cosegregate with the illness can be considered tightly linked to the disease locus.

To date, five DNA marker studies of affective disorders have been carried out. The first by Egeland et al. (1987) examined a large Amish kindred for linkage of bipolar affective disorder to markers on chromosome 11. It was demonstrated in their study that bipolar illness in the Amish kindred was linked to the Harvey-ras oncogene on the short arm of chromosome 11 with a maximum lod score of 4.32 at a recombination fraction of 0. Additionally, a weaker linkage to the insulin locus was shown. The insulin locus is adjacent to the Harveyras locus, and a maximum lod score of 2.63 was obtained at a recombination fraction of 0. Four additional studies of the Harvey-ras oncogene and insulin gene have failed to demonstrate evidence of linkage in other families (Detera-Wadleigh et al., 1987; Gill, McKeon, & Humphries, 1988; Hodgkinson et al., 1987; Wesner, Scheftner, Palmer, Crowe, & Winokur, 1990). In a separate DNA marker study, Mendlewicz et al. (1987) presented evidence of linkage of factor 9 on the X chromosome to bipolar illness in selected kindreds. A maximum lod score of 3.10 was obtained at a recombination fraction of .11.

DNA marker studies of affective disorders are new and they await replication. The fact that no replication has been successful suggests that there are

methodological flaws even within the reported DNA marker studies. DNA marker technology should provide a powerful tool to look at the genetics of all mental disorders. As the technology improves, we would hope that the ability to analyze specific areas of the genome will improve to the point that we will be able to find valid genetic markers for all major psychiatric illnesses.

SUMMARY

Affective disorders appear to have a genetic component. Twin, adoption, family, and biological marker studies all provide some evidence to support this idea. Once valid genetic causes for affective disorder are found, the interaction between the environmental and genetic factors can be better understood.

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