Recent Genetic Studies of Bipolar and Unipolar Depression

David L. Dunner

Essential Papers on Depression
Recent Genetic Studies of Bipolar and Unipolar Depression

David L. Dunner
e-Book 2018 International Psychotherapy Institute

From *Essential Papers on Depression* edited by James C. Coyne

All Rights Reserved

Created in the United States of America

Copyright © 1985 by James C. Coyne
Recent Genetic Studies of Bipolar and Unipolar Depression

David L. Dunner

Classifying depressed patients into bipolar and unipolar subtypes was first proposed in 1962 by Leonhard et al., based on the clinical differentiation of depressed patients with and without mania. (Leonhard et al., 1962) Family history studies noted that patients with bipolar illness had more psychosis and suicide among their relatives than patients with unipolar illness. Since 1962, several studies in Europe and the United States have refined and extended this original observation. More importantly, a model for investigation in psychiatry has been developed to the point that genetic data are important for validating clinical diagnosis in psychiatry,
particularly among the affective disorders.

This chapter will review data supporting evidence for genetic factors in the etiology of affective disorders, the development of methodology for genetic studies, and the resulting classification systems. We will highlight data from three recently completed large American studies of the genetics of bipolar and unipolar depression. We will review the current status of biological markers for affective disorders and finally present some areas of interest for future research.

**EVIDENCE FOR GENETIC FACTORS**

Several lines of evidence suggest that some forms of depression may have an etiology on a genetic basis. In order for a genetic etiology to be proven, several factors should be evident. First of all, the disorder should cluster within families; patients with the illness should have relatives who
also demonstrate the illness. Second, studies of twins should show that the illness is more prevalent among monozygotic than dizygotic twins. A third line of evidence would come from adoption studies. Adoption studies are designed to differentiate environmental from genetic factors. Data from such studies should reveal that subjects who have a biological parent with illness but who were raised in a foster home develop the illness nevertheless; whereas subjects whose biological parents do not have the illness but who were raised in a home where there is affective disorder, do not develop affective disorder in excess of controls. Fourth, the illness could be shown to be linked to a gene of known Mendelian transmission.

Affective disorders, particularly manic-depressive illness, are familial. The evidence that bipolar illness clusters in families was reported by Leonhard et al. (1962). Perris and Angst both
suggested that affectively ill relatives of bipolar patients tended to have bipolar and not unipolar disorders, whereas affectively ill relatives of unipolar patients tended to have unipolar illness and not bipolar illness (Perris, 1966; Angst, 1966). In the 1960s the Washington University group published a series of familial studies in manic-depressive illness, particularly bipolar disorders (Clayton et al., 1965; Winokur et al., 1969). These studies showed a high familial risk for affective disorder in relatives of manic patients. Second, a very comprehensive family study of affective disorder suggested that manic-depressive illness may be linked to a gene transmitted on the X-chromosome (Winokur et al., 1969), subsequent studies in the late 1960s from the National Institute of Mental Health (NIMH) also showed a differential familial loading for relatives of patients with bipolar compared with unipolar
disorders (Dunner et al., 1976). Relatives of bipolar patients had elevated morbid risks for bipolar illness, unipolar illness, and suicide, compared to relatives with unipolar patients.

Few twin studies of affective disorder appear in the literature of the last 10 years or so. Kallmann's study is still considered the definitive work, showing very high concordance rates for bipolar illness in monozygotic compared to dizygotic twins (Kallmann, 1954).

The adoption technique, utilized in the Danish studies of schizophrenia, has been tried in studies of bipolar illness. Data from adoptees in Iowa indicated that primary affective illness may have a familial factor (Cadoret, 1978). Another study of adoptees from manic-depressives also supports the concept of a genetic factor in the etiology of affective disorders (Mendlewicz & Rainer, 1977).
In the search for genetic linkage of affective disorders, the studies of Winokur et al. (1969) pointed toward a genetic factor on the X-chromosome. Attempts to extend and replicate these findings have resulted in considerable controversy. Mendlewicz and coworkers showed linkage of bipolar affective disorder with two markers on the X-chromosome, color blindness, and XG blood type (Mendlewicz et al., 1972; Mendlewicz & Fleiss) Gershon et al. were unable to replicate these findings and subsequently criticized the data from the Mendlewicz studies on methodological grounds (Gershon et al., 1979; Gershon, 1980).

In summary, the separation of bipolar affective disorder as a distinct subtype has resulted in a clearer definition of the genetic factors that may be involved in the etiology of affective disorders. Most studies attempting to assess genetic factors
in affective illness that have separately considered bipolar patients have resulted in positive results. The relatives of bipolar patients show a higher genetic loading and particularly more bipolar illness than relatives of other affectively ill patients. Clearly, unipolar illness as presently defined is a much more heterogeneous collection of disorders than bipolar disorder. Attempts to find subtypes of unipolar disorder using a genetic classification have not been particularly successful. However, Winokur's group separated unipolar patients into women with an early age of onset (depressive spectrum disease) whose relatives showed depression and alcoholism, and depressed men with a late age of onset (pure depressive disease) whose relatives showed depression only (Baker et al, 1971).

METHODOLOGY FOR FAMILY STUDIES
The renewed interest in the genetics of bipolar and unipolar depression in the late 1960s and the interest in defining these disorders led to several family studies in the 1970s. The simplest method, the so-called family history method, was to ask patients about illness in their relatives. This tends to underestimate illness in relatives. An interview (Schedule for Affective Disorders and Schizophrenia—SADS) developed early in the 1970s was used to document illness in relatives (Endicott & Spitzer, 1978). Interviewing relatives directly (the “family study” method) led to greater precision regarding the diagnosis of illness in relatives. In a refinement of this technique, relatives are interviewed blind to the proband diagnosis in order to decrease investigator bias. Most of the recent genetic studies conducted in the United States employed a blind family study method, wherein relatives were interviewed with
a standardized instrument with the interviewer unaware whether the person being interviewed was the patient, relative, or a control.

CLASSIFICATION OF AFFECTIVE DISORDER

Early genetic studies supporting the separation of bipolar from unipolar patients were based on studying families of patients who had been hospitalized for affective disorders. For the most part, patients considered bipolar manic-depressive had been hospitalized for at least one manic episode, whereas patients considered unipolar had at least one episode of depression. In the Perris study (1966), three episodes of depression were required for a patient to be called unipolar. In 1970 we proposed a classification for affective disorder (Dunner et al.). Knowing that some depressions occur in the course of other psychiatric disorders and thus might be viewed as
complications of these primary disorders, we required that patients have a primary affective disorder according to the criteria of Feighner et al. (1972) In reviewing the patients in our sample it was apparent that two groups of patients had manic symptoms. One group of patients had manic symptoms resulting in hospitalization specifically for mania; these patients were termed Bipolar I. These patients were congruent with prior American and European genetic studies of affective disorders by Perris (1966), Angst (1966), and Winokur (Clayton et al., 1965; Winokur et al., 1969). However, there remained a group of patients who had manic symptoms that did not result in hospitalization specifically for mania. These patients had depressions requiring hospitalization and hypomania; we classified them separately from other unipolar and bipolar patients and termed them Bipolar II. It is likely
that many other studies of affective disorders had included such Bipolar II patients as unipolar.

We later extended this classification to include subjects who had never been hospitalized for affective disorder but who had received outpatient treatment (Fieve & Dunner, 1975). Thus our classification system proposed that bipolar patients might be separable into four types: Bipolar I, subjects who have been hospitalized specifically for mania; Bipolar II, subjects with depression and hypomania who had been hospitalized specifically for depression; Bipolar Other, those who had depression and hypomania and who had received outpatient treatment for affective disorder; and a group we term Cyclothymic Personality, referring to subjects who had bipolar affective symptoms but who had not been treated. For Unipolar patients we required at least on depressive episode that met criteria for
primary affective disorder and that resulted in either hospitalization or treatment for depression.

The group termed Bipolar I seems to be relatively homogeneous when data from clinical, biological, pharmacological, and genetic studies are evaluated (Dunner, 1980). Bipolar II patients tend to have the clinical appearance of unipolar patients but tend to be pharmacologically and biologically similar to Bipolar I patients. The Bipolar Other group seems to be congruent with Akiskal’s cyclothymic patients (Akiskal, 1977). Subsequent studies suggest that Bipolar I subjects may well be indistinguishable from Bipolar II subjects (Dunner et al., 1985). In our classification system the group termed Cyclothymic Personality was reserved for diagnosing relatives of subjects in our genetic studies.

The classification system is not entirely
congruent with *DSM III*. The bipolar affective disorder of *DSM III* would include most Bipolar I patients, some Bipolar II patients, and some patients whom we term Bipolar Other. Approximately a third of patients we classified as Bipolar I had mood incongruent delusions and would be Atypical Bipolar disorder or Atypical Psychosis in *DSM III* (Rosenthal et al., 1980). Furthermore, although the term Atypical Bipolar disorder specifically mentions Bipolar II illness, many Bipolar II patients will meet *DSM III* criteria for bipolar affective disorder. The group classified as Cyclothymic disorder in *DSM III* is seemingly not congruent with our Bipolar Other or Akiskal’s Cyclothymic disorder in that such patients meet criteria for more severe disorders in the *DSM III* nomenclature (Akiskal, 1977). The group we considered Unipolar disorder meets the *DSM III* criteria for major affective disorder. However,
major affective disorder in *DSM III* includes both primary and secondary depressions and thus represents a population of depressed patients of greater heterogeneity than we had proposed and studied. *DSM III* will be the standard for diagnosis of the 1980s, but the clinical and genetic studies of the 1970s used slightly different concepts of affective subtypes.

**RECENT FAMILY STUDIES OF BIPOLAR AND UNIPOLAR DEPRESSION**

Three large American studies of the genetics of affective disorders have been recently reported. The New York study was a prospective investigation of approximately 400 patients who met criteria for Bipolar I, Bipolar II, and Unipolar disorders (Dunner et al., 1980). Diagnosis of the probands was confirmed by SADS-L interviews of about 90% of the living relatives available for interview. Diagnosis of relatives was blind to
proband diagnosis and confined to data form the SADS-L. Morbid risks, calculated according to the method of Stromgren, used ages at risk from the New York clinic population. Data regarding ages at risk are presented for first degree relatives age 18 and older. These data were available for approximately 2,000 first degree relatives.

The NIMH sample was also a prospective study consisting of 171 probands separated into Bipolar I, Bipolar II, and Unipolar types (Gershon et al., 1980). Eleven patients termed schizoaffective were also included. Probands had been hospitalized on the research wards of the NIMH and relatives of these subjects were given a structured interview. Data were available for approximately 1,000 first degree relatives.

The Iowa study was a retrospectively obtained sample of 100 bipolar patients, 225 unipolar
patients, and 160 surgical controls (Tsuang et al., 1980). Patients had been hospitalized at the Iowa Psychopathic Hospital 30 to 40 years ago. Approximately 1,600 first degree relatives of these subjects were evaluated blind to proband diagnosis using a structured interview similar to the SADS. In contrast to the New York and NIMH samples, most of the relatives of the Iowa sample who were actually interviewed were siblings and children because the probands' parents were for the most part deceased. Furthermore, the Iowa group did not separate probands into Bipolar I and Bipolar II types, although it could be assumed that most of their bipolar probands were Bipolar I.

Results of these studies are summarized in Table 1. In general, the risk for a first degree relative to have an affective disorder is approximately 15-20%. Second, there is a general consistency in these three studies in that an
increased morbid risk for mania (Bipolar I illness) is shown for relatives of Bipolar I patients as compared to relatives of Unipolar patients. Third, the risk for Unipolar illness exceeds that for bipolar illness in relatives of bipolar patients. Additionally, relatives of bipolar patients generally have about the same rate of unipolar illness as relatives of unipolar patients.
Table 1. Morbid Risk of Affective Disorder in Relatives of Bipolar and Unipolar Patients

<table>
<thead>
<tr>
<th>Patient Diagnosis</th>
<th>Relative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bipolar I</td>
</tr>
<tr>
<td>New York BPI</td>
<td>2.8</td>
</tr>
<tr>
<td>BPII</td>
<td>.8</td>
</tr>
<tr>
<td>UP</td>
<td>.2</td>
</tr>
<tr>
<td>NIMH BPI</td>
<td>3.5</td>
</tr>
<tr>
<td>BPII</td>
<td>2.1</td>
</tr>
<tr>
<td>UP</td>
<td>1.2</td>
</tr>
<tr>
<td>Iowa BPI</td>
<td>5.3</td>
</tr>
<tr>
<td>UP</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Note: Data are morbid risk (%). Morbid risks were calculated by dividing the number of ill subjects by the total number of subjects after the latter were corrected for age of risk for the various disorders.

The Iowa study did not provide a separate comparison of relatives of Bipolar II subjects. In the New York and NIMH data, relatives of Bipolar II patients tend to have an excess of bipolar illness (types I and II) compared to relatives of unipolar patients. This rate of bipolar illness approximates the combined rate of bipolar illness for relatives of Bipolar I patients.
Certain methodological differences in these studies should be noted. The New York study was entirely prospective and was based on an outpatient sample who came to three outpatient research centers. Criteria for determining that a relative was ill required that the relative have treatment or hospitalization for psychiatric illness. The NIMH sample was derived from an inpatient population. Criteria for illness in relatives included illness causing social disability in addition to treatment and hospitalization. This may explain why the rates for affective illness in the NIMH sample are slightly higher than the New York sample. For the Iowa sample, the probands were obtained retrospectively and the data reported were for those relatives actually interviewed or for whom medical charts were available to indicate psychiatric disorder. Thus, whereas the data in the New York and NIMH samples are for all
relatives, the data for the Iowa sample pertain to only approximately 40% of the total number of relatives because many were deceased.

In spite of these methodological differences, the three studies provide a strong data base for an understanding of the genetic contributions to bipolar and unipolar affective disorder. Approximately 400 bipolar probands were studied and the data reflect an analysis of approximately 3,000 first degree relatives. These data clearly demonstrate an increased morbid risk for mania among relatives of manic depressive patients.

Attempts to analyze the genetic data from the New York sample for chromosomal linkage using a Mendelian model were not positive. It should be noted that the hypothesis for an X-linked dominant gene as a major genetic factor in bipolar disorder was not supported by data from the New
York sample. Furthermore, the data from these three studies do not clearly support a specific mode of inheritance for bipolar illness.

**BIOLOGICAL MARKERS**

Research into biological factors associated with affective illness in the 1970s was largely concentrated on attempts to relate biological factors, such as the activities of blood enzymes or concentrations of catecholamine metabolites in cerebrospinal fluid and urine, to depression. The search for biological markers for a genetic disorder should be predicated on the notion of discovering trait rather than state associations. Thus the marker should be present in the well state as well as in the ill state and should be clustered in ill relatives of subjects with the disorder and observed less frequently among well relatives of patients or among controls. Recent
reviews indicate that in general there is no satisfactory marker for bipolar and unipolar affective disorders at this time. Attempts to demonstrate such markers have been extensive over the past 10 years and have produced a strategy for studying relatives of subjects with affective disorder. Not only are standardized interviews used to establish diagnosis, but also blood tests or provocative tests are made to determine if a biological marker is associated with vulnerability to the illness. Some markers that have been studied and found not to be satisfactorily related to affective disorders include the activities of catecholamine metabolizing enzymes, such as monoamine oxidase and catechol-O-methyltransferase. More recently, cholinergic supersensitivity has been suggested as a possible trait marker for affective illness (Sitaram et al., 1980). Further studies of this
system in affectively ill patients are awaited with interest.

**SUGGESTED AREAS FOR FUTURE RESEARCH**

A very pertinent research area for the 1980s is the so-called high risk study wherein children of subjects who have a familial psychiatric disease are studied in order to determine the antecedents of the illness.

The characteristics required for a high risk study include that the disease be familial, such as bipolar manic-depressive illness, and that the proband diagnosis be satisfactory so that the adult probands can be classified in a relatively homogeneous way. The disorder should become clinically evident early in life so that one might have the opportunity of following children into the age of risk. This is particularly true of bipolar disorder, where at least half of the patients have
been hospitalized by the age of 30. A high risk study is dependent on a thoughtful assessment of relevant markers to the illness.

The identification of a trait marker for affective disorder is a goal for research in the 1980s. Bipolar affective disorder is a suitable clinical substrate for such research.


REFERENCES


Fieve RR and Dunner DL. “Unipolar and Bipolar Affective States.” In *The Nature and Treatment of Depression*, edited by Flack FF and Draghi SC. New York: John Wiley


Mendlewicz J, Fleiss JL, and Fieve RR. Evidence for X-linkage


