

Bipolar Disorder: From Families to Genes

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Background: Genetic factors are known to contribute to the etiology of bipolar illness, but the actual genetic mechanisms remain to be clarified.

Methods: This paper reviews the research undertaken to establish the genetic basis of bipolar illness and to elucidate the nature of its genetic predisposition.

Results: The presented findings suggest that bipolar affective disorder is a heterogeneous condition characterized by a complex relationship between the genetic susceptibility and the clinical presentation. Linkage studies have generated promising and replicated findings on chromosomes 18 and 21.

Conclusion: In spite of the methodological difficulties inherent in the genetic study of psychiatric disorders, recent investigations have made important advances and promise to identify specific susceptibility genes.

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Bipolar illness is a major psychiatric disorder with a well-recognized genetic contribution to its etiology. Family, twin, and adoption studies have demonstrated that the illness tends to cluster in families and that this clustering is genetic in nature. Much research has been undertaken in the hope of identifying one or more specific susceptibility genes. Such discovery would have far-reaching implications for the understanding and treatment of the illness.

This paper presents a review of completed investigations and outlines the major obstacles that have hampered the identification of genes and genetic mechanisms in bipolar disorder. The possible ways to overcome these obstacles are also examined. Major improvements in the genetic research strategies have recently emerged and have been reflected in increased research production and in promising and replicated findings.

Of necessity, genetics has become a highly technical field. In order to make this paper useful to a broad readership, technical details are limited to a necessary minimum and/or explained briefly as needed.

Genetic Factors in Bipolar Illness

Family studies have shown that the lifetime prevalence of bipolar and unipolar disorders in the families of bipolar probands is higher than in the families of psychiatrically healthy controls (Table 1).

The estimates of morbidity risks in relatives depend on the diagnostic criteria used and show considerable variability. A more useful variable for assessing the familiarity of a trait is the relative risk (ratio of the risks in relatives of cases and controls). Family studies of bipolar disorder that included control families produced relative risk values of 10 to 15 for bipolar illness and 2 to 5 for major depression (6,9,11,13). The findings from family studies alone are not sufficient to establish a genetic etiology; they merely suggest that there is a familial aggregation which can be genetic or nongenetic.

Twin and adoption studies can differentiate between these 2 possibilities. By comparing prevalences of the illness in identical and fraternal twins of index cases, twin studies control for any possible effects of environment. The weighted concordance rates have been estimated to be 57% in monozygotic twins and 14% in dizygotic pairs (14). It could be argued that the higher concordance in identical twins is at least in part due to a more similar shared environment in comparison with fraternal pairs. The concordance rates in identical twins reared apart, however, do not differ from those in pairs reared together (15), thus strengthening the genetic hypothesis.

Adoption studies provide further support for the notion that the familial clustering of bipolar disorder is genetic in origin. There is an increase in the prevalence of bipolar illness, unipolar depression, and suicide in biological

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relatives of adopted individuals with bipolar disorder (16–18), but not in relatives of nonbipolar probands (19).

What else have we learned from these studies about bipolar illness and its genetics? The genetic factor alone is not sufficient to cause bipolar illness. This is evident, for instance, from lower than 100% concordance rates in identical twins. In addition, bipolar illness is not inherited in a simple Mendelian fashion. Thus, while the importance of genes in the etiology of bipolar disorder cannot be disputed, their actual function is not well understood. We still do not know the nature of the genetic factor or how it is transmitted from one generation to another.

Phenotypic Spectra

Based on family studies, we can assume that not only bipolar illness but also other psychiatric disorders can be manifestations of the same genetic propensity, forming a *phenotypic spectrum*.

Bipolar I and *bipolar II disorders* are usually viewed as part of the same spectrum (20), although several studies have indicated that bipolar II disorder “breeds true” (21,22). This led to a suggestion that at least some cases of bipolar II illness represent a genetically distinct subtype (23,24). The low temporal stability of the diagnosis of hypomania, however, makes this a difficult question to study (25).

Rapid-cycling bipolar illness does not appear to be genetically different from the nonrapid-cycling form (26,27).

Unipolar depression is more prevalent in families of bipolar probands and has been also considered a part of the bipolar spectrum. It has been pointed out that some bipolar patients may not manifest a manic episode until late in the course of the illness. It is possible that some do not develop mania at all, and therefore are never diagnosed as bipolar. At the same time, unipolar depression is common in the general population, and thus it is likely that some depressed relatives of bipolar probands suffer from a different form of depressive illness. Blacker and others (28) estimated that 65% to 75% of depressed first-degree relatives suffer from bipolar spectrum depression, while the remaining cases have clinically similar but genetically unrelated illness.

There has been considerable speculation about a possible genetic link between *schizophrenia* and bipolar disorder. This has fuelled a debate between those supporting the Kraepelinian dichotomy between schizophrenia and manic-depressive illness and those favouring the theory of unitary psychosis (29,30). A recent methodologically rigorous study provides support for the separation of the 2 disorders (31). Other family studies suggest a model with 2 partially overlapping spectra whereby depression and schizoaffective disorder are possible manifestations of both bipolar and schizophrenia genotypes (32,33).

While traditionally considered part of the bipolar spectrum, *alcoholism* does not seem to share any genetic liability

Table 1. Morbidity risks (%) of affective disorders in first-degree relatives of bipolar probands

Study	Morbidity risks in relatives	
	Bipolar disorder	Unipolar disorder
Stenstedt (1)	5.0	8.0
Perris (2)	11.0	0.6
Angst (3)	4.0	14.0
Goetzl and others (4)	4.0	21.0
Helzer and Winokur (5)	5.0	12.0
Gershon and others (6)	4.0	7.0
Videbech (7)	8.0	6.0
James and Chapman (8)	6.0	13.0
Tsuang and others (9)	1.9	11.3
Taylor and Abrams (10)	4.8	4.2
Gershon and others (11)	8.0	14.9
Rice and others (12)	10.4	23.1

with bipolar disorder according to most recent studies (34–36), although some controversy remains (37,38).

The issue of phenotypic spectra is important in daily clinical practice because it directly relates to how we interpret family histories of our patients. In research, phenotypic spectra are critical in molecular genetic studies and in studies of the mode of inheritance in which probands' relatives need to be classified as affected or unaffected. On the one hand, false-positive diagnoses (too liberal diagnostic spectrum) have a damaging effect on studies based on the affected–unaffected dichotomy, while on the other hand, the exclusion of certain diagnoses may reduce statistical power. In the presence of heterogeneity, it is conceivable that there exist subtypes of bipolar disorder, each associated with a different spectrum.

Family studies have produced other findings that are interesting, sometimes replicable, yet not easy to explain. These results should not be overlooked because they might contribute to a better understanding of the clinical genetics of the illness. Examples include findings of increased mortality in maternal grandfathers of bipolar subjects (39) or higher morbidity risks in relatives of female patients (40,41).

Mode of Inheritance

Several hypotheses of the nature of the genetic transmission in bipolar disorder have been proposed, but none of them has been supported consistently. The hypotheses are based on single-gene and polygenic (oligogenic) theories. The X chromosome-dominant mode of inheritance was proposed based on the absence of father-to-son transmission in some families and the finding of linkage between protan–deutan colour blindness and bipolar disorder (42–44). Autosomal-dominant and -recessive models are commonly used in linkage analyses (see below), however, and have been found compatible with the data in several independent samples (8,12,45–51). An interesting continuum hypothesis has been proposed by Goldin and others (52)—a multifactorial model with separate

thresholds for unipolar, bipolar, and schizoaffective disorders. These 3 disorders are thus viewed as manifestations of the same liability but at different degrees of severity.

Caution is required in the interpretation of the results of studies of the mode of inheritance (segregation analyses). Genetic models are an abstraction, and segregation studies do not identify the actual mode of inheritance, but rather compare different models against each other in terms of their likelihoods. They should be viewed as tools for generating hypotheses that can be tested by other methods.

A commonly accepted view at present is that bipolar illness is heterogenous. The genetic predisposition may be conferred by several, but not many, genetic loci (oligogenic model). Generally, the larger the number of genes involved, the lower is the chance that they could be identified by linkage analysis. Given the relatively high prevalence of bipolar illness in the general population, it can be expected that disease-predisposing alleles in at least some of the loci will be very common in the general population. It is also possible that there exist families with an illness caused by a single gene. This will be difficult to prove until actual susceptibility loci are identified, but it represents a reasonable working hypothesis similar to those used in other so-called complex disorders such as asthma or diabetes.

Modern genetic methods allow the mapping of genes that contribute only partially to disease liability. The most commonly used methods at present are linkage and association strategies. Exhaustive reviews of linkage studies in bipolar disorder have been published, for example, by Turecki and others (53); the present paper, therefore, will review only some of the more promising results.

Linkage Analysis

Linkage analysis is a unique tool that can help to locate the genes which play a major role in the pathogenesis of a disorder. Linkage is studied as a cosegregation of a specific form (allele) of a genetic marker with the illness within a particular family (or a set of families). Because of the nature of meiotic processes, this cosegregation will occur only if the disease and the marker genes are located closely together on the same chromosome. Detection of linkage is only the first step in the process of identifying genes through positional cloning. For instance, in the case of Huntington's disease, it took 10 years from the first linkage report to finding the gene. Linkage helps to determine the approximate location of a gene and reduces the number of potential loci, perhaps to a few hundred. Linkage methodology has already recorded successes in simple, Mendelian disorders, as well as complex diseases, for instance, cystic fibrosis (54), Alzheimer's disease (55,56), and diabetes (57,58).

Two types of statistical techniques are available for evaluating the presence of linkage: nonparametric tests (59–61) and the lod score method (62). An important advantage of nonparametric methods is that they do not require any assumptions about the model of inheritance. They tend to

require a large number of proband-affected–relative pairs, but newer methods have improved in this respect (63).

In order to use the lod score method, it is necessary to specify a priori the model of genetic transmission. As this is usually unknown in psychiatric disorders, analyses are carried out with several arbitrary models. Although an incorrectly specified model is not likely to produce false-positive findings in a single analysis, it can lead to a false rejection of linkage or to erroneously high estimates of the recombination fraction.

The problem of phenotype definition has plagued studies of the mode of inheritance as well as linkage studies. The multiplicity of clinical diagnoses is usually converted into a yes–no (affected–unaffected) classification. This is especially important with respect to the diagnosis of unipolar disorder, for which some researchers advocate a more restrictive definition, for instance, adding the criterion of incapacitation and/or recurrent course of illness. Another approach is to carry out several analyses, each time with different diagnostic categories included in the spectrum. This is similar to using several genetic models. In both situations, repeated analyses have a better chance of detecting true linkage at the cost of more frequent false-positive results.

Linkage Studies in Bipolar Disorder

Genetic linkage in bipolar disorder was studied as early as the 1960s (42,43). Studies with such traditional markers as blood groups and blood proteins yielded no conclusive results. One relatively frequent finding did emerge from the earlier linkage studies, however: the X chromosome linkage (42–44). The X chromosome studies, however, suffered from various methodological difficulties (64,65). Furthermore, a review of families included in these studies reveals that X chromosome-dominant transmission cannot be the universal mode of inheritance. If it were, we would expect that father-to-son transmission would be absent and that most daughters of affected men would be affected, which is not the case (66).

Similarly, studies of human leukocyte antigen (HLA) linkage first reported positive results (67–69), but these could not be replicated (70,71). Interestingly, HLA studies suggested that the genetic predisposition was passed from both parental sides, much in agreement with more recent reports of a high prevalence of bilineality (concurrent presence of the illness among both maternal and paternal relatives) in bipolar illness (72).

The older linkage studies were limited by low availability of suitable linkage markers. This changed dramatically in recent years. Psychiatric genetics has embraced the molecular genetic revolution. Thanks to the progress of the field (*Centre d'Etudes du Polymorphisme Humain* [CEPH], Human Genome Project), we now have a new generation of highly polymorphic and ubiquitous markers. At present, almost the entire human genome can be covered with a sufficiently dense set of informative markers (73) that allow automated deoxyribonucleic acid (DNA) typing. This has allowed

several groups to embark on a systematic genome scan—covering the entire human genome by a dense map of markers and studying linkage to each of these. Such a strategy is made possible by automated genotyping facilities and efficient methods of statistical analysis. Essentially, this is a “dragnet approach” as opposed to one that selects markers based on a candidate gene strategy using assumptions about the pathophysiology of the illness.

A number of linkage studies have been carried out thus far, most of them with inconclusive results. Initial positive linkage results on chromosomes 11 (74) and X (75) have failed to be replicated independently (76,77). Moreover, support for chromosome 11 and chromosome X findings has diminished after reanalyses of the original studies using new diagnostic and genotypic information (78,79).

The most promising results so far have been obtained in studies of markers on chromosome 18. Berrettini and others (80) found a suggestive linkage of bipolar disorder to markers in the pericentromeric region of chromosome 18. This finding has been supported by an independent group (81) who found that the linkage was more prominent in families in which the illness was transmitted through the probands' fathers. Excessive sharing of paternal alleles was further found for several markers on the long arm of chromosome 18 in the 18q21 region. Most recent work seems to confirm the existence of at least 2 separate loci: one pericentromeric (18p), possibly recessive, and another on the long arm of chromosome 18 (18q), which appears to be dominant, showing an excessive sharing of paternally transmitted alleles (82). In a combined linkage and association study of families in Costa Rica, Freimer and others (83) also found positive results on the long arm of chromosome 18 (18q22–q23) in 2 close but separate regions. This has been confirmed by genome screen results in the same population (84). These results are promising but need further scrutiny. The regions implicated by these studies span a large (130 cM) segment of the chromosome 18 (85). To make things even more complicated, the regions implicated by Stine and others (81) and by McInnes and others (84) on the long arm of chromosome 18 do not seem to overlap (84). Chromosome 18 continues to be actively investigated, with both positive and negative preliminary results reported. No linkage has been found in ethnically homogenous samples from Quebec (86) or among the Old Order Amish (87,88).

Another promising result comes from Straub and others (89). In their sample, one family out of 47 yielded a significant lod score with the PFKL marker on chromosome 21. As well, 14 other markers on the same chromosome were tested with weakly positive lod scores. Importantly, simulations showed that the observed linkage was unlikely to be a chance result. A study of 23 English and Icelandic pedigrees (90) also found a weak linkage, but with stronger evidence in 2-locus analysis with chromosome 21 markers and with the tyrosine hydroxylase gene on chromosome 11 as the second locus. Further support for a susceptibility gene on chromosome 21 comes from work of Detera-Wadleigh and others (91).

A similar isolated but significant finding represents a recent report by Blackwood and others (92), who found positive linkage in the 4p region.

Ginns and others (93) interpreted data from a genome-wide screen in the Old Order Amish family 110 and its extensions, concluding that the illness was transmitted as a complex trait with susceptibility loci on chromosomes 6, 13, and 15.

How do we reconcile often-conflicting and seemingly nonreplicable results? First, nonreplication can be expected rather commonly in studies of oligogenic diseases (94–96). If the inheritance of bipolar disorder is indeed oligogenic, different susceptibility genes may become fixed, especially in small isolated populations or in high-density families. This might be the reason why high-density families sometimes show Mendelian-like segregation. Variability of different individual genes may then be associated with presence or absence of the illness in different families. At the same time, we should have stricter statistical criteria for replication in originally positive samples (97). As examples of the Amish study or Baron and others show, follow-up of linkage samples and diagnostic reassessments can be very important (78,79).

Association Studies in Affective Disorders

Association studies compare distributions of marker alleles in cases and unrelated controls. Association and linkage strategies are complementary. While linkage analysis is more powerful for detecting the genes immediately involved in the etiology of the illness, association analysis can be more helpful in mapping modifying (susceptibility) genes (98,99). Loci that increase the risk only modestly can hardly be detected by the linkage strategy because of the enormity of the samples required, yet they can be identified through association analysis. Examples of successful applications of the method are associations of ankylosing spondylitis and HLA-B27 (100), narcolepsy and HLA-DR2 (101), and Alzheimer's disease and apolipoprotein E (102).

In principle, a true association between a marker and a disease phenotype can occur if the *marker and disease gene are identical* or the marker and disease loci are in so-called *linkage disequilibrium* (103). In the former case, identified and cloned genes involved in brain functions (for example, neurotransmitters, receptors, early-response genes, and second messengers) can be tested as candidate genes by studying directly allelic variants of these genes in affected and control populations. In the latter case, association will arise in the presence of tight linkage between the 2 loci if one of the genes undergoes a new mutation. Over a number of generations, the disequilibrium will diminish so that only closely linked loci may remain in linkage disequilibrium for a sufficient period of time to be detected through association. The linkage disequilibrium has a good chance to be detected in genetically isolated populations (“founder effect”).

There is a possibility of false-positive results due to ethnic stratification if the population studied is an admixture of 2 or

more populations with different disease and marker allele frequencies. Strategies using internal (family-based) controls (104,105) and the Transmission Disequilibrium Test (106) have been proposed to eliminate this effect.

Previous studies of the association of genetic markers and bipolar illness have been mostly inconclusive. Older studies primarily investigated ABO and MN blood groups (107). Several studies that examined the MN blood group found generally lower frequencies of the NN blood group among bipolar patients (108).

Modern association studies have already investigated a large number of candidate loci. One of the actively investigated genetic regions is the tyrosine hydroxylase locus on chromosome 11, with both positive (109,110) and negative (111–114) results reported. If this association were confirmed, it would not necessarily be discordant with the negative linkage findings. Rather, it could indicate that the tyrosine hydroxylase gene is neither necessary nor sufficient to cause the illness, but it increases susceptibility in genetically predisposed individuals.

Other genes studied so far have been those of the dopaminergic receptors D₁, D₂, D₃, and D₄, with both negative (115) and positive results (116), the pseudoautosomal region of the X chromosome (117,118), the 5-HT_{1A} and 5-HT_{2A} receptor genes (119,120), and the monoamine oxidase-A gene (121–123). Negative results have been also obtained with G_{OLF} protein gene and other markers on chromosome 18 (124).

Rather promising results to date have been obtained with the serotonin transporter gene polymorphisms. Several studies have found associations between this locus and bipolar disorder (125–127) and major depression (128). Negative association (129,130) and linkage (131) results have also been reported. Taken together, such findings could be interpreted as a possible susceptibility locus of a minor effect.

Anticipation, Imprinting

Several aspects of the inheritance of bipolar disorder have puzzled researchers for decades. Although familial, the disease displays an atypical pattern of inheritance. Anticipation and imprinting have been put forth as putative explanations. These are not new concepts, but only recently did genetic studies begin to uncover their molecular mechanisms.

Anticipation refers to a progressive increase in illness severity and decrease in age at onset from one generation to another. This phenomenon was debated earlier in this century in connection with several other disorders, attributed to degeneration, but usually interpreted as a product of ascertainment bias (132,133). Interest in anticipation was revived after discoveries of dynamic mutations in several neurological disorders, such as fragile X syndrome, myotonic dystrophy, and Huntington's disease, as well as other disorders, for instance leukemia (133). The molecular basis of these mutations is an expansion of trinucleotide repeat sequences, for

instance CAG or CGG. The number of such repeats in unaffected subjects is low, but in those affected, the size of these sequences expands and appears to correlate with the severity of the illness and with early onset.

In psychiatry, anticipation has been proposed to play a role in bipolar disorder (134–136) and in schizophrenia (137). The initial report by McInnis and others (134) did indeed show anticipation in bipolar illness in a family sample collected for linkage studies. The issue is, however, far from resolved. The studies showing anticipation attempted to correct for some of the ascertainment biases, but only a few at a time, and their combined effect is as yet unknown. Searches for trinucleotide expansions have also produced tentative results (138–140). Although these studies found that bipolar patients had larger and more frequent CAG/CTG repeats than controls, the size of the repeats did not correlate with the age of onset. Moreover, the trinucleotide repeat expansion could not explain the observed pattern of transmission of the illness. Interestingly, unaffected parents had repeats of comparable size to those in their affected offspring, indicating that the trinucleotide repeat expansion was unlikely to account for a substantial proportion of cases. O'Donovan and others (140) acknowledge that ascertainment bias can produce false evidence of anticipation. It is possible that true anticipation exists in a minority of cases, but because of the "anticipation bias," the evidence for it is inflated.

Imprinting refers to an epigenetic phenomenon of differences between maternally and paternally transmitted illness. It appears to be related to a differential expression of maternally and paternally transmitted disease alleles resulting from methylation during meiosis. McMahan and others (141) found a parent-of-origin effect in unilineal families selected for a linkage study, with a higher prevalence of the illness among maternal relatives.

Mitochondrial inheritance represents another hypothesis. It predicts a complete absence of transmitting fathers. If it exists, it cannot explain a large proportion of cases based on family data.

Heterogeneity

Genetic (locus) heterogeneity is often invoked as an explanation of conflicting genetic findings in bipolar disorder. Thus bipolar illness may reflect a group of underlying conditions rather than a single, etiologically specific entity. Some of these conditions could be caused by different genes, some may be nongenetic in origin. It is important to note that genetic heterogeneity of bipolar illness has not been demonstrated and that inconsistent linkage findings do not prove its existence. Heterogeneity does represent a plausible hypothesis, however. It is common in other complex traits, such as diabetes or Alzheimer's disease, where several different mechanisms lead to the same or similar clinical presentations.

Investigations of heterogeneous groups are likely to obscure the search for major-gene effects. Heterogeneity complicates understanding of the spectra of related disorders and

the mode of inheritance. In analyzing the mode of inheritance, heterogeneity leads to a poor fit of genetic models, it results in high estimates of the rates of sporadic cases, and it favours the model of polygenic transmission (142). In linkage studies, genetic heterogeneity (that is, the presence of families both with and without linkage) may lead to false-negative results or to an overestimation of the recombination fraction.

Diagnosis of bipolar illness is based on clinical description. So far there has been no single biological marker that is present in all affected individuals. Unfortunately, diagnostic habits tend to vary over time, often depending on new discoveries and the availability of effective treatments and/or changes of diagnostic systems used (143,144). The introduction of modern diagnostic criteria, as exemplified by DSM-III and its successors, has contributed to a better reliability of diagnoses but has not substantially improved their validity (145). The effect of changing diagnostic criteria can be seen in family studies done in the last 3 decades, with gradually increasing risks of depression in both relatives and controls.

In the past, different clinical criteria have been used unsuccessfully to define more homogeneous samples. An example of grouping based on phenomenological descriptors is the distinction between bipolar and unipolar disorders. Although these 2 disorders seem to differ with respect to the family history of bipolar disorder, there is considerable overlap with respect to the family history of depressive disorder. Hence it is possible that unipolar depression comprises several disorders, some of which may share the genetic liability with bipolar disease.

This situation leads to a need to identify criteria other than clinical diagnosis to establish more homogeneous patient populations. Some of the strategies used have already been mentioned in this paper. Studies of large families and/or ethnically homogeneous populations represent one such alternative. This is an approach taken by investigators in the Old Order Amish study (74), and also in Quebec (86), Costa Rica (84), and Finland (146).

Some authors suggested that early-onset bipolar disorder represents a subtype characterized by a high genetic liability (147–149).

Another strategy is to narrow the selection of patients according to their response to a specific treatment. The prophylactic response to lithium has been studied extensively in this context. The effect of lithium appears to be based on its action on second-messenger systems and interactions with Na^+ - K^+ adenosinetriphosphatase (150,151). Patients who respond to lithium typically suffer from a primary affective disorder with a recurrent episodic course of illness and with a positive family history of bipolar disorder (108). It has been shown that responders and nonresponders also differ in certain neuroendocrine parameters (152).

Differences between the family histories of patients who respond and those who do not respond to lithium treatment were first described in the early 1970s (153,154). Since then, several family studies have been carried out to confirm the

original findings (41,47,155). In principle, these studies have found a higher frequency of bipolar disorder in families of lithium responders. Some of the studies have shown differences in the mode of inheritance between responders and nonresponders (47,50,51,155). Differences between affected children of responders and nonresponders appear detectable even during prodromal and early stages of the illness (Duffy, unpublished observation). Based on the existing evidence, it is possible to conclude that lithium-responsive patients represent a subgroup of bipolar illness characterized by a higher genetic relative risk and by a distinct mode of inheritance compatible with a major gene effect. These factors, together with an improving knowledge of the mechanism of action of lithium, make this group particularly suited for molecular-genetic investigations.

Future Directions

In spite of the lack of definitive findings, such as unambiguously replicated linkage or the identification of a vulnerability gene, studies to date have made major contributions to our understanding of the genetics of bipolar illness. They have taught us several important lessons:

- 1) There is no single method of choice in the study of the genetics of bipolar disorder. Currently, a host of methods are available including lod score method, nonparametric linkage tests, the Transmission Disequilibrium Test, and association analyses using family-based or population controls. These methods can be used in a complementary way to increase the chance of detecting linkage or association.

- 2) Large samples are needed. Collaborations between several research groups may be necessary for collecting data sets with sufficient power to detect linkage or association. The use of multiple markers and dense maps is another way of improving the statistical power (63).

- 3) Laboratory methodology continues to improve and will not likely be the limiting factor.

- 4) More clinical and basic research is needed to improve definitions of affected phenotype. At present, we rely on clinical description, and most genetic studies use the affected–unaffected dichotomy. It will be important to improve homogeneity of samples studied. Better understanding of the pathophysiology of the illness should lead to a better selection of candidate genes.

- 5) Follow-up of linkage and association samples will remain crucial for updating clinical information and for the replication of positive findings.

- 6) Caution is necessary in interpreting data that can be biased as a result of ascertainment procedures (X chromosome transmission, mitochondrial DNA, paternal–maternal transmission, anticipation).

Conclusion

Bipolar illness is a severe disorder with high morbidity and mortality. Recent molecular genetic studies indicate the

possibility of identifying specific genes involved in its etiology. This would have important implications both for treatment and for understanding the interplay between those factors—genetic susceptibility on the one hand and developmental and environmental factors on the other hand—which eventually lead to a manifestation of the illness.

Clinical Implications

- Knowledge of the genetic basis of bipolar illness can help in the diagnostic assessment of patients and in genetic counselling.
- Identification of susceptibility genes in bipolar disorder promises to lead to the development of novel treatments.
- Genetic research will make it possible to study the effects of stress and environment in genetically predisposed individuals.

Limitations

- The genetic predisposition to bipolar illness is not likely to be conferred by only a single gene.
- New research methods may need to be developed for genetic studies of complex psychiatric diseases.
- The genetic heterogeneity of bipolar illness has to be resolved to improve the chances of major findings.

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Résumé

Toile de fond : *Le rôle des facteurs génétiques dans l'étiologie du trouble bipolaire est connu, mais les mécanismes génétiques réels restent à préciser.*

Méthodes : *Dans cet article, on examine les recherches entreprises afin d'établir le fondement génétique de la maladie bipolaire et d'élucider la nature de sa prédisposition génétique.*

Résultats : *Les constatations présentées laissent croire que le trouble affectif bipolaire est un état hétérogène caractérisé par une relation complexe entre la prédisposition génétique et le tableau clinique. Des études de liaison ont donné lieu à des constatations prometteuses et répétées au sujet des chromosomes 18 et 21.*

Conclusion : *Malgré les difficultés méthodologiques inhérentes à l'étude génétique des troubles psychiatriques, des recherches récentes ont permis de marquer des progrès importants et d'identifier des gènes de susceptibilité spécifiques.*