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Genetic studies in manic-depressive illness

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Since Kraepelin first delineated manic-depressive illness in 1896, clinical observation has suggested that the disease tends to run in families. Since the late 1920s, studies to define the nature of the genetic component in affective psychoses have mushroomed. The work includes family, twin, and adoption studies, statistical analysis of genetic models, and linkage studies. Although interpretation is hampered by the great variance of diagnostic criteria used in these studies, the research has progressed, particularly during the last 20 years.

Family studies were an early means of evaluating the risk for manic-depressive illness in different classes of family members of affected persons (probands). First-degree relatives, including parents, siblings, and children of probands, have a 7.7 to 11.8 percent risk, compared to the general-population risk of about 0.7 percent. If borderline cases are included, the risks increase by 2 to 3 percent. The risk is also higher—about 2 percent—for second-degree relatives like half-siblings, uncles, aunts, and grandchildren (Fuller and Thompson, 1978).

Several studies have shown that the polarity of manic-depressive illness tends to breed true in a given family. Yet a recent report notes the predominance of unipolar illness in relatives of both unipolar and bipolar probands (Gershon, 1980). The discrepancy may be explained by a difference in diagnostic criteria used to establish polarity. Relatives of bipolar probands also appear to be at greater risk of developing manic-depressive illness than are relatives of unipolar probands. The 1980 study by Angst et al., for example, found affective psychoses and suicides in 12.7 percent of relatives of bipolar probands, compared to only 7.4 percent of relatives of unipolar persons.

Twin studies are a powerful means of sorting out genetic factors in familial disorders. Identical twins have all of their genes in common, whereas fraternal twins and full siblings share only half their genes. On the average, concordance for manic-depressive illness has been noted in 66 percent of identical twin pairs in whom one twin was given this diagnosis, compared to an 18-percent concordance rate in fraternal twin pairs (Willerman, 1979). The concordance for polarity is also high in identical twins. In one study of 32 pairs of identical twins concordant for manic-depressive illness, only seven were discordant for polarity, compared to discordance in five of nine fraternal twin pairs (Fuller and Thompson, 1978).

Adoption studies seek to untangle genetic from environmental effects by evaluating individuals separated at birth from their biologic parents. In one large study, three of eight adoptees (35 percent) born to mothers who had an affective psychosis subsequently developed depressive illness, compared to only 5 percent of the offspring of mothers who had other psychiatric disorders. Another study observed affective disorder in 31 percent of the biologic relatives of adoptees with bipolar affective psychosis, whereas only 2 percent of the biologic relatives of normal adoptees had an affective disorder. The incidence of affective disorder in the adoptive relatives was similar for the two groups. Although the number of persons studied was small, the research strongly suggests the operation of a genetic factor, independent of family environment (Willerman, 1979).

Statistical models of gene transmission are newer and more sophisticated methods of evaluating family data on manic-depressive illness. One such model is that of an autosomal dominant single gene. The model accounts well for the nearly equal risk to parents, siblings, and offspring of affected individuals and for the difference in risks to first-, second-, and third-degree relatives. It does not explain the appreciable gender difference in incidence (the male-to-female ratio is 1.0 to 1.5), since males and females would be expected to be equally affected. The presence of a single dominant gene located on the X chromosome has been proposed also, because high rates of mother-to-son transmission—with father-to-son transmission virtually absent—have been noted in some families (Gershon, 1980). (Fathers donate only Y chromosomes to their sons.) Other studies have, however, noted no absence of father-to-son transmission of manic-depressive illness (Angst et al., 1980).

A third model is that of multifactorial inheritance in which several genes inherited from both parents interact with environmental factors to produce the manic-

depressive phenotype. These genetic and environmental factors are combined into a single continuous variable called liability. Recent analyses indicate that manic-depressive illness may be determined by multiple levels of liability, subdividing affected individuals into severe and mild categories (Gershon, 1980). Those in the severe category have a higher liability level and manifest biopolar illness. Despite these results, no tested exhibit unipolar illness. Despite these results, no tested model of genetic transmission consistently fits the data from different research centers, suggesting that different genetic subtypes exist.

Linkage studies have been used recently to sort out this heterogeneity. A disease exhibits linkage when it is transmitted from parent to child together with a genetic marker like color blindness or white blood-cell antigens. Several studies of families who exhibit bipolar manic-depressive illness and no father-to-son transmission have suggested linkage of affective illness to X chromosome markers including Protan and Deutan color blindness, the blood-group antigen Xg, or the red blood-cell enzyme G6PD (Gershon, 1980). Other studies have failed to show such linkages. Still other research has demonstrated association of biopolar illness with human leukocyte antigen (HLA), whose genetic loci are on the short arm of chromosome 6 (Weitcamp et al., 1981). Although some of these studies lack statistical significance, the method promises to be useful, especially as more markers are identified.

An ever-growing body of knowledge suggests and further delineates the nature of the genetic component of manic-depressive illness. The knowledge will contribute significantly, not only to risk-counseling of relatives of affected persons, but also to diagnostic accuracy and treatment.

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