Evidence for X-Linkage in the Transmission of Manic-Depressive Illness

Julien Mendlewicz, MD; Joseph L. Fleiss, PhD; and Ronald R. Fieve, MD

Seven families were found in which manic-depressive illness and either protan or deutan color blindness (X-linked recessive traits) occurred in successive generations. In these seven families, as well as in two others previously reported in the literature, detailed analysis suggests that the genetic loci for manic-depressive illness and the two kinds of color-blindness may be located on the same chromosome. A dominant X-linked gene may thus be involved in the pathogenesis of manic-depressive illness.

Hereditity has been shown to be an important contributing factor in the etiology of manic-depressive illness. The mode of transmission, however, is still unknown, the main controversy being between polygenic and single-gene inheritance. Slater et al and Perris studied the progenitors of manic-depressive patients and found evidence for polygenic inheritance. Rosanoff et al, on the basis of twin studies, proposed that two dominant genes, one X-linked, were involved in the transmission of manic-depressive illness. Reich et al and Winokur et al, on the basis of linkage studies in two large families, also suggested the presence of an X-linked factor in the transmission of manic-depressive illness. Here we report the results of linkage studies in seven additional families.

Subjects and Methods

In the present study we describe seven families in which manic-depressive illness and either protan or deutan color blindness (recessive X-linked traits) occurred in successive generations. The index cases (proband or propositus) were all from a sample of more than 80 carefully diagnosed manic-depressive patients consecutively admitted during an 18-month period to the Lithium Treatment and Research Clinic at the New York State Psychiatric Institute.

All patients as well as their spouses and their available first-degree (sibs, parents, and offspring), second-degree (aunts, uncles, grandparents) and third-degree (more distant) relatives on both the maternal and paternal sides were personally examined for color blindness and psychopathology.

Manic-depressive illness, like any phenotypic (ie, outwardly observable) entity, may be influenced in its clinical manifestations by environmental factors. Thus, within given families sharing the genotype for manic-depressive illness, a predisposed individual can, depending on his internal and external environment, develop either depression alone (unipolar illness) or manic-depression (bipolar illness). Even though a number of studies have indicated that unipolar and bipolar affective illness may be genetically different, most of them have found a higher than expected prevalence of unipolar illness in the relatives of bipolar probands. Furthermore, Zerbin-Rudin, in a review of twin studies published in the literature, showed that a high proportion of pairs of monozygotic twins, both of whom had an affective illness, were such that one member suffered from unipolar illness and the other from bipolar illness.

These findings might be explained by one's environment or personality affecting the outward expressivity of the bipolar genotype, and suggest that unipolar relatives of bipolar probands might have the bipolar genotype. Our assumption is, therefore, that, within a family unit identified by a bipolar proband, bipolar illness and unipolar illness are genetically related and express the same genotype.

The diagnosis of bipolar illness in probands was made separately by two investigators using criteria similar to those of Leonhard et al, Perris, and Winokur et al. A clinical semi-structured interview was used for the evaluation of current psychopathology and history in probands and relatives. Bipolar depression was diagnosed in probands and relatives who had a history of clear-cut manic behavior and of depressive episodes severe enough to require treatment or hospitalization, or to cause a disruption in everyday activities for at least three weeks. Periodicity of illness with symptom-free intervals was among the criteria used for the diagnosis of bipolar illness. This diagnosis

From the departments of medical genetics and internal medicine (Dr. Mendlewicz), the Department of Internal Medicine (Metabolic Unit and Lithium Clinic) (Dr. Fleiss), New York State Psychiatric Institute; the Biometrics Research Unit, New York State Department of Mental Hygiene (Dr. Fleiss); and the College of Physicians and Surgeons, Columbia University, New York. Dr. Mendlewicz is on leave from the Brugmann Psychiatric Institute, University of Brussels.

Reprint requests to 722 West 168th St, New York 10032 (Dr. Mendlewicz).
was made, when deemed clinically appropriate, irrespective of the subject's age.

For the purposes of this study, unipolar depression was diagnosed in individuals who had never experienced mania or hypomania but had experienced one or more depressive episodes severe enough to require treatment or hospitalization. In order to exclude possible schizophrenics, a firm diagnosis of unipolar illness was made only if the subject was at least 40 years of age. For both bipolar and unipolar illness, there had to be no personality disintegration before or following psychotic episodes, and no other preexisting psychiatric or medical disease which might be associated with an affective symptomatology.

The family study method (ie, personal interview with the relatives) was used because this method has been proved to be more reliable than the family history method (ie, family history data collected from the proband). Pertinent medical and social records for probands and relatives were used when available. The material also reflects information on unavailable relatives gained from recollections of subjects who were interviewed. This information has been used in three families (families 2, 4, and 7 described here).

A standard illumination source was used to test for color vision. Two methods were used for testing color-vision anomalies, the Hardy-Rand-Rittler test, ed 2,13 and the Farnsworth-Munsell 100-Hue Test.16 These tests of color vision were always performed after the psychiatric evaluations in order to reduce the possibility of bias entering into the psychological assessments.

Four of the seven families to be described (families 3, 4, 5, and 7) were identified by a male proband who was color-blind, and one (6) by a female proband who exhibited signs of color blindness. In the remaining two (families 1 and 2) the probands were female with normal color vision, and color blindness was detected in their male relatives as a result of our routine examination of all available relatives.

Statistical Methods

The study of the genetic linkage between pairs of traits is complicated by the phenomenon of crossing over. The 22 human autosomes (nonsex chromosomes) as well as the female X-chromosome occur in pairs. Suppose that a female subject carries on one of her X-chromosomes the genetic alleles A and B, and that she carries on the other X-chromosome the alleles a and b. A and a represent the dominant and recessive alleles for one trait, B and b represent those for the other trait.

Each of the female subject's ova has only one X-chromosome. During the process of meiosis, some material from one X-chromosome may be exchanged for material from the other (ie, crossing over may occur). Thus, whereas the majority of her ova will have X-chromosomes with alleles AB or ab, some will have X-chromosomes with alleles Ab and some with alleles aB.

The relative frequency of "recombinants," ie, of offspring exhibiting crossing over, is a function of the distance between the two loci: the closer the loci, the more unlikely, on the basis of the laws of probability,17 is recombination to occur. Linkage between pairs of traits is, in fact, usually assessed by estimating the relative frequency of recombinants to nonrecombinants (technically, the "recombination fraction," denoted \( \theta \)). The minimum value of \( \theta \) is zero, which indicates that the loci for the two traits coincide. The maximum value is .50, which indicates either that the loci for the two traits are on opposite ends of the same chromosome or that they are on two different chromosomes. The closer the value of \( \theta \) is to zero, the stronger the evidence is for linkage. Edwards18 presents tables which facilitate the estimation of \( \theta \), and gives formulas for its standard error which permit the construction of a confidence interval for \( \theta \). If this interval fails to include the value \( \theta = .50 \), the inference may be drawn that \( \theta \) is significantly less than .50; ie, that the loci for the two traits are linked.

Results

Protein Color-Blindness.—Family 1.—The proband, II-2, has two sons. One of them, III-1, is color-blind and has been hospitalized for depression. The proband's other son, III-2, is neither color-blind nor depressed. Because III-1 is too young (80 years old) to be given a definite diagnosis of unipolar depression, we consider III-1 to be a recombinant and III-2 to be a nonrecombinant. Considering III-1 as a recombinant underestimates the degree of linkage between the illness and protein color blindness.

Family 2.—The proband has a first cousin, III-1, who is color-blind and has bipolar depression. He is considered to be a nonrecombinant because his maternal grandfather, I-1, was color-blind and had been hospitalized several times for depression.

Family 3.—The proband, III-2, is considered a definite nonrecombinant. His mother, II-2, is depressed and a carrier of color blindness, and his maternal grandfather, I-1, is manic-depressive and color-blind.

Family 4.—The proband's brother, III-1, is neither color-blind nor depressed. The mother's brother, II-1, was recollected to be color-blind and had been treated as an outpatient for depression. The proband and his brother are counted as two nonrecombinants.

The detailed mathematical analysis of the information from these four families, as well as of the information from the Alger family studied by Winokur et al,14 is available from the authors. Table 1 summarizes the results. The estimate of the recombin-

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### Table 1

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*Estimated recombination fraction, \( \theta = .11; \) standard error = .08.

### Table 2

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*Estimated recombination fraction, \( \theta = .19; \) standard error = .10.
tion fraction \( \theta \) is .11, with a standard error of .08. A 95% confidence interval for the recombination fraction is \( \theta \leq .24 \). Close linkage is therefore indicated between the loci for protan color-blindness and manic-depressive illness. Even closer linkage (estimated \( \theta = .0 \)) would have been inferred had we considered individual III-1 in family 1 to be definitely a unipolar depressive.

Two individuals used in this analysis, III-2 in family 1 and III-1 in family 4, are symptom-free but are still young enough that the likelihood of a future affective illness cannot be ruled out. A third, III-1 in family 1, has an uncertain diagnosis of unipolar depression. We therefore reanalyzed the data by considering each possible pattern of future disease occurrence, nonoccurrence, or change in diagnosis. Statistically significant linkage was confirmed by the reanalyses.

Deutan Color Blindness.—Family 5.—The proband, III-2, is manic-depressive and color-blind. His brother, III-3, is not color-blind but has been hospitalized for depression. III-3 is too young (29) to be diagnosed a definite unipolar depressive, however. Their maternal uncle, II-1, is color-blind but not affectively ill. If II-1 is himself a nonrecombinant, we may count III-2 and III-3 as two recombinants.

Family 6.—The proband, III-1, has mildly impaired color vision, having exhibited some signs of deutan color blindness on separate examinations of both eyes. One of her brothers, III-2, has bipolar depression but is not color-blind. The proband’s maternal grandfather, I-2, is manic-depressive.
and color-blind, implying that III-1 is a nonrecombinant and that III-2 is a recombinant. The proband's younger brother, III-3, is color-blind but too young (14) to be informative about affective illness.

Family 7.—Two portions of this pedigree are informative. The proband, III-6, has both an affective illness and color blindness, as do two of his brothers, III-2 and III-5. Because the proband's other living brother, III-1, is neither depressed nor color-blind, members III-1, III-2, III-5, and III-6 are counted as four nonrecombinants. Their mother, II-2, was recollected by her children to have been treated several times as an outpatient for depression. The proband's cousins, III-7, III-8, and III-9, are also informative. Their mother, II-3, had bipolar depression (she had been hospitalized for mania) and was obviously a carrier of deutan color blindness. Because III-7 is both manic-depressive and color-blind, and because III-8 and III-9 are neither depressed nor color-blind, these three are counted as three nonrecombinants.

The detailed analysis of the information from these three families, as well as of the information from the Calvert family studied by Reich et al., is available from the authors. Table 2 summarizes the results. The estimate of the recombination fraction $\theta$ is .19, with a standard error of .10. A 95% confidence interval is $\theta \pm .35$. The evidence for linkage between the loci for manic-depressive illness and deutan color blindness is, therefore, statistically significant, although not quite as strong as for linkage between the loci for the illness and protan color blindness. Had we considered individual III-3 in family 5 to be a certain case of affective illness, the estimated linkage would have been even closer (estimated $\theta = .12$).

Seven individuals used in the analysis, including two from the Calvert family, are symptom-free, but not yet past the age of risk of an affective illness. The diagnosis of affective illness for an eighth individual, III-8 in family 5, is an uncertain one. Reanalysis of all possible $2^8 = 256$ patterns of future disease occurrence or change in diagnosis confirmed the finding of statistically significant linkage between the loci for manic-depressive illness and for deutan color blindness.

Examining all seven pedigrees, we see that the transmission of manic-depressive illness fits the model of dominant inheritance: the illness occurs in successive generations, and all heterozygous women (who carry one dominant allele for the illness) are affected.

Comment

We have reported previously on differences in course of illness and response to lithium maintenance therapy between manic-depressive patients with and without a family history of the illness. Specifically, patients with a family history have an earlier age of onset, run a more severe course of illness, and show a greater response to long-term lithium therapy.

These and other family studies have not, however, been able to establish whether the transmission of the illness is via purely environmental factors associated with having an ill relative within one's family, or whether it is genetic in origin. Our present results suggest that, within the families described, the transmission is genetic.

Specifically, close and statistically significant linkage was found between the locus for manic-depressive illness and the loci for both of the X-linked genetic markers studied. Perris has cast doubt on the hypothesis of X-linkage because some affected fathers have affected sons, a finding inconsistent with X-linked inheritance. However, the presence of undetected affective illness on the mother's side of the family might explain the apparent father-son transmission.

Another factor which might account for previous contradictory findings in the genetic characterization of manic-depressive patients is genetic heterogeneity. That is, there may be more than a single variant allele at one locus; there may be an involvement of different alleles and different loci; or there may be polygenic inheritance. None of these models can be ruled out by our data.

In any event, results from several informative families, seven from our population and two from Winokur's group, support the presence of a dominant X-linked gene in the transmission of manic-depressive illness.

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References