Genetics of bipolar disorder

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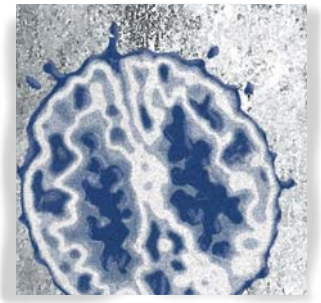

Bipolar disorder, especially the most severe type (type I), has a strong genetic component. Family studies suggest that a small number of genes of modest effect are involved in this disorder. Family-based studies have identified a number of chromosomal regions linked to bipolar disorder, and progress is currently being made in identifying positional candidate genes within those regions. A number of candidate genes have also shown evidence of association with bipolar disorder, and genome-wide association studies are now under way, using dense genetic maps. Replication studies in larger or combined datasets are needed to definitively assign a role for specific genes in this disorder. This review covers our current knowledge of the genetics of bipolar disorder, and provides a commentary on current approaches used to identify the genes involved in this complex behavioral disorder.

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Bipolar affective disorder, type I (BP-I) is a severe mental illness marked by periodic extremes of mood state (manias), as well as (in most cases) episodes of depression and (in many cases) psychosis. The consequences of BP-I are severe, and involve both direct and indirect issues. Rates of suicide in BP-I patients are high,[1,2] and BP-I subjects also suffer from poorer quality of life and lower productivity than unaffected individuals.[3] Annual public health costs (combined direct and indirect) of BP have been estimated to be between 24 billion and 45 billion dollars.[4,5] BP-I occurs in all populations that have been studied, with lifetime prevalence rates worldwide of the order of one per every 100 individuals.[6] Segregation analyses, adoption studies, and twin studies have consistently shown that, regardless of the population studied, genetic factors play an important role in determining one's risk of developing BP-I.[7-9] Since little is known about the actual etiology of BP, it would be a major contribution to our understanding of the pathophysiology of BP if the genes responsible for the neurobiologic changes which underlie this disorder could be identified. The difficulty in finding genetic loci that are involved in BP most likely derives from the complex nature of the illness. When multiple transmission models for BP-I (the most severe form of BP) have been tested, oligogenic epistatic models are found to be the best fit, rather than models which purport one major locus. Craddock et al[10] reviewed epidemiologic, family, and twin studies, and showed that two, three, or four locus models

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of BP-I were formally consistent with observed data, but suggested that a three- or four-locus model (with site-specific λ_R of 1.7 to 2.0) best fit the parameters of their mathematical models of BP-I transmission. Indeed, the concordance for BP in monozygotic twins (0.67), when compared with concordance in dizygotic twins (0.10 to 0.20)[11] and the relative risk in first-degree relatives (0.10 to 0.20),[12] strongly suggests that more than one locus is involved.[13] Moreover, genome scans from several groups have been conducted to date on the "BP spectrum" phenotype, with evidence for a "BP" gene locus varying by study, including findings of possible loci on chromosome 18q21-23,[14-17] chromosome 4p12-13,[18,19] chromosome 13q31-33,[20] and other loci (see section on linkage scans below). Tellingly, no study has shown predominant linkage to just one site in their sample, even when the sample is drawn from a more homogenous population.[19,27] Although reasonably strong evidence for linkage has been found in several studies (an LOD score of 3.8 in 20 pedigrees,[21] a multipoint LOD score of 3.92 in 2 families from Quebec,[22] a combined linkage/association score of 4.01 in two Costa Rican pedigrees[15]), replication and identification of genes for BP has been elusive.

Overcoming the key obstacles to mapping BP gene loci (etiological heterogeneity, imprecision in the definition of affected phenotypes, and uncertainty regarding mode of genetic transmission), will likely require the collection of a very large sample of families, consisting of rigorously diagnosed BP-I individuals drawn from genetically homogeneous populations. The National Institute of Mental Health Genetics Initiative[23] was driven by the philosophy that disorders such as BP may have quite low genetic risk ratios for any given locus. While this is based in part on the failure of previous studies to identify and replicate a BP locus, we do not feel that this failure in previous studies should be taken as proof that no major locus for a BP gene exists. Rather, it is clear that no previous study in the field of bipolar genetics has focused on the most severe phenotype (BP-I) in a large-scale study which utilizes sib-pair and nonparametric analyses to attempt to map predisposition genes. If current estimates that there are a few (or at least one to two) loci with genetic (locus-specific) risk ratios for BP-I above 1.5 are correct,[10] failure to identify these loci may be attributed to problems in phenotype definition (only recently have studies restricted analyses to BP-I,[27,28,29-41] heterogeneity of the samples (few have focused on a single ethnic group), model specification difficulties, and insufficient sample sizes.

Recent advances in identifying genes for schizophrenia (SC) are of particular interest here. In early linkage studies of SC, researchers initially relied heavily on SC spectrum diagnoses which included schizotypal disorder, brief psychosis, and others, before limiting their "affected category" to the most reliably diagnosed, narrowest, and most severe phenotype, SC itself. Following years of studies reporting weak and nonreplicable findings, substantial evidence for SC gene loci finally came from studies that confined themselves to a narrow diagnostic classification (SC only), focused on many small families (mostly sib pairs), and concentrated on one major ethnic group.[42,43] In these studies, sib-pair or nonparametric analyses were used to identify loci on chromosomes 13 and 8. In each case, subsequent studies supported SC genes being linked to these loci. This has led to identification of genes in both regions,[44,45] which give strong evidence of being SC predisposition genes and, in turn, stimulated a reappraisal of the pathogenic mechanisms underlying SC.[46]

Bipolar genetic research is currently at a similar state to where research on SC was prior to the studies by Blouin et al[43] and Pulver et al.[42] BP mapping studies conducted up until 2004 (and most since that time) consisted of small sample sizes (from 1 to 98 pedigrees) with wide phenotype definitions (BP-I, BP-II and recurrent depression). In the last couple of years, a few larger sets of data, such as the that from the Wellcome Trust UK and Ireland[47] have been analyzed. At best, with very small sample sizes, previous studies have narrowed the phenotypic definition to "BP-I and BP-II"—yet, even these subtypes of BP have questionable congruence at the biologic level (many studies, for instance, now suggest that BP-I and BP-II are fundamentally different illnesses).[48-50] While it is true that the BP spectrum includes BP-I, BP-II, and recurrent depression at some level,[9] past genetic mapping studies have shown clearly that using this broad definition of BP cannot successfully identify the genes involved in any of these categorical illnesses. Such studies actually might work against being able to find BP genes, as the population prevalence of the combined "extended" phenotype increases (the lifetime prevalence of depression in women from the United States, for instance, is over 10% in both the Epidemiological Catchment Area [ECA] and National Comorbidity Survey [NCS] studies) while the heritability of their proposed phenotype decreases (depression is less heritable than mania).[12]

BP-I is the most severe, most reliably diagnosed,[51-53] and most genetic form of BP,[12] yet almost all previous genetic studies of BP have failed to study the BP-I phenotype without clouding the picture by including BP-II and recurrent depression in the phenotype definition. No doubt, a major limitation to performing studies on the most severe phenotype, BP-I, has been the fact that finding families with large sibships, who are intact and agreeable to participate, has been prohibitively difficult in mainstream United States society. Indeed, the original NIMH Bipolar Genetics Initiative, consisting of three sites (Washington University in St Louis, Indiana University, and Johns Hopkins University) collected a total of only 145 affected sib pairs with the most severe diagnosis (BP-I or schizoaffective, bipolar) over 10 years, as their pedigree selection was based, whether by design or practicality, on a wider phenotype (NIMH Center for Genetic Studies; http://zork.wustl.edu/nimh).

Risch and Merikangas[54] have estimated that for a genetic risk ratio of λ=1.5, approximately 500 sib pairs will be necessary to have adequate power of mapping a disease gene in an outbred population such as that of the United States, although they acknowledge that in a more homogeneous population the number of sib pairs needed may be less. The difficulty of obtaining such samples may be the most important limiting factor in confirming linkage analysis of BP, as evidenced by recent efforts to develop multicenter collaborations for pedigree collections for both SC[55] and BP.[12] Nevertheless, there have been a number of linkages reported to BP spectrum diseases, as described in the next section.

Linkage studies

Pedigree-based linkage analyses have been quite successful in identifying the genes for hundreds of simple Mendelian diseases (like Huntington's disease), and for a few complex diseases (like early-onset Alzheimer's and early-onset breast cancer). Although a few groups have focused on a small number of large, extended pedigrees,[27,56] due to the difficulty of obtaining large multiplex families, genome-wide scans using dense maps of polymorphic markers in small pedigrees have become the standard strategy for finding bipolar genes through linkage.[57] To circumvent problems inherent in complex diseases, nonparametric methods have recently been utilized, where mode of inheritance, allele frequency, or penetrance parameters (currently unknown for bipolar disorder) are not needed to assess linkage between phenotype and genotype. In what may be a preview of things to come, investigators from several countries recently pooled their genotypic information from 11 different genome-wide linkage scans, (with a total sample of 5179 individuals from 1067 families), and found successful, genome-wide significant evidence of linkage to chromosomes 6q and 8q.

Table I summarizes key findings from a number of linkage analyses performed over the last 20 years, indicating the chromosomal regions, phenotypes focused on, and the LOD scores for each region. As we increase our sample sizes (mainly through collaborative efforts from multiple sites), improve the phenotypic definition of bipolar disorder (possibly through endophenotype discoveries) and discover improved meta-analysis tools, it is hoped that linkage analyses will assist the field in better understanding where the most critical loci for bipolar disorder (predisposition genes of moderate effect) are located in the human genome. In the current excitement over genome-wide association (GWA) analyses (see section below), it would certainly be unwise to overlook the benefits of family-based linkage analyses to contribute to the identification of genes for complex diseases.

Association studies

Candidate genes

Until recently, it was not practical to consider GWA studies to try to detect genes for bipolar disorder. To screen the whole genome and detect genes that are associated with bipolar disorder requires that the gene variant responsible for the phenotype (ie, bipolar disorder) is in tight linkage disequilibrium with the variant (typically either a microsatellite or a single nucleotide polymorphism, SNP) being studied. Linkage disequilibrium is a technical term that indicates that two genetic loci are so close that specific alleles for the loci segregate together more often than would be expected by chance. At the genome level, areas of linkage disequilibrium, at least in outbred populations, are very small,[79] thus requiring that hundreds of thousands of SNPs be genotyped per person. Although such studies are now becoming possible (see the "Genome-wide Association Studies" section below), many investigators have focused on particular genes, to determine whether they might be associated with bipolar disorder. This candidate gene approach usually

Chromosomal region (marker)	Phenotype	Main author	Reference	Maximum LOD Score
1p35-p36	(DSM-IV) BP-I, BP-II, SABP, or recurrent MD	Schumacher J et al	59	(NPL=3.97)***
1q31-q32	BP-I, BP-II with major depression, SCA, and UPR	Detera-Wadleigh SD et al	20	2.67
1q42 (D1S2800)	(DSM-IV) SABP, BP-I, or SC	Hamshere ML et al	58	3.54
2p13-16	BP-I or SCA-manic type	Liu J et al	44	3.20
2q24	SCA-manic type, BP-I, BP-II with recurrent MD	Zandi PP et al	60	1.99
3q14 (D3S1300)	BP-I or BP-II or SABP, regardless of age of onset, or if they had a major depressive episode with an age of onset of ≤21	Etain B et al	61	(NPL=3.51)***
3p21 (D3S1285)	BP-I	McInnes LA et al	27	2.26
3q28 (D3S2418)	SCA-manic type, BP-I, BP-II with recurrent MD, or MDD-R	Zandi PP et al	60	1.94
4p (D4S394)	BP-I and BP-II	Blackwood DH et al	18	4.1
4q12-q21 (D4S392)	BP-I, BP-II with MD, SCA, and UPR including individuals with 2 or more episodes of MD	Detera-Wadleigh SD et al	20	1.77
4q21	BP-I, BP-II, SCA and recurrent MD	Cassidy F et al	37	(NPL-2.23)***
4q31 (D4S1625)	BP-I or SCA-manic type	Liu J et al	29	3.16
4q31	(DSM-IV) BP-I, BP-II, SABP, or recurrent MD	Schumacher J et al	59	(NPL=5.49)***
4q35 (between D4S3051-4qTEL13)	BP-I, BP-II, SCA-manic type, or UPR	Badenhop RF et al	62	3.2
Chrom 5 (D5S207)	BP-I or SABP, BP-II with recurrent depression, plus UPR	Dick DM et al	63	2.8
5q31-33 (D5S2049)	BP-I	Herzberg I et al	30	(NPL=4.395)***
5q33-34 (GABRA1)	BP-I or SCA with presence of hallucinations and delusions	Kerner B et al	31	(P<0.00001)
Chrom 6 (108.5 Mb)	(DSM-IV, RDC, DSM-III-R) BP-I only	McQueen MB et al	32	4.19
6p (D6S7)	BP-I (RDC)	Ginns EI et al	33	2.2
6q (D6S1021)	BP-I, SABP, BP-II, or UPR	Dick DM et al	36	3.61
6q16-q21 (D6S1021)	(DSM-IV) BP-I, BP-II, BP-NOS, MDD-R	Lambert D et al	47	2.62
6q22	(DSM-IV) BP-I or SABP	Pato CN et al	34	3.56 (NPL=4.20)***
6q24	(DSM-IV) BP-I, BP-II, SABP, or recurrent MD	Schumacher J et al	59	(NPL=4.87)***
7p (between D7S1802- D7S1869)	BP-I, BP-II, and SCA or UPR (RDC and DSM III-R)	Detera-Wadleigh SD et al	64	(P≤ 0.05)*
7q31 (between D7S1799-D7S501)	BP-I, BP-II with MD, and SCA or individuals with two or more episodes of MD	Detera-Wadleigh SD et al	20	2.08
7q34 (D7S1824)	BP-I or SCA-manic type or BP-II	Liu J et al	29	2.78
7q36	BP-I, BP-II, SCA, recurrent MD	Cassidy F et al	37	(NPL=2.11)***
Chrom 8 (135.4 Mb)	DSM-IV, RDC, DSM-III-R) BP-I only	McQueen MB et al	32	1.99
8q (D8S256)	BP-I or SABP	Dick DM et al	36	2.46
8q24 (D8S284)	Female participants with history of puerperal psychosis, defined as a mania or psychosis with onset within 6 weeks of delivery	Jones I et al	65	2.03
8q24 (D8S256)	Included BP-I, BP-II with UPR, and SABP	McInnis M et al	66	2.1
8q24.21-qter	BP-I or SABP	Segurado R et al	35	(P_{AvgRnk} ≤0.05)**
Chrom 9 (24.5 Mb)	(DSM-IV, RDC, DSM-III-R) BP-I only	McQueen MB et al	32	2.04
9p21-q21	BP-I, BP-II, SCA and recurrent MD	Cassidy F et al	37	(NPL=2.41)***

Table I. Bipolar linkage studies. *, multilocus ASP analysis; **, Genome scan meta-analysis (GSMA); *** multipoint nonparametric (NPl) and parametric linkage analyses; æ, Multiple scan probability (MSP); BP-I, bipolar disorder type I; BP-II, bipolar disorder type II); SABP, schizoaffective disorder, bipolar type; UPR, recurrent unipolar depression; MD, major depression; SCA, schizoaffective disorder; SC, schizophrenia; MDD-R, major depressive disorder recurrent

Chromosomal region (marker)	Phenotype	Main author	Reference	Maximum LOD Score
9p21.1-q21.1	BP-I or SABP	Segurado R et al	35	(P_{AvgRnk} ≤0.05)**
Chrom 10 (D10S1423)	SABP, BP-I, and BP-II	Foroud T et al	68	2.5
10p (between *INS* and *HRAS1*)	(RDC) BP-I, BP-II, SCA (manic-depressive type), atypical psychosis with prominent affective features, and Unipolar MD	Egeland et al	56	4.904 (note: further analysis of this data set yielded negative LOD scores in this region)
10p12 (D10S1423)	BP-I, SABP, and BP-II	McInnis M et al	67	2.2
10q11.21-q22.1	BP-I or BP-I and SABP	Segurado R et al	35	(P_{AvgRnk}=.008)**
10q24 (D10S169)	manic syndrome, mostly BP-I	Liu J et al	29	2.79
10q25-q26 (D10S217)	BP-I, BP-II with major depression, and SCA and those individuals with two or more episodes of MD	Cichon et al	70	2.86
10q26 (D10S217)	included bipolar disorder, single episode mania or SCA, manic and depressed type	Ewald et al	69	2.17
11p15.5 (between D11S1984-D11S2362)	(DSM-III-R and RDC) SABP, BP-I, and BP-II	Zandi PP et al	41	(NPL = 2.19 near marker D11S1923, peak HLOD of 2.00) ***
12q23-q24	BP-I, SABP, BP-II, and UPR	Morissette J et al	72	1.327
12q24 (D12S378)	BP-I, SABP and BP-II recurrent episode, and recurrent MD	Shink E et al	71	3.35
12q24	BP-I only	Cassidy F et al	37	(NPL=2.20)***
13q	"SCA, BP-I and BP-II, and narrower models"	Badner JA et al	74	(MSP=6x10-6)ψ
13q14–32	SABP or BP-I	Stine OC et al	38	1.12
13q31 (D13S317)	All subjects with a mood disorder	Potash JB et al	75	2.52 (NPL=3.56)***
13q31-q34	BP-I, BP-II, SABP and recurrent MD	Kelsoe JR et al	73	2.4
13q32 (between D13S1252–D13S1271)	BP-I, BP-II with MD, SCA and individuals with two or more episodes of MD	Detera-Wadleigh SD et al	20	3.5
13q32 (near D13S779)	manic syndrome, mostly BP-I, plus BP-II	Liu J et al	29	2.2
14q24 (D15S1014)	BP-I only	Cassidy F et al	37	(NPL=3.27)***
15q26 (D15S1014)	(DSM-IV) SC, SCA, Bipolar Disorder	Vazza G et al	39	(NPL=3.05)***
Chrom 16 (D16S749)	BP-I or SABP, BP-II with recurrent depression, and UPR	Dick DM et al	63	2.8
16p13	BP-I only	Cassidy F et al	37	(NPL=2.23)***
16p13 (D16S423)	Female participants with history of puerperal psychosis (see above)	Jones I et al	65	4.07
17q (D17S928)	BP-I, SABP, BP-II and UPR	Dick DM et al	36	3.63
17q11-12 (D17S921)	manic syndrome, mostly BP-I	Liu J et al	29	2.68
Chrom 18 (D18S21)	SCA, BP-I, and BP-II with major depression and UPR	Berrettini WH et al	26	2.38
18pter-p11 and 18p11-q12.3	BP-I, SABP BP-II, and recurrent major depressive disorder	Segurado R et al	35	(P_{AvgRnk} ≤0.05)**
18p11.2 (between D18S1150–D18S71)	BP-I, BP-II with MD, and SCA	Detera-Wadleigh SD et al	20	2.32
18q22-23 (D18S61)	BP-I	McInnes et al.	27	2.26
19q13 (D19S221)	(DSM-IV) SABP, BP-I, or SC	Hamshere ML et al	58	1.85
Chrom 20 (4.2 Mb)	(DSM-IV, RDC, DSM-III-R) BP-I only	McQueen MB et al	32	1.91
20p12 (D20S162)	BP-I, BP-II, SABP, and UPR	Willour VL et al	77	1.82 (nonparametric LOD score of 2.38)
21q22 (PFKL locus)	(RDC) Bipolar disorder or recurrent MD	Straub RE et al	24	3.41

Table I. Continued (and on next page)

requires an a priori hypothesis that a gene, due to its location near a linkage peak and/or because of the function of its gene product, might play a role in bipolar disorder. Systematic analyses of genes in peak regions found from linkage studies have been rare (ie, where all genes under the linkage peak are carefully screened). However, analyses of genes in these peak regions (positional candidates) have led to positive associations for a number of genes on chromosomes including 5, 12, 13,[80] 18,[81-85] and 22.[86] A large number of genes have been studied because of a hypothesized role based on neurophysiology, including genes that play a role in circadian rhythms,[87,88] the dopaminergic pathway (*DRD1*, *DRD4*, *DAT1*[89-91]), the serotinergic pathway (*HTTLPR*,[92] *HTR2A*[93]), neural development and neurotrophism (*BDNF*,[94] *NCAM 1*[95]). In addition, as genes have been discovered for schizophrenia, investigators have also analyzed whether these genes might be associated with bipolar disorder, with several studies now suggesting that variations in the Neuregulin 1 gene[96,97] and the G72/30 gene[98,99] are associated with bipolar disorder or manic psychosis. Replication of genetic association studies has been difficult, in part because the sample sizes necessary to detect genes are of small effect size. Other difficulties in candidate gene studies are similar to problems faced in all association studies: poorly matched cases and controls can lead to false-positive or -negative results, definitions of bipolar disorder vary across studies, and genes may have different effects based on background population issues (genetic background and environmental background). Of all the specific candidate genes shown in one study or another to be associated with bipolar disorder, at this point none of these findings have been robust enough or tested in large enough samples to definitively implicate them in the genesis of bipolar disorder.

Genome-wide association studies

Recently, with the advent of genetic chips that can analyze over 500 000 SNPs, and the knowledge-base provided by analysis of the human genome, it has become possible to construct GWA studies in outbred populations. In this approach, a case-control or trio approach (affected subjects, plus their parents) is utilized, typically requiring thousands of subjects, and 500 000 or more SNPs are analyzed in order to determine specific genes or regions associated with a disorder. The approach has recently provided promising results in studies of type II diabetes, cancer, and other medical conditions which can be classified as common and complex diseases, and this has led to efforts in the United States, the United Kingdom, and elsewhere, to pursue GWA studies on a large scale.[100,101] The potential advantage of whole-genome association studies is that such studies may be able to pick out associations of genes that do not have major effect on a disease, and (if the sample size is big enough) potentially overcome complications when disorders are multigenic. On the other hand, sample sizes needed for analyses may be difficult to reach without major investments, the cost of the technology is not trivial, rare alleles with major effects may be overlooked, stratification issues and multiple testing issues become even more crit-

Chromosomal region (marker)	Phenotype	Main author	Reference	Maximum LOD Score
21q (D21S212)	BP-Iand BP-II, with major depression and schizoaffectives	Detera-Wadleigh SD et al	78	1.79
21q22 (D21S1260)	BP-I, unipolar manic, SCA, BP-II, plus UPR and recurrent unipolar and "individuals who do not quite meet criteria but are judged to possibly have above diagnoses"	Liu J et al	76	3.56
22q	"SCA, bipolar I and bipolar II, and narrower models"	Badner JA et al	74	(MSP=3x10-5)[v]
22q11 (D22S420)	(DSM-IV) SABP, BP-I or SC	Hamshere ML et al	58	1.96
22q12 (D22S278)	(DSM-III-R) BP-I, BP-II, SABP, and recurrent MD	Kelsoe JR et al	73	3.84
22q12-13 (D22S277)	All subjects with a mood disorder	Potash JB et al	75	3.06
Xp22 and Xq26–28	SABP, BP-I anf SABP, BP-I, BP-II (respectively)	Stine O et al	38	0.94 and 1.34 (respectively)
Xp11.3 (GATA144D04)	(DSM-III-R) SABP and BP-I	Zandi PP et al	41	(NPL =2.19; HLOD=2.25) ***
Xq24-q26 (DXS994)	BP-I, BP-II, BP-NOS or SCA	Pekkarinen P et al	40	3.54

Table I. Continued

ical than in linkage studies, selection of individual cases may dilute the study of "genetic" forms of bipolar disorder, and replication will remain a difficult issue, leading some to temper the expectations we might expect from GWA analyses.[102]

GWA studies in bipolar disorder were initially pursued in the Costa Rican population, with microsatellites placed relatively sparsely across the genome.[103-105] Although these studies yielded potentially interesting linkage disequilibrium between bipolar disorder and specific chromosomal regions, the sparseness of the map did not allow specific genes to be implicated at the screening level. Two recent GWA studies of bipolar disorder, using dense SNP maps, have been reported thus far. Baum et al[106] used a two-stage strategy, beginning with 461 bipolar cases and 563 controls and following up significant findings in a sample of 772 bipolar cases and 876 controls, and found evidence for novel genes potentially associated with bipolar disorder, including a gene for diacylglycerol kinase, which plays a key role in the lithium sensitive phosphatidyl inositol pathway. A study by the Wellcome Trust Case Control Consortium utilized 2000 bipolar cases and 3000 controls, and reported on a number of SNPs showing evidence of association, some at specific loci that had not formerly been implicated in studies of bipolar disorder. For both of these recent GWA studies, additional genes or regions have been added to the list of possible genes involved in bipolar disorder. Comparisons across studies, replication studies for specific genes in new samples, combined analyses and even larger case-control studies will be necessary to adequately separate the wheat from the chaff. An additional GWA study of bipolar disorder is currently under way in the United States, as part of a private-public joint venture known as the GAIN collaborative group.[100] The true cost versus benefit of such massive ventures, compared with the potentially more modest costs of continuing and combining linkage studies and following these up with focused fine mapping, has yet to be determined.

Endophenotypes

It is known that neuropsychiatric disorders and their phenotypes do not follow classic Mendelian genetics, but rather a complex genetic pattern where multiple genes are involved and environment also modifies the course of illness. It is the interaction of all these aspects that lead to the phenotypic appearance of these complex disorders. These difficulties, as well as the relatively slow process in identifying genes for complex disorders, has led many investigators to begin to focus on identifying genes for "endophenotypes." The term endophenotype has been defined as an internal, intermediate phenotype that may fill the gap in the causal chain between genes and distal diseases.[107] An endophenotype can be an inherited neurophysiological, neuropsychological, cognitive, neuroanatomical, biochemical, or endocrinological trait.[108]

The current diagnostic and classification of psychiatric disorders is not based on pathophysiology or etiology, but is based on nosological tradition, expert consensus, psychometric reliability and clinical utility.[109] Endophenotypes, if accurately defined, could represent more basic biological phenomena than the more complex related phenotype. Theoretically, it might then be easier to identify genetic variants associated with an endophenotype than it would be to identify variants associated with a more complex phenotype. Ideally endophenotypes would stem from a monogenic etiology, but this is generally not the rule. Because they are often quantitative and occur in affecteds and unaffecteds, endophenotypes also allow more persons per family to participate and contribute linkage information. Quantitative linkage and association methods can also be utilized.

In order for an endophenotype to be useful in the identification of genetic markers for a disorder it must meet several criteria: (i) it has to be associated with the illness in the population; (ii) it has to be heritable; (iii) it should be primarily state-independent (manifests in an individual whether or not the illness is active); (iv) it should segregate with illness within families; and finally (v) the endophenotype found in affected family members should be found in nonaffected family members at a higher rate than in the general population.[110,111] Another aspect which should be taken into consideration when identifying an endophenotype is the feasibility and reliability of its measurement.

Following are a number of preliminary studies which suggest possible endophenotypes for bipolar disorder that derive from neuroanatomy and neuropsychology. Importantly, we do not know at this point whether any of these meet all of the criteria necessary to be fully considered as an endophenotype for bipolar disorder. Future studies need to be done, especially in terms of measuring heritability and segregation with disease, for these and other potential endophenotypes.

Potential neuroanatomical endophenotypes

When looking at biological structures of the brain, there are studies that suggest specific regions of the brain as endophenotypes for bipolar disorder. MacDonald et al[112] indicated that a genetic risk for bipolar disorder was specifically associated with gray-matter deficits in the right anterior cingulate gyrus and ventral striatum. Two studies revealed that the risk of white-matter abnormalities is more than threefold higher in patients with bipolar disorder than in healthy controls.[113,114] A meta-analysis of magnetic resonance imaging (MRI) brain measurements done in multiple studies reviewed by McDonald et al[115] showed right lateral ventricular volume was increased in bipolar subjects.

Potential neuropsychological endophenotypes

Some studies focus on brain function as endophenotypes for bipolar disorder. Attention deficits have been considered as an endophenotype, where it was found to be present early in the disorder and was more pronounced with recurring episodes of bipolar.[116] Poor performance on verbal memory tests was consistently found as a characteristic of bipolar disorder.[117] Impaired planning (speed of information processing) after reduced tryptophan availability could represent another endophenotype.[118] Lithium is a treatment for bipolar disorder, and has been shown to modify the phase and period of circadian rhythms in a variety of species involving the glycogen synthase kinase 3 (GSK-3) inhibitor.[119,120] There is preliminary evidence of an association between a polymorphism in the GSK-3-β promoter gene and bipolar disorder, suggesting that genetic factors involved in the regulation of the human circadian clock might represent another endophenotype for bipolar disorder.[121]
For more thorough reviews of the role of endophenotypes for bipolar disorder, see refs 122 and 123.

Summary and future directions in genetic studies of bipolar disorder

The last two decades have been a time of vigorous activity in the field of bipolar disorder genetic studies. Although success in the ultimate goals of clearly identifying which genes play a role in this disorder has been modest, this is not unusual, given the complexity of the disorder and the challenge of identifying genes for any disorder that is not caused by a single major gene. Moving from the pioneering work in the 20th century to define the genetic basis of bipolar disorder, through carefully designed family and twin studies, a number of teams throughout the world have focused their energies on gathering large numbers of multiplex families, in order to carry out genome-wide linkage studies to identify bipolar gene loci. These studies have used fairly modest numbers of families, compared with the recommended number for complex diseases,[54] and, perhaps as could be expected, the linkage scores have been modest in all studies published, ranging at best up to LOD scores in the range of 3 to 4. Although meta-analyses have been performed, few studies have combined large numbers of families to interrogate specific loci, with the largest systematically gathered samples coming primarily from the NIMH Genetics Consortium and the UK Wellcome Trust Consortium. Joint analyses combining data from multiple groups are only just now beginning to occur.[32] Smaller sets of families, from special populations known as "population isolates"[124] have also yielded a number of linkage regions with modest LOD scores. Systematic fine mapping of these regions may yield specific genes of interest for bipolar disorder, as was seen in similar linkage studies of schizophrenia. Candidate genes studies have also yielded a number of potentially associated genes deserving of further study in combined, large samples. New technologies now make GWA studies possible, and such studies will soon add a number of additional genes to the pool of potentially associated genes for bipolar disorder. Endophenotype studies will most likely also add a number of novel genes to consider in terms of how they might indirectly contribute to bipolar disorder of mood destabilization. Technologies that allow detection of copy number variants and chromosomal variations, as well as analyses of methylation patterns (epigenetics), genomic expression, and proteomic analyses will add further gene candidates which can be targeted for study at the genomic level. As each new piece of data comes in from these studies, a major challenge for the field will be to sort out and keep track of the various findings. The use of bioinformatics to review convergent evidence from multiple types of studies will become a critical component of research planning and interpretation of results.[125,126] Iterative research, in which variants are discovered for a bipolar phenotype, and then those subjects who carry the variant are studied in more detail ("deep phenotyping") may help to more clearly link gene vari-

ants to bipolar phenotypes. Ultimately large collaborative studies, which clearly delineate specific phenotypes (categorical and quantitative) and take population genetics carefully into account, will be needed to, one by one, determine the exact correlation between gene variants and risk for the disease (or trait) of interest.

Scientists and clinicians who may have hoped that one or a few genes would eventually be identified that would explain the majority of risk for bipolar disorder must face the reality that there are likely to be many genes of relatively small effect involved in bipolar disorder, and the genetic dissection of this disorder will be a subtle and complex process. Genetic testing for bipolar disorder will likely ultimately require careful weighing of the presence or absence of many gene variants, when counseling is being done at the population level. As specific genes are clearly identified to play a role in bipolar disorder, it remains quite possible that within specific families or clusters, genes of moderate effect will be discovered, but we must face the fact that thus far, no clear bipolar disease causing variant has been discovered in any family studied. In the next decade, a feasible goal might be to clearly implicate at least a handful of genes (through well-powered replication studies or meta-analyses), from which the biochemical pathways underlying the disease can be more thoroughly studied at the level of cell biology and physiology. Such approaches may yield clear pharmacologic targets which can intervene in disease processes that have their origin in genetic risk variants, at times by acting on an enzyme or protein that is part of the biochemical pathway rather than on the gene or gene product itself.[127]

It is likely that over the next decade, the field of bipolar genetics will shift from the current emphasis on identifying the genes which play a role in this disease, to understanding the pathophysiology of the disease from a new perspective (ie, by study of the pathways tied to the genes which play a role in the disease). Along with this work, we might also cautiously expect that bipolar disorder may at last begin to be understood to be a complex behavioral phenotype, with many components and subtypes. For a "disorder" that involves some of the fundamental behaviors and experiences of relevance to the human race, including regulation of activity levels, the ability to feel euphoria and dysphoria, to control social impulses, to create, to have racing thoughts, and to over- or undervalue one's capacities, it is perhaps not surprising that the molecular underpinnings of the bipolar condition will prove to be complex and subtle, and span a multiplicity of gene and protein networks. Indeed, the gene variants which contribute to bipolar disorder may have evolved because of their specific value in helping individuals or groups adapt to socially and physically challenging and changing environments.[128] To understand the genetics of bipolar disorder may, in the end, not be any less of a task than to understand the genetics of human psychology and behavior. ❑

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Genética del trastorno bipolar

El trastorno bipolar, especialmente el tipo más grave (tipo I), tiene un fuerte componente genético. Los estudios en familias sugieren que un pequeño número de genes de efecto modesto están involucrados en este trastorno. Estudios basados en familias han identificado un número de regiones cromosómicas que se relacionan con el trastorno bipolar y actualmente el progreso está orientado a identificar la posición de genes candidato dentro de esas regiones. Un número de genes candidato también ha demostrado evidencia de asociación con el trastorno bipolar, y actualmente se están desarrollando estudios de asociación del genoma completo utilizando numerosos mapas genéticos. Se requieren estudios de replicación en conjuntos de datos más grandes o combinados para asignar definitivamente un papel a genes específicos en este trastorno. Esta revisión cubre nuestro conocimiento actual de la genética del trastorno bipolar y entrega un comentario acerca de las aproximaciones actualmente utilizadas para identificar los genes involucrados en este complejo trastorno conductual.

Génétique des troubles bipolaires

Les troubles bipolaires, surtout la forme la plus sévère (type 1), ont une composante génétique importante. D'après des études familiales, un petit nombre de gènes à effet modeste sont impliqués dans la maladie. Ces mêmes études ont identifié des régions chromosomiques liées à la maladie bipolaire et des progrès sont actuellement réalisés dans la définition de la position des gènes candidats au sein de ces régions. L'association d'un certain nombre de gènes candidats avec la maladie bipolaire a été démontrée et des études d'association avec l'ensemble du génome sont en cours, en utilisant des cartes génétiques denses. Des études de réplication sur des bases de données plus importantes ou combinées sont nécessaires pour attribuer définitivement un rôle à des gènes spécifiques dans cette maladie. Cet article passe en revue nos connaissances actuelles sur la génétique des troubles bipolaires et commente les approches actuelles d'identification des gènes impliqués dans ce trouble complexe du comportement.

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