The Implications of Genetic Studies of Major Mood Disorders for Clinical Practice

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Background: This article is a selective review and synthesis of relevant research findings from genetic studies of major mood disorders and the application of these to clinical practice.

Method: The article discusses the application of genetic research findings in major mood disorders, including epidemiologic and family study risk estimates, risk modifiers, and the concepts of etiologic and phenotypic heterogeneity, to 3 clinical domains: risk counseling, diagnosis, and treatment prediction.

Results: Epidemiologic and family studies have provided general risk estimates useful in counseling mood-disordered patients and their relatives. A complete and accurate family pedigree provides more individualized risk estimates for specific cases and is useful in identifying the phenotypic spectrum of the disorder being transmitted in the family. Both proband course parameters and familial loading for psychiatric illnesses may be relevant for the prediction of treatment response. However, the hypothesis of inherited pharmacologic selectivity remains to be proven.

Conclusion: Genetic studies of mood disorders have not yet provided conclusive evidence of specific susceptibility genes or their pattern of inheritance. However, they have generated information that is useful to clinical practice.

(J Clin Psychiatry 2000;61:630–637)

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Recognizing that mood disorders are complex illnesses with multifactorial determinants, there is substantial evidence that genetic factors play a significant role. Accumulating data from family, twin, and adoption studies[1] and more recently from molecular genetic studies[2] suggest that genes play a critical role in the manifestation of bipolar disorders. Major depressive disorders represent a more heterogeneous group, with a varying degree of genetic risk.[3]

The recognition that part of the vulnerability to affective disorders is inherited enables the identification of individuals at risk, thereby facilitating early diagnosis and treatment. At the same time, there is a need to counsel patients and their relatives about the risk of developing affective disorders. Although we still do not understand the specific genetic determinants of mood disorders, genetic studies have provided a large body of information that can be helpful in caring for patients and their families. The purpose of this article is to selectively review the genetic research findings in mood disorders relevant to clinical practice in the following 3 domains: (1) risk estimation/counseling, (2) diagnosis, and (3) prediction of treatment response.

The starting point for working with genetically based illnesses is the collection of family history and construction of a complete and accurate family tree (pedigree). It is critical to systematically document the psychiatric status of each first-degree relative (parents, siblings, and offspring). Expansion of the pedigree from this point depends on the question being asked and the quality (validity and reliability) of the information available. In research settings, often the family tree is expanded to include all first-degree relatives of affected members,[4] while information on the first-degree relatives of the index patient is often sufficient for clinical purposes.

Generally, it is easier to determine the presence of a psychiatric illness in a relative than to establish a specific diagnosis if there is only indirect information to rely on. In genetic studies, where diagnostic accuracy in relatives is paramount, it is preferable to interview all available relatives face to face or obtain information from multiple informants when a direct interview is not possible. In clinical practice, exhaustive family interviews are usually not practical. However, the addition of another family informant substantially increases the sensitivity of diagnosing mood disorders in family members.[5] To further increase the informativeness of family history, each relative should be discussed individually in terms of psychiatric symptoms, clinical course, degree of incapacity, treatment intervention, and associated response. General questions such as "Does anyone in the family suffer from mental ill-

ness" are less likely to yield reliable information at a level of detail that will be useful.

RISK COUNSELING

Patients and their relatives increasingly want to be informed of the risks to their children, as they learn more about the importance of genetic factors in mood disorders. Moreover, families with several affected members seek genetic counseling particularly often. Thus, psychiatrists need to become more knowledgeable about morbidity risk estimation. Morbidity risks can be assessed on the basis of different sources of information: (1) risk estimates based on family studies and (2) individualized risk estimates for a specific family.

Epidemiologic Studies

Population-based prevalence rates provide an important background against which specific risks derived from family studies can be compared. Epidemiologic surveys suggest that the lifetime prevalence of affective disorders is quite high in the general population. While early epidemiologic studies provided widely disparate risk estimates, more recent epidemiologic studies, using standardized interviews and diagnostic criteria, have provided more consistent and comparable results. In a cross-national collaborative study, the lifetime risk of a major depressive episode ranged from 1.5% in Taiwan to 19% in Beirut.[6] The combined U.S. Epidemiologic Catchment Area (ECA) study and a Canadian study reported lifetime rates of 5.2% and 9.6%, respectively.[6,7] Across all studies, the lifetime rate of major depression was higher in women, ranging from 1.6- to 3.1-fold.

The remaining variability in the risk estimates for major depressive disorder despite standardized methods may reflect difficulty gauging the threshold for diagnosis of a clinically significant depressive episode together with the high prevalence of affective symptoms in the population.[8] Depressive symptoms are nonspecific. They represent a number of underlying problems including normal grief, dysphoria associated with other psychiatric disorders (e.g., anxiety disorder, personality disorder), and a variety of underlying medical illnesses. Moreover, large-scale epidemiologic surveys are limited to self-report symptoms and do not take into account other information helpful in validating diagnoses such as clinical course, family history, and treatment response.

The lifetime rate of bipolar disorder is more consistent across studies. In the cross-national epidemiologic study, rates of DSM-III bipolar disorder ranged from 0.3% in Taiwan to 1.5% in Christchurch,[6] with the U.S. ECA combined studies and the Canadian study reporting 0.9% and 0.6%, respectively. In U.S. studies reporting on the lifetime rate of bipolar II disorder, the estimate is around 0.6%,[9,10] which agrees with other international surveys.

There is increasing recognition that the phenotypic spectrum of bipolar disorder is wider than current standard diagnostic measures have allowed for. Specifically, there are reports of clinically significant brief recurrent hypomania and sporadic hypomania occurring in the general population with an estimated lifetime prevalence ranging from 3% to 6.5%.[11] Similarly, there has been a case made to broaden the bipolar spectrum to include depressed patients who experience hypomanic episodes shorter than the 4-day DSM-IV criterion minimum (bipolar II ½), hypomania associated with antidepressant use (bipolar III), a premorbid history of hyperthymic temperament (bipolar IV), as well as patients from bipolar families with soft bipolar symptoms including depressive, cyclothymic, or hyperthymic temperaments.[12] It has been estimated that the lifetime rate of this "soft" bipolar spectrum may be as high as 5%.[13]

Risk Estimates Based on Family Studies

Family studies of patients with a carefully diagnosed affective illness have provided more reliable information about the increased risk for different classes of relatives[11–16] by comparing them to relatives of normal controls. While the absolute risks vary, all studies carried out with rigorous methodology and standardized criteria have found a several-fold increased risk of primary affective disorder in the first-degree relatives of probands (Table 1). The risk is greater for the relatives of bipolar probands as compared to unipolar probands.

All risks we mention here refer to first-degree relatives (sibling, parent, offspring). A relative of a patient with a bipolar spectrum illness (bipolar I, bipolar II, and schizoaffective disorders) has about a 20% lifetime risk of developing some type of major affective disorder (assuming the illness segregates in one family line only).[1] When the numbers of relatives at risk are taken into account across the cited studies (the weighted average risk), the risk for relatives of bipolar patients is 6.7% for bipolar and 12.5% for unipolar disorder. The weighted average risk in relatives of a unipolar patient is 1.9% for bipolar and 14.2% for unipolar disorders. However, as the estimates vary significantly between studies, it may be more appropriate to express the risk in ranges: relatives of a patient with bipolar disorder have about an 8- to 10-fold risk of bipolar disorder and a 2- to 3-fold risk of unipolar disorder compared to relatives of control subjects. Similarly, relatives of a unipolar patient have a 1.5- to 2-fold risk of bipolar disorder and a 3- to 4-fold risk of unipolar disorder.

It must be stressed that some relatives of bipolar probands may only ever manifest depressive episodes. Consequently, bipolar patients tend to have relatives with elevated rates for not only bipolar but also unipolar disorders, while unipolar patients tend to have relatives with elevated rates of unipolar disorders only. This observation has strong support in both twin and family studies.[3]

Table 1. Risk of Bipolar (BP) and Unipolar (UP) Disorder in the First-Degree Relatives of Bipolar and Unipolar Probands[a]

Study	Diagnostic Criteria	Age-Corrected No. of Relatives at Risk (BP/UP)	Morbidity Risk in %	
			Bipolar Disorder	Unipolar Disorder
Bipolar disorder				
Perris, 1966[16]	Clinical	627	10.2	0.5
Angst and Perris, 1968[14]	Clinical	290	3.7	11.2
James and Chapman, 1975[17]	Clinical	239	6.4	13.2
Gershon et al, 1975[18]	WUC	341/264	3.8	8.7
Tsuang et al, 1980[19]	WUC	169	5.3	12.4
Angst et al, 1980[20]	ICD8	401	2.5	7.0
Baron et al, 1982[21]	RDC	135	14.5	16.3
Gershon et al, 1982[15]	RDC	598/572	8.0	14.9
Weissman et al, 1984[22]	RDC	508	9.3	14.3
Coryell et al, 1984[23]	RDC	389	7.0	22.4
Fieve et al, 1984[24]	RDC	1309	2.9	8.4
Rice et al, 1987[25]	RDC	838	10.6	24.3
Weighted average			6.7	12.5
Unipolar disorder				
Perris, 1966[16]	Clinical	684	0.3	6.4
Angst and Perris, 1968[14]	Clinical	1527	0.3	5.1
Gershon et al, 1975[18]	WUC	96/77	2.1	14.3
Tsuang et al, 1980[19]	WUC	362	3.0	15.2
Angst et al, 1980[20]	ICD8	766	0.1	5.9
Baron et al, 1982[21]	RDC	144	2.2	17.7
Gershon et al, 1982[15]	RDC	138/133	2.9	16.6
Coryell et al, 1984[23]	RDC	572	2.8	29.4
Fieve et al, 1984[24]	RDC	265	1.5	8.7
Rice et al, 1987[25]	RDC	1176	5.4	28.6
Weighted average			1.9	14.2
Normal controls				
Gershon et al, 1975[18]		518/411	0.2	0.7
Tsuang et al, 1980[19]		345/345	0.3	7.5
Gershon et al, 1982[15]		217/208	0.5	5.8
Weissman et al, 1984[22]		521	1.3	5.9
Weighted average			0.6	4.8

[a]Abbreviations: ICD8 = International Classification of Diseases, 8th ed.; RDC = Research Diagnostic Criteria; WUC = Washington University criteria.

Several explanations have been offered for this observation. It is likely that a proportion of unipolar relatives of bipolar probands are assessed early in their own course of illness and have yet to manifest manic or hypomanic episodes—they are in fact latent bipolars. Alternatively, unipolar and bipolar disorders may not be genetically distinct in all cases. Some unipolar relatives may represent a genetic variant of the core bipolar phenotype segregating in the family and/or have modifying genes preventing the full phenotypic expression of the bipolar genotype. It has been estimated that the proportion of depressed first-degree relatives of a bipolar proband who suffer from what is potentially a bipolar disorder is about 70%.[26] Furthermore, these depressions may be difficult to distinguish from other genetically unrelated forms of depression. This observation has important treatment implications as these depressed patients may be vulnerable to the effects of antidepressants and their propensity to induce mania and/or rapid cycling.

Individualized Risk Estimate

While an individualized alternative to risk estimation is particularly useful, this approach can be combined with general risk estimation using family studies to provide a range of morbidity risks to the relatives of the patient. Depending on the number of ill relatives in different generations (the degree of loading), the risks in a family can vary significantly (Appendix 1). Generally speaking, the more distant the relative is to the proband, the lower the risk of developing the illness. However, this general rule may not apply uniformly to pedigrees with multiple affected members. The following are key aspects of the pattern of inheritance of affective disorders that should be taken into account in each individual pedigree.

Lineality. It is important to determine whether the illness is passed through one side of the family only (unilineal) or if members on both sides of the family are affected (bilineal). Bilineality in bipolar disorder is common, especially when second-degree or more distant relatives are considered.[27] Such bilineality was not typically considered in family studies and therefore risk estimates cited do not reflect strict unilineal transmission. However, cases in which both parents were affected were typically excluded. In the event that both parents are affected, the risk to offspring is further elevated.[28] For example, if both parents are affected with bipolar illness, the risk of a primary affective illness in the offspring is similar to the monozygotic (MZ) twin concordance rate of about 70%. In comparison, if both parents have a primary unipolar illness, the risk of an affective illness in offspring would be around 50%.[29]

Risk modifiers. In order to tailor the risk to the specific individual in question, the contribution of certain factors known to modify the risk of developing an affective disorder can also be taken into account. These risk modifiers pertain both to the patient and to the relatives and include the pattern of transmission in the family, the age of the proband at onset, and the birth cohort and sex of the relative.

1. Pattern of transmission. Primary affective illnesses do not appear to follow simple Mendelian patterns of inheritance and may be due to several (oligogenic transmission) rather than one major gene.[30] However, certain families seem to exhibit Mendelian-like patterns of inheritance, possibly reflecting either a single-gene variant or the segregation of a specific contributing gene against a uniform background of other common susceptibility genes in the family. For example, in some families roughly half of the members in each generation may be affected, approximating an autosomal dominant pattern of inheritance. In this case, the risk to offspring of an affected parent would rise from 20% to 50% assuming complete penetrance (all those with the "affected genotype" express the illness). However, the penetrance for

affective disorders is known to be incomplete. Based on the MZ twin concordance rate for primary affective disorders, the penetrance can be estimated at about 65%. The penetrance is higher for bipolar disorder (MZ concordance rate of 70%) than for unipolar disorder (MZ concordance rate of 50%).

2. Age at onset. Most family studies have reported a strong association between the age at onset of affective illness (bipolar and unipolar) in the proband and the risk of illness in the relatives, such that the earlier the onset of illness in the patient, the higher the morbidity risk in the relatives.[25,31–33] This observation supports the hypothesis that early onset may be a clinical marker of a more severe form (higher liability) of affective illness,[34] a model that is seen in other genetically based diseases (e.g., breast cancer). Although there is a paucity of reliable data as to the specific magnitude of this risk, a recent comprehensive review[35] concluded that the relatives of child probands clearly have a significantly elevated risk (up to several fold) compared to relatives of patients with mood disorder onset in adulthood. Alongside the genetic endowment, children of mood-disordered parents also face the stress associated with a parent's illness. The genetic predisposition may interact with the psychosocial stress and in that way result in an earlier onset.

3. Birth cohort. It is well recognized that there is an increased risk of affective illness (bipolar and unipolar) in more recently born generations.[25] This effect has been tied to the "cohort" and "period" effects described in epidemiologic and referred samples of bipolar and unipolar depressed patients.[36] It appears that the prevalence of affective disorders has been increasing and the age at onset has been decreasing in successive birth cohorts since 1940. The interpretation of this trend is complex. In part, the increase may be caused by the unmasking of vulnerable genotypes earlier due to environment-gene interactions, as well as possibly to the expression of more penetrant forms of these illnesses.

4. Gender. There is agreement across most studies of bipolar patients that neither the sex of the proband nor the sex of the relative contribute to the risk of bipolar illness in the relatives. However, in some studies female relatives of female bipolar and schizoaffective probands have been reported as being most at risk for developing a major mood disorder.[20,37–39] Such observations, together with a reported lack of father-to-son transmission, led in the past to the hypothesis of X-chromosome inheritance.[40,41] Since the 1960s, this has been a much debated issue.[42,43] Whereas some linkage studies support the view that perhaps in a fraction of families the illness may be linked to the chromosome X,[44,45] many linkage studies have been negative (for a recent review see Paterson et al.[46]). In addition, separation of families into those with maternal or paternal transmission has been used in linkage studies.[47] Finally, some authors suggested the mitochondrial inheritance as a possible genetic mechanism of bipolar disorder following observations of increased maternal transmission.[48]

In contrast, there is substantial evidence that female relatives of probands (male or female) with depressive disorders are at a significantly higher risk than male relatives for depressive disorders.[49–51] A genetic hypothesis regarding gender differences in depression has not been supported because sex of the proband does not seem to affect the risk in relatives.[52]

DIAGNOSIS AND THE INTERPRETATION OF FAMILY HISTORY

The reliability and validity of psychiatric diagnoses have been ongoing problems for the clinician and researcher alike, given that diagnosis is based solely on the assessment of clinical syndromes. Eventually, it is hoped that the identification of genetic markers for the primary affective disorders will provide not only validation of clinical diagnoses, but also the possibility of identifying those at risk prior to the manifestation of the illness. Even before linkage to specific markers is firmly established, information from genetic studies can be used to improve the accuracy of clinical diagnosis and increase our understanding as to which clinical syndromes represent variants of the same underlying disease (phenotypic spectrum) and which represent distinct disease processes (genetic heterogeneity).

To this end, family studies enable us to determine which psychiatric illnesses are transmitted together. Disorders that cosegregate in a family are thought to represent alternative manifestations of the same genetic condition. Substantial convergent evidence suggests that bipolar I, bipolar II, and schizoaffective disorders cosegregate in some families and are therefore part of the phenotypic spectrum of bipolar disorders.[53]

However, the relationship of other mood syndromes to the bipolar spectrum is less clear. For example, cyclothymia is often considered a mild form of bipolar disorder that in some cases is an antecedent condition predicting the manifestation of full-blown bipolar disorder.[54,55] Given the difficulty in accurately diagnosing cyclothymia, relatives with this diagnosis are conservatively considered unaffected in some genetic studies. Nonetheless, it is likely that a certain proportion of cyclothymic patients do suffer from a variant of bipolar disorder, particularly if there is associated incapacity and/or a positive family history of bipolar disorder.

As previously mentioned, there is significant uncertainty in genetic studies as to how to classify unipolar relatives of bipolar probands. While unipolar depression is common in the general population and could occur in relatives by chance, evidence suggests that some depressed relatives of bipolar patients may be manifesting a

variant of the bipolar genotype. The likelihood that unipolar depression in a relative represents part of the bipolar spectrum segregating in the family is increased if the illness course is clearly episodic and recurrent and if the depressive episodes are associated with clear incapacitation, psychotic features, a positive response to pharmacologic treatment, and hypomanic switching on antidepressant treatment.[56,57]

The conceptualization of schizoaffective disorder from a genetic perspective remains unclear. A number of studies have reported that relatives of schizoaffective probands are at increased risk for both schizophrenia and mood disorders.[38,39,58,59] Furthermore, there is consistent evidence that schizoaffective illness does not represent a completely separate disorder with homogeneous genetic determinants. It is likely that, as with other major mood disorders, schizoaffective disorder represents an etiologically heterogeneous condition; that is, different genetic forms of the clinical syndrome exist. To date, attempts to subdivide schizoaffective probands on the basis of clinical subtypes (depressed vs. bipolar, chronic vs. remitting) have not been validated by family history.[58]

In contrast, while having primary affective disorder (particularly bipolar disorder) increases the risk for that individual to develop a secondary substance abuse problem, it is now recognized that primary alcoholism is probably a separate genetically based illness[60]; that is to say, alcoholism and major affective disorders are not alternative forms of the same genotype, so that relatives of probands with primary affective disorder are not at increased risk for alcoholism compared to the general population.

THE PREDICTION OF TREATMENT RESPONSE

The identification of accurate predictors of treatment response in patients experiencing major affective disorders has been hampered by inconsistent results. To date, reliable predictors including family history data have been identified with respect to long-term lithium treatment. Success of other treatments is more difficult to predict.

Some studies have suggested that certain clinical parameters (age at onset, specific symptoms, course, frequency of episodes, psychological profile) are reliable predictors of response to lithium prophylaxis in patients with primary affective disorders.[61] However, other studies have failed to replicate many of these findings. As pointed out by Grof and others,[62] much of the inconsistency between studies can be attributed to methodological problems and differences including patient selection, study design, outcome definition, and statistical analyses. In order to determine the effectiveness of lithium prophylaxis, the outcome should be mood stabilization (the reduction in intensity and/or frequency of episodes), and the lithium trial should be long enough to differentiate the effect of lithium from the natural course of remission and recurrence. Finally, the trial should be unconfounded by other psychotropic medications (i.e., monotherapy). In methodologically sound studies, specific proband parameters have been found to reliably predict response to lithium stabilization including a diagnosis of primary affective disorder, as well as an episodic course with typical frequency (non–rapid cycling) and with complete remissions.[63]

Genetic studies have enhanced our ability to predict response to lithium prophylaxis in patients with a recurrent mood disorder. It has been consistently reported that a positive family history of primary affective disorders predicts a good response to lithium stabilization in a patient with a primary affective disorder.[64–66] Moreover, a positive family history of bipolar disorder in particular predicts an excellent response to long-term lithium therapy, while a positive family history of schizophrenia predicts a poor response to lithium stabilization.[37] A family history of other psychiatric illnesses including schizoaffective disorder and unipolar depression does not significantly contribute to the likelihood of lithium response, probably because these disorders are more heterogeneous.

CONCORDANCE OF TREATMENT RESPONSE

Despite the often-quoted suggestion that a positive response to a particular class of antidepressant in an index patient predicts a good response to that antidepressant class in other ill family members, there has been little systematic research of this hypothesis. The reasoning is clear in that depressive disorders are known to be a heterogeneous group of illnesses likely reflecting different underlying genetically based biochemical abnormalities. Therefore, it is postulated that the particular form of depression segregating in a family would represent the same genetic condition that would have a selective response to antidepressant therapy shared by other affected family members. While often presented as fact in psychiatric textbooks, the hypothesis that antidepressant response breeds true in families is supported by only a few studies typically based on small numbers of retrospectively reviewed families.[67–69] Specifically, these studies documented similarities of treatment response to imipramine[67] and specificity of response to tricyclics versus monoamine oxidase inhibitors (MAOIs)[68] and to tranylcypromine.[69] Most recently, a series of studies examined similarity of treatment response to fluvoxamine in families.[70] The positive response to fluvoxamine was associated with the serotonin transporter (5-HTT) gene polymorphism,[71] and responder families exhibited single-gene mode of transmission.[72] Prospective studies of treatment response in pairs of relatives would be very useful heuristically, but they may be hard to conduct from a methodological point of view, requiring large samples of family members treated according to the same research protocol.

Similarly, no substantial evidence yet supports the view that an excellent lithium response in one affected relative selectively predicts for an excellent lithium response in other affected family members and a comparatively poor response to other mood stabilizers.[73] However, earlier case reports suggest that affectively ill children of lithium-responsive parents also seem to benefit from lithium.[74–77] Furthermore, we have shown that affectively ill children of excellent lithium responders experience a remitting and episodic illness course that is a predictor for a favorable response to lithium prophylaxis.[78] In our family studies of excellent lithium responders and clear lithium nonresponders, we are attempting to systematically assess the lithium responsivity in affected and treated relatives. It is not clear at this time whether lithium responsivity is attributable entirely to the disease genotype or to separate genetic factors. The former case would predict that lithium response breeds true in affected relatives of lithium responsive probands, while the latter case would predict a partial overlap of affected status and lithium responsivity but not complete cosegregation.

CONCLUSION

In this article, we have reviewed the clinical application of findings from genetic studies of patients with primary affective disorders and their families. An accurate and complete family pedigree documenting the psychiatric status (onset, course, phenomenology, degree of incapacity) and treatment response in any affected members provides important information that can be used to determine what illnesses are segregating in the family (phenotypic spectra), the estimation of morbidity risk to relatives, and a rational approach to treatment intervention.

There remain many clinical research questions that need systematic investigation to better understand the nature of the primary affective disorders including the identification of triggering/protective factors influencing illness onset, the identification of chronobiological factors (i.e., endocrine) influencing the periodicity of the course (cycle length), and the investigation of familial (pharmacogenetic) and course (developmental) parameters affecting treatment response. It is hoped that when susceptibility genes are identified, the biochemical abnormalities can be characterized. Then, those carrying the disease genes can be identified and specific treatments developed. One could speculate that treatment response may differ according to genotype. However, enthusiasm needs to be tempered with the recognition that as yet no specific susceptibility genes have been identified, and there is the possibility that once genes are known they may be of small effect and the usefulness of genetic (DNA) tests may be of limited clinical value.

Drug names: fluvoxamine (Luvox), tranylcypromine (Parnate).

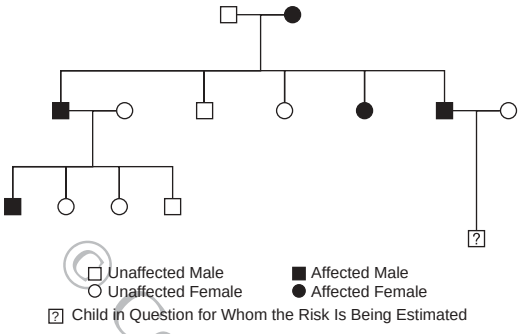
REFERENCES

1. Gershon ES, Berrettini W, Nurnberger JI Jr, et al. Genetics of affective illness. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987:481–491
2. Alda M. Bipolar disorder: from families to genes. Can J Psychiatry 1997; 42:378–387
3. McGuffin P, Katz R. The genetics of depression and manic-depressive disorder. Br J Psychiatry 1989;155:294–304
4. Cannings C, Thompson EA. Ascertainment in sequential sampling of pedigrees. Clin Genet 1977;12:208–212
5. Andreasen NC, Rice JP, Endicott J, et al. The family history approach to diagnosis: how useful is it? Arch Gen Psychiatry 1986;43:421–429
6. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996;276:293–299
7. Bland RC. Epidemiology of affective disorders: a review. Can J Psychiatry 1997;42:367–377
8. Boyd JH, Weissman MM. Epidemiology of affective disorders: a reexamination and future directions. Arch Gen Psychiatry 1981;38:1039–1046
9. Weissman MM, Myers JK. Affective disorders in a US urban community: the use of research diagnostic criteria in an epidemiological survey. Arch Gen Psychiatry 1978;35:1304–1311
10. Weissman MM, Bruce ML, Leaf PJ. Affective disorders. In: Robins LN, Regier DA, eds. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press; 1990:53–80
11. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
12. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517–534
13. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16:4S–14S
14. Angst J, Perris C. Zur nosologie endogener depressionen: vergleich der ergebnisse zweier untersuchungen. Arch Psychiatrie Nervenkrankheiten 1968;210:373–386
15. Gershon ES, Hamovit J, Guroff JJ, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar and normal control probands. Arch Gen Psychiatry 1982;39:1157–1167
16. Perris C. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses, I: genetic investigation. Acta Psychiatr Scand Suppl 1966;194:15–44
17. James NM, Chapman CJ. A genetic study of bipolar affective disorder. Br J Psychiatry 1975;126:449–456
18. Gershon ES, Mark A, Cohen N, et al. Transmitted factors in the morbid risk of affective disorders: a controlled study. J Psychiatr Res 1975;12: 283–299
19. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 1980; 137:497–504
20. Angst J, Frey R, Lohmeyer B, et al. Bipolar manic-depressive psychoses: results of a genetic investigation. Hum Genet 1980;55:237–254
21. Baron M, Gruen R, Asnis L, et al. Schizoaffective illness, schizophrenia and affective disorders: morbidity risk and genetic transmission. Acta Psychiatr Scand 1982;65:253–262
22. Weissman MM, Gershon ES, Kidd KK, et al. Psychiatric disorders in the relatives of probands with affective disorders. Arch Gen Psychiatry 1984; 41:13–21
23. Coryell W, Endicott J, Reich T, et al. A family study of bipolar II disorder. Br J Psychiatry 1984;145:49–54
24. Fieve RR, Go R, Dunner DL, et al. Search for biological/genetic markers in a long-term epidemiological and morbid risk study for affective disorders. J Psychiatr Res 1984;18:425–445
25. Rice J, Reich T, Andreasen NC, et al. The familial transmission of bipolar illness. Arch Gen Psychiatry 1987;44:441–447
26. Blacker D, Tsuang MT. Unipolar relatives in bipolar pedigrees: are they bipolar? Psych Gen 1993;3:5–16
27. Simpson SG, Folstein SE, Meyers DA, et al. Assessment of lineality in bipolar I linkage studies. Am J Psychiatry 1992;149:1660–1665
28. Gershon ES. Genetics. In: Goodwin FK, Jamison KR, eds. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990: 373–401
29. Nurnberger JI Jr, Gershon ES. Genetics of affective disorders. In: Friedman E, ed. Depression and Antidepressants: Implications for Cause and

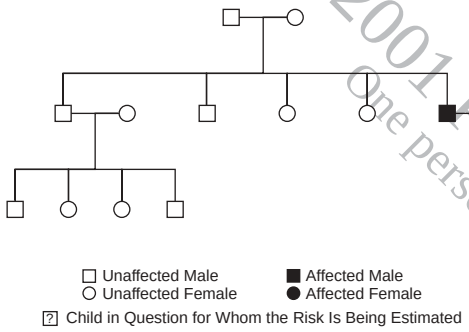
Treatment. New York, NY: Raven Press; 1983:75–98
30. McGuffin P. Major genes for major affective disorder? Br J Psychiatry 1988;153:591–596
31. Weissman MM, Wickramaratne PJ, Merikangas KR, et al. Onset of major depression in early adulthood. Arch Gen Psychiatry 1984;41:1136–1143
32. Weissman MM, Merikangas KR, Wickramaratne P, et al. Understanding the clinical heterogeneity of major depression using family data. Arch Gen Psychiatry 1986;43:430–434
33. Strober M, Morrell W, Burroughs J, et al. A family study of bipolar I disorder in adolescence: early onset of symptoms linked to increased familial loading and lithium resistance. J Affect Disord 1988;15:255–268
34. Strober M. Relevance of early age-of-onset in genetic studies in bipolar affective disorder. J Am Acad Child Adolesc Psychiatry 1992;31:606–610
35. Strober M. Family-genetic aspects of juvenile affective disorders. In: Goodyear IM, ed. The Depressed Child and Adolescent: Development and Clinical Perspectives. New York, NY: Cambridge University Press; 1995: 149–170
36. Klerman GL, Weissman MM. Increasing rates of depression. JAMA 1989; 261:2229–2235
37. Grof P, Alda M, Grof E, et al. Lithium response and genetics of affective disorders. J Affect Disord 1994;32:85–95
38. Angst J, Felder W, Lohmeyer B. Are schizoaffective psychoses heterogeneous? results of a genetic investigation, II. J Affect Disord 1979;1: 155–165
39. Angst J, Felder W, Lohmeyer B. Schizoaffective disorders: results of a genetic investigation, I. J Affect Disord 1979;1:139–153
40. Winokur G, Tanna VL. Possible role of X-linked dominant factor in manic depressive disease. Dis Nerv Syst 1969;30:89–94
41. Reich T, Clayton PJ, Winokur G. Family history studies, V: the genetics of mania. Am J Psychiatry 1969;125:1358–1369
42. Gershon ES, Bunney WEJ. The question of X-linkage in bipolar manic-depressive illness. J Psychiatr Res 1977;13:99–117
43. Hebebrand J. A critical appraisal of X-linked bipolar illness: evidence for the assumed mode of inheritance is lacking. Br J Psychiatry 1992;160: 7–11
44. Baron M, Risch N, Hamburger R, et al. Genetic linkage between X-chromosome markers and bipolar affective illness. Nature 1987;326:289–292
45. Pekkarinen P, Terwillinger J, Bredbacka PE, et al. Evidence of a predisposing locus to bipolar disorder on Xq24-q27.1 in an extended Finnish pedigree. Genome Res 1995;5:105–115
46. Paterson AD, DeLisi LE, Faraone SV, et al. Sixth World Congress of Psychiatric Genetics X Chromosome Workshop. Am J Med Genet 1999;88: 279–286
47. Stine OC, Xu J, Koskela R, et al. Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. Am J Hum Genet 1995; 57:1384–1394
48. McMahon F, Stine O, Meyers D, et al. Patterns of maternal transmission in bipolar affective disorder. Am J Hum Genet 1995;56:1277–1286
49. Weissman MM, Leaf PJ, Tischler GL, et al. Affective disorders in five United States communities. Psychol Med 1988;18:141–153
50. Rice J, Reich T, Andreasen NC, et al. Sex-related differences in depression: familial evidence. J Affect Disord 1984;71:199–210
51. Taylor MA, Abrams R. Gender differences in bipolar affective disorder. J Affect Disord 1981;3:261–277
52. Merikangas KR, Weissman MM, Pauls DL. Genetic factors in the sex ratio of major depression. Psychol Med 1985;15:63–69
53. Baron M, Hamburger R, Sandkuyl LA, et al. The impact of phenotypic variation on genetic analysis: application to X-linkage in manic-depressive illness. Acta Psychiatr Scand 1990;82:196–203
54. Blacker D, Tsuang MT. Contested boundaries of bipolar disorder and the limits of categorical diagnosis in psychiatry. Am J Psychiatry 1992;149: 1473–1483
55. Akiskal HS, Downs J, Jordan P, et al. Affective disorders in referred children and younger siblings of manic-depressives. Arch Gen Psychiatry 1985;42:996–1003
56. Strober M, Carlson G. Bipolar illness in adolescents with major depression. Arch Gen Psychiatry 1982;39:549–555
57. Akiskal HS, Walker P, Puzantian VR, et al. Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. J Affect Disord 1983;5:115–128
58. Kendler KS, McGuire M, Gruenberg AM, et al. Examining the validity of DSM-III-R schizoaffective disorder and its putative subtypes in the Roscommon family study. Am J Psychiatry 1995;152:755–764
59. Stassen HH, Scharfetter C, Winokur G, et al. Familial syndrome patterns in schizophrenia, schizoaffective disorder, mania and depression. Eur Arch Psychiatr Neurol Sci 1988;237:115–123
60. Duffy A, Grof P, Grof E, et al. Evidence supporting the independent inheritance of primary affective disorders and primary alcoholism in the families of bipolar patients. J Affect Disord 1998;50:91–96
61. Abou-Saleh M. Who responds to prophylactic lithium therapy? Br J Psychiatry 1993;21:20–26
62. Grof P, Hux M, Grof E, et al. Prediction of response to stabilizing lithium treatment. Pharmacopsychiatria 1983;16:195–200
63. Grof P, Alda M, Grof E, et al. The challenge of predicting response to stabilising lithium treatment. Br J Psychiatry 1993;163:16–19
64. Mendlewicz J, Fieve RR, Stallone F. Relationship between the effectiveness of lithium therapy and family history. Am J Psychiatry 1973;130: 1011–1013
65. Prien RF, Caffey EM, Klett CJ. Factors associated with treatment success in lithium carbonate prophylaxis: report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1974;31:189–192
66. Stallone F, Shelley E, Mendlewicz J, et al. The use of lithium in affective disorders, 3: a double-blind study of prophylaxis in bipolar illness. Am J Psychiatry 1973;130:1006–1010
67. Angst J. A clinical analysis of the effects of tofranil in depression: longitudinal and follow-up studies: treatment of blood-relations. Psychopharmacologia 1961;2:381–407
68. Pare CMB, Mack JW. Differentiation of two genetically specific types of depression by the response to antidepressant drugs. J Med Genet 1971;8: 306–309
69. O'Reilly RL, Bogue L, Singh SM. Pharmacogenetic response to antidepressants in a multicase family with affective disorder. Biol Psychiatry 1994;36:467–471
70. Franchini L, Serretti A, Gasperini M, et al. Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. J Psychiatr Res 1998;32:255–259
71. Smeraldi E, Zanardi R, Benedetti F, et al. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998;3:508–511
72. Serretti A, Franchini L, Gasperini M, et al. Mode of inheritance in mood disorder families according to fluvoxamine response. Acta Psychiatr Scand 1998;98:443–450
73. Alda M. Pharmacogenetics of lithium response in bipolar disorders. J Psychiatry Neurosci 1999;24:154–157
74. McKnew DH, Cytryn L, Buchsbaum MS, et al. Lithium in children of lithium-responding parents. Psychiatry Res 1981;4:171–180
75. Delong GR. Lithium carbonate treatment of select behavior disorders in children suggesting manic-depressive illness. J Pediatr 1978;93:689–694
76. Youngerman J, Canino I. Lithium carbonate use in children and adolescents: a survey of the literature. Arch Gen Psychiatry 1978;35:216–224
77. Annell AL. Manic-depressive illness in children and effect of treatment with lithium carbonate. Acta Paedopsychiatrica 1969;36:292–301
78. Duffy A, Alda M, Kutcher S, et al. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. Am J Psychiatry 1998;155:431–433

Editor's note: Appendix 1 appears on page 637.

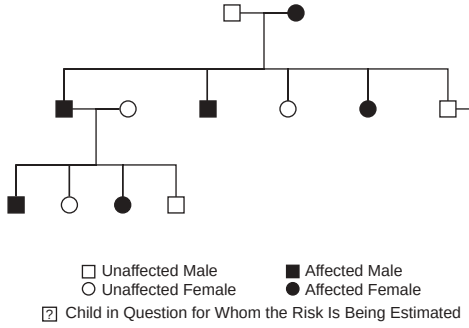
Appendix 1. Examples of Genetic Risk Estimation



In family 1, the pattern of transmission appears to resemble autosomal dominant inheritance. Therefore, the risk of a mood disorder to a child of an affected parent in this case could very likely be significantly higher than the risk based on family studies (i.e., higher than 20%, but less than 50% predicted by an autosomal dominant model with complete penetrance).



An opposite situation is illustrated in family 2. In this case, the illness appears sporadic (i.e., not transmitted) and therefore the estimated risk of a major mood disorder in a child of an affected parent would be lower than the risk based on family studies (i.e., less than 20%). It is important to stress that the family history of the unaffected parent may also influence the estimated risk to the child and should be also reviewed.



Family 3 illustrates yet another dimension to risk estimation. Here, an unaffected person from a genetically loaded family inquires about the risk of illness in his child. In this case, the simple application of risk estimates for a second-degree family member could be misleading given the high number of affected relatives. For instance, if the disease was transmitted as a dominant trait as it appears to be, then either the seemingly unaffected father is truly genetically unaffected, in which case the risk to his child is low, or he may be genetically affected but not yet manifesting the illness, in which case the risk to his child could be quite high.