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ARTICLE

Family, Twin, and Adoption Studies of Bipolar Disorder

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Family, twin, and adoption studies have been essential in defining the genetic epidemiology of bipolar disorder over the past several decades. Family studies have documented that first-degree relatives of affected individuals have an excess risk of the disorder, while twin studies (and to a lesser extent, adoption studies) suggest that genes are largely responsible for this familial aggregation. We review these studies, including the magnitude of familial risk and heritability estimates, efforts to identify familial subtypes of bipolar disorder, and the implications of family/genetic data for validating nosologic boundaries. Taken together, these studies indicate that bipolar disorder is phenotypically and genetically complex. © 2003 Wiley-Liss, Inc.

KEY WORDS: family studies; twin studies; adoption studies; bipolar disorder; genetic epidemiology

INTRODUCTION

Family, twin, and adoption studies represent different approaches to estimating the effect of familial and genetic influences on a disorder. Studies examining the contribution of these influences to bipolar disorder have set the stage for the intensive efforts currently under way to identify specific bipolar disorder susceptibility genes. In addition to defining the genetic epidemiology of the disorder, these studies provide information that may be of great interest to clinicians, patients, and families. For example, family studies can provide empiric estimates of recurrence risk (the probability that a relative of an affected individual will develop the disorder). Bipolar disorder has been among the most extensively studied psychiatric disorders from a familial/genetic standpoint. Despite differences in study methodology, sample ascertainment, and diagnostic conventions, available family, twin, and adoption studies have been consistent overall in documenting that bipolar disorder runs in families and that this familial aggregation is strongly influenced by genes.

A key consideration in interpreting genetic studies (whether they are epidemiologic or molecular) is the impact of phenotype definition. The nature and strength of genetic influences observed may vary substantially depending on how precisely or how broadly the phenotype is defined. Prior to about 1960, the definition of manic depressive illness generally followed Emil Kraepelin's conception, which included syndromes of both mania and depressive episodes as well as recurrent depression alone (see Angst and Marneros [2001] and Baldessarini [2000] for recent reviews of the evolution of the nosology of bipolar disorder). The modern emphasis on distinguishing bipolar from unipolar affective illness is often attributed to Leonhard [1959] and has been incorporated into most studies appearing after 1960. The 1970s saw the development of standardized diagnostic criteria [Feighner et al., 1972; Spitzer et al., 1978], enhancing the reliability and comparability of research diagnoses assigned in different studies. These efforts also led to the elaboration of standardized diagnostic criteria for clinical practice with the publication of Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980 [American Psychiatric Association, 1980] and culminating most recently in the DSM-IV criteria [American Psychiatric Association, 1994]. The latter includes a further evolution of the bipolar phenotype: the distinction between bipolar I disorder (requiring an episode of mania) and bipolar II disorder (in which hypomanic episodes occur along with depressive episodes) [Dunner et al., 1976]. Throughout this historical development, family, twin, and adoption studies have played a key role in testing the validity of nosologic distinctions by examining whether these diagnostic categories are themselves familial and heritable.

In this article, we will summarize highlights of the extensive literature on the genetic epidemiology of bipolar disorder. The interested reader should also be aware of previous reviews, including Tsuang and Faraone's [1990] comprehensive review of studies published prior to the 1990s. We will focus on studies that have used modern diagnostic definitions, and study methods and review evidence addressing the magnitude of familial and genetic influences on bipolar disorder and putative

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subtypes. We will also examine the implications of family, twin, and adoption data for defining the boundaries of the bipolar phenotype, and briefly consider the clinical implications of familial risk estimates for genetic counseling of patients and families.

FAMILY STUDIES

Family studies attempt to answer the question of whether a disorder of interest aggregates in families. To do this, studies typically compare the prevalence of the disorder among first-degree relatives of affected probands (cases) to the prevalence in the population or among relatives of unaffected probands (controls). (Because younger relatives may not have passed through the period of risk for the disorder, prevalence estimates are typically adjusted to yield more informative age-corrected morbid risks.) A higher morbid risk among relatives of affected probands indicates that the disorder can be familial, but it does not necessarily mean that genes are involved; a disorder may run in families for nongenetic reasons (i.e., because of shared environment). Some family studies compare familial risks in relatives of those affected with one disorder (e.g., bipolar disorder) to relatives of those affected with another disorder (e.g., unipolar disorder); these studies may clarify whether disorders coaggregate in families and may also bear on the validity of diagnostic distinctions between disorders. An important methodologic distinction is that between studies using the family history method (in which relative diagnoses are based on indirect reports of probands or other family members) and direct-interview family studies (in which diagnoses are based primarily on direct reports from interviewed family members). The family history method tends to be less sensitive than the family study method and thus may underestimate the prevalence of disorders in families [Andreasen et al., 1986]. In the following review, we focus on studies that have relied primarily on direct-interview assessments of family members.

Family studies published prior to 1960 did not distinguish between unipolar and bipolar disorders when studying risks of affective illness in families [Tsuang and Faraone, 1990]. Additional methodological limitations included the lack of control groups, structured assessments, standardized diagnostic criteria, and age correction of risk estimates. Despite these shortcomings, as reviewed by Tsuang and Faraone [1990], 13 studies appearing before 1960 were consistent with an increased risk of major mood disorder among relatives of affected probands compared to available estimates of mood disorder risk in the general population.

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Table I summarizes family studies published after 1960 that examined the transmission of bipolar disorder and unipolar disorder separately. Studies that relied only on the family history method are not included. Despite methodologic differences among them, these studies consistently reported excess risks of bipolar disorder among first-degree relatives of bipolar probands. Most of the estimates included in Table I are age-corrected morbid risks. For the uncontrolled studies, the magnitude of risk can be compared to available epidemiologic estimates of population risk (on the order of 0.5–1.0% for bipolar I disorder [Tsuang and Faraone, 1990; Weissman et al., 1996; Kessler et al., 1997]). For the controlled studies, the risks can be directly compared to risks among relatives of controls. Table I also includes risk estimates, when available, for probands and relatives with unipolar disorder. As we discuss later, these estimates are relevant to the familial/genetic relationship between bipolar and unipolar disorder.

The controlled family studies listed in Table I are particularly informative because they are methodologically rigorous (e.g., predominant use of direct, semistructured interviews and diagnoses of relatives blind to proband affection status). The inclusion of a control group can be important to the calibration and interpretation of results for relatives of affected probands. For example, the risk of unipolar disorder among relatives of controls in the studies described below varies up to 10-fold. Thus, while Gershon et al. [1975] found a lower risk of unipolar disorder among relatives of bipolar probands (8.7%) than did Tsuang et al. [1980] (12.4%), the risk relative to controls is substantially higher in the former study (12-fold) than in the latter (2-fold) because of a 10-fold difference in the base rate of unipolar depression among control relatives in the two studies.

In the first of the controlled studies, Gershon et al. [1975] reported a 19-fold greater risk of bipolar disorder (3.8%) and 12.4-fold greater risk of unipolar disorder risks (8.7%) among first-degree relatives of 54 bipolar probands than among relatives of controls (0.2%) in an Israeli sample. Subsequently, Tsuang et al. [1980] reported a family study of probands with schizophrenia, affective disorders and controls that included numerous methodological strengths (direct interviews; blinded, structured assessments; and a best-estimate diagnostic procedure). They observed a nearly 18-fold risk of bipolar disorder among relatives of bipolar probands compared to controls. The risk of bipolar disorder was also significantly elevated among relatives of unipolar probands (10-fold) compared to controls. The risk of unipolar disorder was nonsignificantly elevated in relatives of bipolar probands (12.4% vs. 7.5% for controls) and significantly elevated in relatives of unipolar probands (15.2% vs. 7.5%).

Somewhat different results were observed in a subsequent large, methodologically rigorous family study by Gershon et al. [1982] of five proband groups: bipolar I, bipolar II, schizoaffective, and unipolar disorders and normal controls. First-degree relatives of probands with bipolar I disorder had similar

TABLE I. Morbid Risk Estimates of Bipolar and Unipolar Disorder From Family Studies of Bipolar Disorder

Reference	Proband group	Relatives at risk: bipolar/unipolar	Morbid risk, FDR (%)	
			Bipolar disorder	Unipolar disorder
Uncontrolled Studies				
Perris [1966]	Bipolar	574	10.1	0.5
	Unipolar	684	0.3	6.4
Mendlewicz and Rainer [1974]	Bipolar	606/544	17.7	22.4
Helzer and Winokur [1974]	Bipolar	151	4.6	10.6
James and Chapman [1975]	Bipolar	265	6.4	13.2
Smeraldi et al. [1977]	Bipolar	173	5.7	6.9
	Unipolar	185	1.0	8.1
Johnson and Leeman [1977]	Bipolar	180	15.5	19.8
Petterson [1977]	Bipolar	472	4.4	—
Trzebiatowska-Trzeciak [1977]	Bipolar	289	11.4	0
	Unipolar	256	0.3	7.41
Abrams and Taylor [1980]	Bipolar	47	8.5	6.4
	Unipolar	107	4.7	7.5
Andreasen et al. [1987][a]	Bipolar I	569	3.9[b] (8.1)[c]	22.8
	Bipolar II	267	1.1[b] (9.3)[c]	26.2
	Unipolar	1171	0.6[b] (3.5)[c]	28.4
Pauls et al. [1992]	Bipolar	408	8.7[b] (12.4)[c]	11.6
Grigoroiu-Serbanescu et al. [2001]	Bipolar	867	5.3	—
Controlled Studies				
Gershon et al. [1975]	Bipolar (I and II)	341/264	3.5[b] (3.8)[c]	8.7
	Unipolar	96/77	0[b] (2.1)[c]	14.2
	Controls	518/411	0.2[b] (0.2)[c]	0.7
Tsuang et al. [1980]	Bipolar	169	5.3	12.4
	Unipolar	362	3.0	15.2
	Controls	345	0.3	7.5
Gershon et al. [1982a]	Bipolar I	441/422	4.5[b] (8.6)[c]	14.0
	Bipolar II	157/150	2.6[b] (8.1)[c]	17.3
	Unipolar	138/133	1.5[b] (3.0)[c]	16.6
	Controls	217/208	0[b] (0.5)[c]	5.8
Weissman et al. [1984]	Unipolar[d]	287	0.8[b] (2.0)[c]	18.4
	Controls	521	0.2[b] (1.3)[c]	5.9
Maier et al. [1993]	Bipolar	389	7.0	21.9
	Unipolar	697	1.8	21.6
	Unscreened controls	419	1.8	10.6
Heun and Maier [1993]	Screened controls	221	1.0	7.7
Weighted summary estimate[e]	Bipolar	6365/4861	8.7	14.1
	Unipolar	3983/3959	2.2	17.9
	Controls	1822/1706	0.7	5.2

[a]Number at risk and rates not age-corrected.

[b]Risk of bipolar I.

[c]Risk of bipolar I + bipolar II disorder combined.

[d]Includes some probands from Gershon et al. [1982].

[e]Includes bipolar I and II probands independently for studies separating these proband groups. For relatives, morbid risk of bipolar I and II have been combined for studies estimating risk of each subtype. For control estimates derived from the family study of Maier et al. [1993], data from screened controls [Heun and Maier, 1993] rather than unscreened population controls [Maier et al., 1993] were used.

risks of bipolar I (4.5%) and bipolar II disorder (4.1%) compared to risks of 0% and 0.5%, respectively, for relatives of controls. Relatives of probands with bipolar II disorder also had increased risks of bipolar I (2.6%) and bipolar II (4.5%) disorder. Relatives of bipolar I and bipolar II probands had elevated risks of unipolar disorder as well (14.0% and 17.3%, respectively) compared to relatives of controls (5.8%). On the other hand, risk of bipolar disorder was not significantly elevated among relatives of unipolar probands. (In an expanded report, adding probands with unipolar depression and controls ascertained at Yale, Weissman et al. [1984] also found stronger aggregation of bipolar I disorder among relatives of bipolar probands than among those with depression.) Gershon et al. [1982] also estimated the risk of affective illness (including bipolar, unipolar, or schizoaffective disorder) among offspring and found a significantly higher risk if two parents have affective illness (74%) than if only one parent is affected (27%). Finally, these authors report age-corrected risks of illness in second-degree relatives (aunts, uncles, and grandparents) of affected individuals. Although the quality of the data for second-degree relatives was not as strong as for first-degree relatives, these estimates suggest that risks are comparable to population risks, i.e., 0.4–1.1% risk of bipolar I or II disorder and 3.6–5.4% risk of unipolar disorder among relatives of bipolar probands. The absence of elevated risks of these disorders among second-degree relatives was also observed in an earlier study [Smeraldi et al., 1977].

First-degree relatives of probands with bipolar I disorder had similar risks of bipolar I and bipolar II disorder compared to risks of 0% and 0.5%, respectively, for relatives of controls.

Finally, Maier et al. [1993] conducted a family study of psychotic and affective disorders in a German sample. Consistent with previous studies, they observed a significantly increased risk of bipolar disorder in relatives of bipolar probands but not relatives of unipolar probands, while the risk of unipolar disorder was increased in relatives of both proband groups. This study is additionally of interest because the general population controls were not screened for psychiatric illness. Thus, the risk of illness in these probands and their relatives should approximate that of the underlying population. An estimate of the recurrence risk ratio (sometimes referred to as λ_1)—the ratio comparing risk of disorder among first-degree relatives of affected individuals to the population risk of the disorder—could therefore be made (with precision limited by the sample size). The prevalence of illness in control families suggests a λ_1 of 4 for bipolar disorder and 2 for unipolar disorder. Using the weighted average of risk estimates from the controlled studies in Table I, relatives of bipolar probands have a 10-fold excess risk of bipolar disorder compared to relatives of controls and a 2.96-fold risk of unipolar disorder.

Overall, a summary estimate of morbid risk based on the studies listed in Table I, weighting studies by the number of relatives at risk, indicates that the recurrence risk of bipolar disorder for first-degree relatives of bipolar probands is 8.7%, while the risk for unipolar depression is 14.1%.

CLINICAL MARKERS OF FAMILIAL RISK

Several studies have examined clinical features that might be associated with greater familiality of bipolar disorder. Overall, family studies have not found evidence that risk of mood disorder in relatives of bipolar probands varies with sex of the proband or relative [Gershon et al., 1982; Faraone et al., 1987; Rice et al., 1987; Pauls et al., 1992]. On the other hand, earlier-onset bipolar disorder in probands has been associated with greater familial risk of mood disorder in several studies that used age cutoff points of 20 years [Pauls et al., 1992], 25 years [Grigoroiu-Serbanescu et al., 2001; Somanath et al., 2002], 30 years [James, 1977; Taylor and Abrams, 1981], or even 50 years old [Angst et al., 1980]. In addition, there is evidence that pediatric bipolar disorder may represent a distinct form of the disorder, and that it may be genetically related to disruptive behavior disorders, particularly attention-deficit/hyperactivity disorder [Spencer et al., 2001; Todd, 2002]. In general, early-onset disorder may represent a more severe subtype with stronger genetic loading [Schurhoff et al., 2000]. In a study of adolescent bipolar probands, Strober et al. [1988] found that those with prepubertal onset of psychopathology had a poorer response to lithium treatment and their first-degree relatives had fourfold greater risk (29.4%) of bipolar disorder than relatives of probands with adolescent-onset bipolar disorder (7.4%). In the large NIMH Collaborative Program on the Psychobiology of Depression, Rice et al. [1987] also observed an increase in familial risk with early-onset disorder, even controlling for a cohort effect in which more recent birth cohorts were associated with an earlier age of onset. In a segregation analysis, they found evidence supporting the possibility of a single major locus when an age of onset effect was included. This is consistent with findings from a recent study of Romanian families in which the risk of bipolar disorder in first-degree relatives of probands with early-onset disorder (age ≤ 25) was significantly greater

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(9.4%) than the risk to relatives of later-onset probands (5.5%), and segregation analysis suggested different modes of illness transmission in the two subtypes, with evidence for a major gene effect in the early-onset families.

A number of investigators have examined the possibility that response to antimanic medication, specifically lithium, might provide a basis for identifying familial subtypes of bipolar disorder. Studies examining the relationship between familial loading for bipolar disorder and lithium responsiveness have had mixed results with some finding better response among patients with a positive family history [Mendlewicz et al., 1973; Smeraldi et al., 1984; Grof et al., 1994] while others have found no significant relationship or even an inverse relationship [Engstrom et al., 1997; Coryell et al., 2000]. However, using a stringent definition requiring years of no bipolar disorder episodes in patients who had multiple episodes prior to lithium prophylaxis, Alda et al. [1994, 1997] have observed familial clustering of lithium responsiveness and report segregation analyses consistent with single major gene transmission [Grof et al., 2002].

The existence of other putative familial subtypes of bipolar disorder have been supported by recent family studies. In an analysis of multiplex families with bipolar spectrum disorders, Potash et al. [2001, 2003] found that a history of psychotic bipolar disorder (with hallucinations and delusions) in probands conferred increased risk of bipolar disorder among relatives; furthermore, psychotic bipolar disorder itself clustered in families of probands with psychotic bipolar disorder, suggesting that this phenotype may breed true to some extent. Degree of psychosis also appeared to be familial in another sample of families ascertained for linkage studies of bipolar disorder [Omahony et al., 2002].

A subtype of bipolar disorder comorbid with panic disorder has also been proposed; data from independent family sets suggest that risk for panic disorder in families segregating bipolar disorder is a familial trait [MacKinnon et al., 1997, 2002]. Another recent analysis [Jones and Craddock, 2002] suggests that puerperal manic or hypomanic episodes may confer increased familial risk of bipolar disorder. The effort to identify familial subtypes is important for molecular genetic studies of bipolar disorder. Given the complexity and heterogeneity of the bipolar disorder phenotype, delineation of more genetically homogeneous subtypes might significantly enhance the power to detect susceptibility loci relevant to the disorder. Linkage and association analyses using this strategy have focused on lithium-responsive bipolar disorder and are illustrated by a report linking this phenotype to a locus on chromosome 15q [Turecki et al., 2001]. The subtyping of bipolar disorder on the basis of comorbid panic disorder has also had utility in molecular genetic studies [MacKinnon et al., 1998; Rotondo et al., 2002].

TWIN STUDIES

As we have mentioned, while evidence of familiality supports the possibility that genes influence a disorder, family studies cannot establish the role of genes or estimate the magnitude of their influence. Twin studies, by essentially comparing groups of twin pairs matched for shared environment but differing in degree of genetic relatedness, can help parse genetic and environmental contributions. Twin studies typically compare the concordance rates of a disorder between monozygotic (MZ) twins (who are essentially genetically identical) and dizygotic (DZ) twins (who share on average half of their genes). Assuming that shared environmental influences on MZ twins are not different from environmental influences on DZ twins (the equal environments assumption), significantly higher concordance rates in MZ twins reflect the action of genes. Nevertheless, an MZ concordance rate that is less than 100% means that environmental factors influence the phenotype. Twin studies can also be used to estimate the contribution of genetic and environmental factors to the variance in liability to the disorder [Kendler, 2001]. These are often partitioned into three components: additive genetic influences, shared familial environment (e.g., social class during childhood, parents' rearing style), and individual-specific environment (e.g., stressful life events). The heritability of the disorder is an estimate of the proportion of phenotypic variance that can be attributed to genetic influences. Heritability refers to the strength of genetic influences in a population—not a particular individual—and heritability estimates may differ depending on the population studied.

As was the case with family studies, the interpretation of early twin studies of bipolar disorder is complicated by methodological shortcomings (including lack of blinded and structured assessments and lack of specificity in diagnostic procedures). These early studies were comprehensively reviewed by Tsuang and Faraone [1990], who summarized the concordance rates and derived heritability estimates where possible from the data provided in these studies. Because many of these studies did not distinguish bipolar from unipolar mood disorders, the summary measures reported by Tsuang and Faraone [1990] refer to the composite phenotype of mood disorder. Combining the results of 11 twin studies published between 1928 and 1986, comprising 195 MZ pairs and 255 same-sex DZ pairs, they report a proband-wise concordance rate of 78% for MZ twins and 29% for DZ pairs. The summary estimate of heritability was 63%. In the largest and most informative of these studies, Bertelsen et al. [1977] ascertained, from the Danish Psychiatric Twin Register, 55 MZ and 52 DZ twin pairs in which the proband had been psychiatrically hospitalized and was diagnosed with manic depressive disorder. Although diagnostic interviews were unstructured and not blinded, the diagnosis of manic depressive disorder involved recurrent, episodic disorders of mood (including both bipolar and unipolar cases). The proband-wise concordance rate for MZ twins (67%) was significantly greater than that observed for DZ twins (20%). Similar differences were observed when the analysis was restricted to bipolar/bipolar twin pairs (62% vs. 8%).

Kendler et al. [1993] reported a study of 486 twin pairs ascertained through either the Swedish Psychiatric Twin Register (probands hospitalized for affective illness) or the population-based Swedish Twin Registry. DSM-III-R diagnoses were made using a self-report questionnaire containing sections of the Structured Clinical Interview for DSM-III-R for mania and major depression. Bipolar disorder was diagnosed in five of the 13 co-twins of a bipolar twin proband (concordance = 38.5%), but only one of 22 DZ pairs (4.5%). Model fitting indicated that the heritability of bipolar illness was 79%, with a residual 21% of the variance attributable to individual-specific environment [Kendler et al., 1995]. In this best-fitting model, there was no significant contribution of shared family environment to the liability to bipolar disorder.

Finally, a study of 224 twin pairs ascertained from the Maudsley Twin Register reported significantly higher concordance rates for mania plus hypomania, defined by Research Diagnostic Criteria, in MZ twins (44%) than DZ twins (9.1%) [Cardno et al., 1999]. On the other hand, the difference in MZ versus DZ concordance rates for mania alone (36.4% vs. 7.4%) did not reach statistical significance, perhaps due to lower power for this comparison. As observed in the Swedish twin sample, the best-fitting biometrical model included no significant contribution from common environment. The heritability for mania plus hypomania, which may correspond to a combination of bipolar I and II disorder cases, was substantial (87%) and similar to that for mania alone (84%). Table II summarizes data from the three largest and most methodologically rigorous twin studies that used modern definitions of bipolar disorder and included more than 20 pairs with a bipolar proband.

Despite differences in ascertainment, assessment, and diagnostic methods, twin studies of bipolar disorder are generally consistent in observing greater concordance among MZ twins than DZ twins. This provides compelling evidence for the hypothesis that susceptibility genes contribute to the familiality of bipolar disorder. In fact, the results of biometrical modeling suggest that familial aggregation is due predominantly to genetic factors, with heritability estimates in the range of 60–85% and little evidence that shared family environment plays a major role. However, MZ concordance rates and heritability estimates are less than 100%, demonstrating that environmental factors are also influential.

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ADOPTION STUDIES

Adoption studies can help distinguish genetic and environmental influences on family resemblance by comparing rates of a disorder in biological family members to those in adoptive family members. If genes influence the risk of a disorder, biological (genetically related) family members should resemble each other more than do adoptive (environmentally related) family members. Unfortunately, because they are logistically difficult to conduct and subject to a number of potential confounds [Kendler, 1993], the availability and interpretability of adoption studies of mood disorders has been limited.

Although there have been several adoption studies addressing genetic and environmental contributions to mood disorders, only two have examined the inheritance of bipolar disorder using a modern definition of the phenotype [Mendlewicz and Rainer, 1977; Wender et al., 1986]. Mendlewicz and Rainer [1977] compared rates of illness in adoptive and biological parents of 29 bipolar adoptees and those of 22 unaffected adoptees; they also studied two additional sets of controls: parents of 31 bipolar patients who were not adopted, and parents of 20 individuals who had contracted polio during childhood or adolescence. The last group was intended to control for factors involved

TABLE II. Largest Recent Twin Studies of Bipolar Disorder

	MZ twins		DZ twins		
Reference	Number of pairs[a]	Concordance	Number of pairs[a]	Concordance	Heritability
Bertelsen et al. [1977]	34	62%	37	8%	59%
Kendler et al. [1993, 1995]	13	38.5%	22	4.5%	79%
Cardno et al. [1999][b]	25	44%	33	9.1%	87%

[a]Number of pairs with affected bipolar proband.

[b]Data for phenotype of "mania plus hypomania."

with raising a disabled child. Bipolar patients were ascertained from review of inpatient and outpatient medical records, and parents were assessed by semistructured interviews blind to clinical and adoptive status of the proband offspring. The frequency of affective illness (comprising bipolar, unipolar, schizoaffective, and cyclothymic disorders) was significantly greater in the biological parents (31%) than in the adoptive parents (12%) of bipolar probands. The risk of affective illness was similar in the biological parents of adopted and nonadopted bipolar probands; lower risks, comparable to those in the adoptive parents of bipolar probands, were observed in biological and adoptive parents of normal adoptees and biological parents of probands with polio. These results implicate genetic factors in the familial aggregation of affective illness, although small numbers precluded meaningful analyses of bipolar disorder alone.

Similar conclusions emerge from a Danish adoption study reported by Wender et al. [1986]. They compared rates of illness in biological and adoptive parents of 71 adoptees who had been hospitalized with affective disorders (including 27 with unipolar and 10 with bipolar disorder), as well as 71 control adoptees matched for age, sex, time spent with biological mother, age at adoption, and socioeconomic status. They observed a significantly higher frequency of major mood disorder (including bipolar and unipolar disorder) in biological parents of ill adoptees than in biological relatives of controls. The prevalence did not differ significantly between adoptive relatives of ill versus control probands. Again, the small number of cases of bipolar disorder did not permit meaningful statistical comparisons for this disorder per se. Also, because of differences in the demographic characteristics of biological and adoptive relatives, direct comparisons were not made between these two groups. Overall, then, the evidence from adoption studies bearing directly on the heritability of bipolar disorder has been limited; however, the available data are consistent with a role for genetic transmission of risk for mood disorders, including bipolar disorder.

FAMILIAL/GENETIC BOUNDARIES OF BIPOLAR DISORDER

In addition to demonstrating the familiality of a disorder, family, twin, and adoption studies can provide crucial information about the etiologic relationships and boundaries between disorders. For example, if two disorders, A and B, share familial determinants, relatives of probands with either disorder A or B should show increased risks of both disorders. On the other hand, if the disorders are distinct entities from a familial/genetic standpoint, relatives will be at risk only for the disorder affecting the proband (i.e., the disorders will breed true). Family/genetic data have helped clarify the boundaries of the bipolar disorder phenotype, although ambiguities remain [Blacker and Tsuang, 1992].

One distinction relevant to the nosology of bipolar disorder is the status of bipolar II disorder, characterized by episodes of hypomania and depression. Although the reliability of the bipolar II diagnosis has been considered lower than that of bipolar I, recent work suggests that good reliability can be achieved with direct interviews of relatives and careful diagnostic procedures [Simpson et al., 2002]. Family studies using direct interviews of first-degree relatives have provided some evidence that bipolar II disorder is a distinct entity. Risks of bipolar II disorder have tended to be highest among relatives of bipolar II probands as opposed to those with bipolar I or unipolar depression [Gershon et al., 1982; Coryell et al., 1984; Endicott et al., 1985; Andreasen et al., 1987; Heun and Maier, 1993; Simpson et al., 1993]. However, the observation that familial risks of unipolar disorder are similar across these proband groups and (in some studies) that risk of bipolar I is also elevated in relatives of bipolar II probands suggests that these affective disorders are not completely etiologically distinct [Gershon et al., 1982a; Andreasen et al., 1987; Heun and Maier, 1993]. It seems likely that bipolar II is a heterogeneous entity in which some cases are more closely related to bipolar I, some to unipolar depression, and others may represent a genetically distinct disorder that breeds true [Blacker and Tsuang, 1992; Heun and Maier, 1993].

Most of the family studies reviewed earlier examined the familiality of both bipolar and unipolar disorder. The cross-phenotype familial risks (i.e., the risk of bipolar disorder among relatives of unipolar probands and the risk of unipolar disorder among relatives of bipolar probands) speak to the familial/genetic relationship between the disorders. As summarized in Table I, there is some variability in risk estimates across studies. Focusing on the controlled family studies, one can compare illness risks in relatives of affected probands to risks in relatives of controls. In these studies, the risk of unipolar disorder among relatives of bipolar probands is comparable to the risk among relatives of unipolar probands and generally higher than the risk among relatives of controls. On the other hand, the risk of bipolar disorder among relatives of unipolar probands tends to be the same or intermediate between the risk to bipolar relatives and the risk to control relatives. The studies differ somewhat with respect to this last point, however. For example, Tsuang et al. [1980] found that relatives of unipolar probands had a statistically significant 10-fold relative risk of bipolar disorder compared to relatives of controls, whereas Maier et al. [1993] found identical risks of bipolar disorder among relatives of unipolar or control probands. A controlled, longitudinal family study from the multicenter Collaborative Depression Study [Winokur et al., 1995] also found indistinguishable rates of bipolar I disorder among relatives of unipolar or control probands. Overall, the available family studies support the conclusions that: 1) relatives of bipolar probands have an elevated risk of both bipolar disorder and unipolar disorder, and 2) relatives of unipolar probands are at increased risk for unipolar disorder but do not appear to have a substantially elevated risk of bipolar disorder. Twin

Overall, the available family studies support the conclusions that: 1) relatives of bipolar probands have an elevated risk of both bipolar disorder and unipolar disorder, and 2) relatives of unipolar probands are at increased risk for unipolar disorder but do not appear to have a substantially elevated risk of bipolar disorder.

studies have had limited power to examine the genetic relationship between bipolar and unipolar disorders; cross-phenotype (e.g., unipolar/bipolar) MZ twin pairs have been reported, but statistically meaningful comparisons to DZ twin concordance rates have generally not been possible [Bertelsen et al., 1977; Torgersen, 1986; Kendler et al., 1993].

Variability in risks across studies may reflect, in part, differences in criteria applied to define cases. Tsuang and Faraone [1990] pointed out that studies requiring recurrent depressive episodes for the diagnosis of unipolar disorder in probands tended not to find elevated rates of bipolar disorder among their relatives. They suggest that probands with nonrecurrent depression may be more likely to represent latent cases of bipolar disorder in which a manic episode has not yet occurred. Consistent with this, a controlled study that included probands with recurrent unipolar depression found no increased risk of bipolar disorder in their families compared to families of unaffected controls [Heun and Maier, 1993]. On the other hand, the risks of recurrent and nonrecurrent depression were similar among relatives of bipolar probands. It is also possible that the excess risk of unipolar disorder among relatives of bipolar probands may be overestimated if some apparently unipolar relatives are actually latent cases of bipolar disorder [Blacker and Tsuang, 1992, 1993]. Analyses aimed at clarifying these subgroups have not been able to identify robust indicators of bipolarity among unipolar relatives of bipolar probands [Blacker et al., 1996].

Kraepelin's fundamental diagnostic distinction between manic depressive illness and schizophrenia (dementia praecox) was based in part on his conclusion that these disorders have a distinct hereditary basis. Nevertheless, there is symptomatic overlap in that psychotic symptoms can be a feature of both disorders. The etiologic boundary between psychotic disorders and bipolar disorder has been the subject of much attention, particularly in light of recent observations that genetic loci influencing these disorders may overlap [Badner and Gershon, 2002]. While some studies have suggested elevated risks of schizophrenia among relatives of bipolar or affective disorder probands [Tsuang et al., 1980; Taylor et al., 1993; Valles et al., 2000], several controlled direct-interview family studies have not supported this [Gershon et al., 1975, 1982; Weissman et al., 1984; Maier et al., 1993]. A similar picture emerges in studies of schizophrenic probands and their relatives; while one controlled study [Taylor et al., 1993] found evidence of increased familial risk of affective disorder (unipolar and bipolar combined), most have not found an increase in bipolar disorder among relatives of schizophrenic probands [Tsuang et al., 1980; Gershon et al., 1988; Maier et al., 1993; Kendler and Gardner, 1997]. Kendler and Gardner [1997] performed a meta-analysis of three controlled, direct-interview studies of schizophrenic probands (the Danish Adoption Study, the Iowa 500 Non-500 Family Study, and the Roscommon Family Study) and found that familial risk estimates of bipolar disorder were homogeneous across the studies, with an nonsignificant common odds ratio of 1.9 (95% confidence interval (CI) = 0.7–5.2) for risk of bipolar disorder in relatives of schizophrenic versus control probands.

The boundary between schizoaffective disorder and bipolar disorder has been more difficult to define. This is perhaps not surprising given that the definition of schizoaffective disorder includes prominent mood symptoms. Taken together, the available data argue for etiologic overlap in the familial/genetic basis of these disorders, particularly with the schizoaffective-bipolar or manic subtype. In several studies, the risk of bipolar disorder among relatives of schizoaffective probands has been comparable to or greater than the risk among bipolar probands [Gershon et al., 1982; Andreasen et al., 1987; Rice et al., 1987; Maier et al., 1993]. On the other hand, relatives of bipolar probands have not been shown to have substantially elevated risks of schizoaffective disorder [Angst et al., 1980; Gershon et al., 1982; Pauls et al., 1992; Maier et al., 1993].

The overlap of genetic influences on schizophrenic, schizoaffective, and manic disorders was also examined in a recent analysis of twins from the Maudsley Twin Register [Cardno et al., 2002]. Cardno et al. [2002] applied nonhierarchical diagnostic definitions such that twins could be assigned lifetime diagnoses for more than one of these disorders. They report significant correlations in genetic liability among the three syndromes; the genetic correlations were 0.68 for schizophrenic and manic syndromes and 0.88 for schizoaffective and manic syndromes. The genetic liability to schizoaffective disorder was entirely shared with the two other syndromes. Kendler [2002] has pointed out that interpretation of this study is complicated because it is not clear how often mania occurred in the absence of schizophrenia in co-twins of schizophrenic probands. Nevertheless, this intriguing analysis supports the possibility that recent reports of overlapping linkage findings for bipolar disorder and schizophrenia represent shared genetic risk factors [Berrettini, 2001; Badner and Gershon, 2002].

Overall, then, genetic epidemiologic studies suggest that the bipolar disorder phenotype is etiologically heterogeneous and that at least some proportion of cases are genetically related to unipolar depression and psychotic

disorders, particularly schizoaffective disorder. The identification of specific susceptibility genes through molecular genetic studies should help clarify the boundaries between bipolar disorder and other psychiatric disorders.

CLINICAL IMPLICATIONS

As we have seen, family, twin, and adoption studies have provided strong evidence that familial and heritable factors contribute to the etiology of mood disorders and, in particular, bipolar disorder. In addition to providing motivation and justification for molecular genetic efforts to identify susceptibility genes, these studies also have relevance to clinical practice. For example, discussing the contribution of genetic and biological risk factors can be an important component of psychoeducation with patients and families and may overcome misconceptions about the causes of bipolar disorder. As an illustration, although bipolar disorder can clearly run in families, the available evidence does not suggest that shared family environment (e.g., parenting style) plays a substantial role in the development of the disorder.

Studies documenting the familiality and heritability of bipolar disorder are also clearly relevant when patients or families have questions related to genetic counseling. For example, affected individuals planning to have children may have questions about familial recurrence risks. In the absence of identified susceptibility genes for bipolar disorder, family, twin, and adoption data represent the primary basis for risk prediction. A thorough discussion of the issues and techniques involved in genetic counseling in psychiatry is beyond the scope of this article, and the interested reader is referred to recent work devoted to this topic [Moldin, 1997; Hodgkinson et al., 2001; Tsuang et al., 2001]. We would emphasize here, however, that some familiarity with the results of family/genetic studies is important for clinicians working with patients and families affected with mood disorders; this includes familiarity not only with what is known but also with what is not known.

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For example, family studies have provided useful empiric estimates of recurrence risk for first-degree relatives. At the same time, the precision of these estimates is likely to be limited, as is clear from the range of risks listed in Table I. In addition, empiric risks from available studies may not reflect the risks in individual families; those risks may be far higher or lower depending on the mode of transmission in a given family and the particular configuration of affected family members. As an alternative approach, theoretical recurrence risks can be derived using estimates of certain epidemiologic parameters. Moldin [1997] calculated lifetime recurrence risks for a child born into a five-member family with varying configurations of affected relatives using knowledge of disease prevalence and heritability and assuming a polygenic mode of inheritance. The risks for bipolar disorder vary from about 5–6% when there is only one affected first-degree relative to more than 50% when there are four. He notes that, like empiric risks, these can serve as a guide but do not represent individualized risk estimates. In general, when discussing recurrence risks with patients or their family members, it is important to highlight the limitations of the information and to discuss how risks are generated, the spectrum of diagnoses assessed in the supporting family studies, and the difference between empiric and individualized risks. In our experience, it is most helpful to provide a range of risk, accompanied by the above caveats.

SUMMARY

Family studies of bipolar disorder have consistently demonstrated that the disorder can run in families. First-degree relatives of affected individuals have approximately a 10-fold increased risk of the disorder compared to relatives of unaffected controls. Twin studies (and to a lesser extent adoption studies) have further provided evidence that genes contribute strongly to familial transmission of the disorder. Earlier-onset bipolar disorder appears to be associated with increased familial risk, and studies have identified other putative familial subtypes, including lithium-responsive bipolar disorder and bipolar disorder with psychosis or comorbid panic disorder. Family and twin studies have generally supported the validity of the bipolar disorder phenotype and its separation from unipolar depression or psychotic disorders. However, the data also suggest that the familial/genetic determinants of these disorders are not entirely distinct and/or that they are heterogeneous, with the existence of both distinct and overlapping forms of these phenotypes. Ultimately, molecular genetic studies will help clarify how strong and how variably expressed the genetic influences on bipolar disorder may be.

REFERENCES

Abrams R, Taylor MA. 1980. A comparison of unipolar and bipolar depressive illness. Am J Psychiatry 137:1084–1087.

Alda M, Grof P, Grof E, Zvolsky P, Walsh M. 1994. Mode of inheritance in families of patients with lithium-responsive affective disorders. Acta Psychiatr Scand 90:304–310.

Alda M, Grof E, Cavazzoni P, Duffy A, Martin R, Ravindran L, Grof P. 1997. Autosomal recessive inheritance of affective disorders in families of responders to lithium prophylaxis? J Affect Disord 44:153–157.

American Psychiatric Association. 1980. Diagnostic and statistical manual of mental disorders, 3rd edition. Washington, DC: American Psychiatric Association.

American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC: American Psychiatric Association.

Andreasen NC, Rice J, Endicott J, Reich T, Coryell W. 1986. The family history approach to diagnosis. How useful is it? Arch Gen Psychiatry 43:421–429.

Andreasen NC, Rice J, Endicott J, Coryell W, Grove WM, Reich T. 1987. Familial rates of affective disorder. A report from the National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 44: 461–469.

Angst J, Marneros A. 2001. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord 67:3–19.

Angst J, Frey R, Lohmeyer B, Zerbin-Rudin E. 1980. Bipolar manic-depressive psychoses: results of a genetic investigation. Hum Genet 55:237–254.

Badner JA, Gershon ES. 2002. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 7:405–411.

Baldessarini RJ. 2000. A plea for integrity of the bipolar disorder concept. Bipolar Disord 2: 3–7.

Berrettini WH. 2001. Molecular linkage studies of bipolar disorders. Bipolar Disord 3:276–283.

Bertelsen A, Harvald B, Hauge M. 1977. A Danish twin study of manic-depressive disorders. Br J Psychiatry 130:330–351.

Blacker D, Tsuang MT. 1992. Contested boundaries of bipolar disorder and the limits of categorical diagnosis in psychiatry. Am J Psychiatry 149:1473–1483.

Blacker D, Tsuang MT. 1993. Unipolar relatives in bipolar pedigrees: are they bipolar? Psychiatr Genet 3:40–51.

Blacker D, Faraone SV, Rosen AE, Guroff JJ, Adams P, Weissman MM, Gershon ES. 1996. Unipolar relatives in bipolar pedigrees: a search for elusive indicators of underlying bipolarity. Am J Med Genet 67:445–454.

Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM. 1999. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 56: 162–168.

Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. 2002. A twin study of genetic relationships between psychotic symptoms. Am J Psychiatry 159:539–545.

Coryell W, Endicott J, Reich T, Andreasen N, Keller M. 1984. A family study of bipolar II disorder. Br J Psychiatry 145:49–54.

Coryell W, Akiskal H, Leon AC, Turvey C, Solomon D, Endicott J. 2000. Family history and symptom levels during treatment for bipolar I affective disorder. Biol Psychiatry 47:1034–1042.

Dunner DL, Fleiss JL, Fieve RR. 1976. The course of development of mania in patients with recurrent depression. Am J Psychiatry 133:905–908.

Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W. 1985. Bipolar II. Combine or keep separate? J Affect Disord 8:17–28.

Engstrom C, Astrom M, Nordqvist-Karlsson B, Adolfsson R, Nylander PO. 1997. Relationship between prophylactic effect of lithium therapy and family history of affective disorders. Biol Psychiatry 42:425–433.

Faraone SV, Lyons MJ, Tsuang MT. 1987. Sex differences in affective disorder: genetic transmission. Genet Epidemiol 4:331–343.

Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. 1972. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26:57–63.

Gershon ES, Mark A, Cohen N, Belizon N, Baron M, Knobe K. 1975. Transmitted factors in the morbid risk of affective disorders: a controlled study. J Psychiatr Res 12:283–299.

Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, Targum SD, Nurnberger JI Jr, Goldin LR, Bunney WE Jr. 1982. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. Arch Gen Psychiatry 39: 1157–1167.

Gershon ES, Dehisi LE, Hamovit J, Nurnberger JI Jr, Maxwell ME, Schrelber J, Davphinais D, Dingman CW 2nd, Guroff JJ. 1988. A controlled family study of chronic psychoses. Schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 45:328–336.

Grigoroiu-Serbanescu M, Martinez M, Nothen MM, Grinberg M, Sima D, Propping P, Marinescu E, Hrestic M. 2001. Different familial transmission patterns in bipolar I disorder with onset before and after age 25. Am J Med Genet 105:765–773.

Grof P, Alda M, Grof E, Zvolsky P, Walsh M. 1994. Lithium response and genetics of affective disorders. J Affect Disord 32: 85–95.

Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, O'Donovan C, Alda M. 2002. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 63:942–947.

Helzer JE, Winokur G. 1974. A family interview study of male manic depressives. Arch Gen Psychiatry 31:73–77.

Heun R, Maier W. 1993. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. Acta Psychiatr Scand 87:279–284.

Hodgkinson KA, Murphy J, O'Neill S, Brzustowicz L, Bassett AS. 2001. Genetic counselling for schizophrenia in the era of molecular genetics. Can J Psychiatry 46: 123–130.

James NM. 1977. Early- and late-onset bipolar affective disorder. A genetic study. Arch Gen Psychiatry 34:715–717.

James NM, Chapman CJ. 1975. A genetic study of bipolar affective disorder. Br J Psychiatry 126:449–456.

Johnson GF, Leeman MM. 1977. Analysis of familial factors in bipolar affective illness. Arch Gen Psychiatry 34:1074–1083.

Jones I, Craddock N. 2002. Do puerperal psychotic episodes identify a more familial subtype of bipolar disorder? Results from a family history study. Psychiatr Genet 12: 177–180.

Kendler KS. 1993. Twin studies of psychiatric illness. Arch Gen Psychiatry 50:905–915.

Kendler KS. 2001. Twin studies of psychiatric illness: an update. Arch Gen Psychiatry 58: 1005–1014.

Kendler KS. 2002. Hierarchy and heritability: the role of diagnosis and modeling in psychiatric genetics. Am J Psychiatry 159:515–518.

Kendler KS, Gardner CO. 1997. The risk for psychiatric disorders in relatives of schizophrenic and control probands: a comparison of three independent studies. Psychol Med 27:411–419.

Kendler KS, Pedersen N, Johnson L, Neale MC, Mathe AA. 1993. A pilot Swedish twin study of affective illness, including hospital- and population-ascertained subsamples. Arch Gen Psychiatry 50:699–700.

Kendler KS, Pedersen NL, Neale MC, Mathe AA. 1995. A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. Behav Genet 25:217–232.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. 1997. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 27:1079–1089.

Leonhard K. 1959. Aufteilung der endogenen Psychosen. Berlin: Akademie Verlag.

MacKinnon DF, McMahon FJ, Simpson SG, McInnis MG, DePaulo JR. 1997. Panic disorder with familial bipolar disorder. Biol Psychiatry 42:90–95.

MacKinnon DF, Xu J, McMahon FJ, Simpson SG, Stine OC, McInnis MG, DePaulo JR. 1998. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. Am J Psychiatry 155:829–831.

MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, Nurnberger J, Reich T, DePaulo JR. 2002. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. Am J Psychiatry 159:30–35.

Maier W, Lichtermann D, Minges J, Hallmayer J, Heun R, Benkert O, Levinson DF. 1993. Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. Arch Gen Psychiatry 50:871–883.

Mendlewicz J, Rainer JD. 1974. Morbidity risk and genetic transmission in manic-depressive illness. Am J Hum Genet 26:692–701.

Mendlewicz J, Rainer J. 1977. Adoption study supporting genetic transmission in manic-depressive illness. Nature 268:326–329.

Mendlewicz J, Fieve RR, Stallone F. 1973. Relationship between the effectiveness of lithium therapy and family history. Am J Psychiatry 130:1011–1013.

Moldin SO. 1997. Psychiatric genetic counseling. In: Guze SB, editor. Washington University adult psychiatry. St. Louis: Mosby. p 365–381.

Omahony E, Corvin A, O'Connell R, Comerford C, Larsen B, Jones R, McCandless F, Kirov G, Cardno AG, Craddock N, Gill M. 2002. Sibling pairs with affective disorders: resemblance of demographic and clinical features. Psychol Med 32:55–61.

Pauls DL, Morton LA, Egeland JA. 1992. Risks of affective illness among first-degree relatives of bipolar I old-order Amish probands. Arch Gen Psychiatry 49:703–708.

Perris C. 1966. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. Introduction. Acta Psychiatr Scand Suppl 194:9–14.

Petterson U. 1977. Manic-depressive illness. A clinical, social and genetic study. Acta Psychiatr Scand Suppl 269:1–93.

Potash JB, Willour VL, Chiu YF, Simpson SG, MacKinnon DF, Pearlson GD, DePaulo JR Jr, McInnis MG. 2001. The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. Am J Psychiatry 158: 1258–1264.

Potash JB, Chiu YF, Mackinnon D, Miller EB, Simpson SG, McMahon FJ, McInnis MG, DePaulo JR. 2003. Familial aggregation of psychotic symptoms in a replication set of 69 bipolar disorder pedigrees. Am J Med Genet 116B:90–97.

Rice J, Reich T, Andreasen NC, Endicott J, Van Eerdewegh M, Fishman R, Hirschfeld RM, Klerman GL. 1987. The familial transmission of bipolar illness. Arch Gen Psychiatry 44:441–447.

Rotondo A, Mazzanti C, Dell'Osso L, Rucci P, Sullivan P, Bouanani S, Gonnelli C, Goldman D, Cassano GB. 2002. Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. Am J Psychiatry 159:23–29.

Schurhoff F, Bellivier F, Jouvent R, Mouren-Simeoni M, Bouvard M, Allilaire J, Leboyer M. 2000. Early and late onset bipolar disorders: two different forms of manic-depressive illness? J Affect Disord 58:215–221.

Simpson SG, Folstein SE, Meyers DA, McMahon FJ, Brusco DM, DePaulo JR Jr. 1993. Bipolar II: the most common bipolar phenotype? Am J Psychiatry 150:901–903.

Simpson SG, McMahon FJ, McInnis MG, MacKinnon DF, Edwin D, Folstein SE, DePaulo JR. 2002. Diagnostic reliability of bipolar II disorder. Arch Gen Psychiatry 59:736–740.

Smeraldi E, Negri F, Melica AM. 1977. A genetic study of affective disorders. Acta Psychiatr Scand 56:382–398.

Smeraldi E, Petroccione A, Gasperini M, Macciardi F, Orsini A, Kidd KK. 1984. Outcomes on lithium treatment as a tool for genetic studies in affective disorders. J Affect Disord 6:139–151.

Somanath CP, Jain S, Janardhan Reddy YC. 2002. A family study of early-onset bipolar I disorder. J Affect Disord 70:91–94.

Spencer TJ, Biederman J, Wozniak J, Faraone SV, Wilens TE, Mick E. 2001. Parsing pediatric bipolar disorder from its associated comorbidity with the disruptive behavior disorders. Biol Psychiatry 49:1062–1070.

Spitzer RL, Endicott J, Robins E. 1978. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 35:773–782.

Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R. 1988. A family study of bipolar I disorder in adolescence. Early onset of symptoms linked to increased familial loading and lithium resistance. J Affect Disord 15:255–268.

Taylor MA, Abrams R. 1981. Early- and late-onset bipolar illness. Arch Gen Psychiatry 38:58–61.

Taylor MA, Berenbaum SA, Jampala VC, Cloninger CR. 1993. Are schizophrenia and affective disorder related? Preliminary data from a family study. Am J Psychiatry 150:278–285.

Todd RD. 2002. Genetics of early onset bipolar affective disorder: are we making progress? Curr Psychiatry Rep 4:141–145.

Torgersen S. 1986. Genetic factors in moderately severe and mild affective disorders. Arch Gen Psychiatry 43:222–226.

Trzebiatowska-Trzeciak O. 1977. Genetical analysis of unipolar and bipolar endogenous affective psychoses. Br J Psychiatry 131: 478–485.

Tsuang MT, Faraone SV. 1990. The genetics of mood disorders. Baltimore: Johns Hopkins University Press. p 31–101.

Tsuang MT, Winokur G, Crowe RR. 1980. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 137:497–504.

Tsuang DW, Faraone SV, Tsuang MT. 2001. Genetic counseling for psychiatric disorders. Curr Psychiatry Rep 3:138–143.

Turecki G, Grof P, Grof E, D'Souza V, Lebuis L, Marineau C, Cavazzoni P, Duffy A, Betard C, Zvolsky P, Robertson C, Brewer C, Hudson TJ, Rouleau GA, Alda M. 2001. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry 6:570–578.

Valles V, Van Os J, Guillamat R, Gutierrez B, Campillo M, Gento P, Fananas L. 2000. Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. Schizophr Res 42:83–90.

Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Hamovit J, Thompson WD, Pauls DL, Guroff JJ. 1984. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University—National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 41:13–21.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu H-G, Joyce PR, Karam EG, Lee C-K, Lellouch J, Lepine J-P, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H-U, Yeh E-K. 1996. Cross-national epidemiology of major depression and bipolar disorder. JAMA 276:293–299.

Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. 1986. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 43:923–929.

Winokur G, Coryell W, Keller M, Endicott J, Leon A. 1995. A family study of manic-depressive (bipolar I) disease. Is it a distinct illness separable from primary unipolar depression? Arch Gen Psychiatry 52:367–373.