Molecular linkage studies of bipolar disorder

Wade H. Berrettini, MD, PhD

Wade H. BERRETTINI

Linkage studies have defined at least five bipolar (BP) disorder susceptibility loci that meet suggested guidelines for initial identification and subsequent confirmation. These loci, found on 18p11, 18q22, 21q21, 4p16, and Xq26, are targets for BP candidate gene investigations. Molecular dissection of expressed sequences for these regions is likely to yield specific BP susceptibility alleles in most cases. In all probability, these BP susceptibility alleles will be common in the general population, and, individually, will be neither necessary nor sufficient for manifestation of the syndrome. Additive or multiplicative oligogenic models involving several susceptibility loci appear most reasonable at present. It is hoped that these BP susceptibility genes will increase understanding of many mysteries surrounding these disorders, including drug response, cycling patterns, age-of-onset, and modes of transmission.

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From: the department of Psychiatry and the Center for Neurobiology and Behavior, University of Pennsylvania, USA
Address for correspondence: Dr Wade H. Berrettini, Department of Psychiatry and the Center for Neurology Behavior, University of Pennsylvania, 415 Curie Boulevard, Room 111, Philadelphia, PA 19107, USA
E-mail: wadeb@mail.med.upenn.edu

Bipolar (BP) disorders are common, chronic, recurrent, and episodic mood disturbances, associated with variable dysfunctions in sleep, appetite, libido, activity, and cognition. These disorders are typically so severe that they impair occupational functioning. Bipolar disorders are characterized by recurrent episodes of mania and depression, both of which are defined below.

Mania represents a state of persistently elevated (predominantly euphoric) mood with increased activity, intrusive social behavior, irritability (unpredictable angry outbursts are common), decreased need for sleep, grandiosity, excessive energy, increased libido, spending sprees, racing thoughts, and poor judgement (inability to perceive possible adverse consequences of dangerous behavior). Mania represents a more severe syndrome than **hypomania**, and is often accompanied by psychotic symptoms, including hallucinations and delusions. Hypomania is a less severe form of mania. Mania causes impairment in functioning, whereas hypomania (by definition) does not. Untreated episodes of mania or hypomania are typically 1 to 3 months in length, although this duration is quite variable.

Depression represents a state of persistent and pervasive sadness, accompanied by crying spells, decreased energy, suicidal ideation, decreased libido, anhedonia (inability to experience pleasure), decreased cognitive ability, sleep dysfunction (insomnia or hypersomnia), and appetite disturbance (with or without weight change). The duration of an untreated episode of depression is typically 6 to 9 months.

Bipolar disorder is characterized by repeated manic or hypomanic episodes and recurrent depressive episodes. Two subtypes of BP disorder are recognized: the BP II category is reserved for persons who have never had an episode of frank mania, but have experienced hypomania with recurrent episodes of depression; the BP I category describes individuals with the full syndrome of manic and depressive episodes. Individuals with BP disorder have a median of 10 episodes of illness during their lifetime, even with treatment. The diagnosis of **unipolar disorder** describes individuals who have recurrent episodes of depression but no (hypo)manic episodes. Persons with unipolar (UP) illness have a median of 4 episodes during their lifetime. The mean age at onset for BP

disorders is ≈25 years, and for UP disorders it is ≈35 years, although onset in adolescence is becoming increasingly common among generations born after World War II.[1-5] UP illness affects females twice as often as males, but BP illness affects both sexes equally. BP illness affects ≈1% of the general population, while UP illness occurs in ≈10% of people.[6] Suicide is the sole reason for shortened life expectancy among BP and UP individuals, and suicide occurs in ≈10% of cases.[7]

Selected abbreviations and acronyms

APM *affected pedigree member*
ASP *affected sibling pair*
BP *bipolar disorder*
BP I *bipolar disorder I—manic and depressive episodes*
BP II *bipolar disorder II—hypomanic and depressive episodes*
IBD *identical-by-descent*
LOD *logarithm of the odds of linkage*
MZ *monozygotic*
UP *unipolar disorder*

Genetic epidemiology of bipolar disorders

Twin, family, and adoption studies have indicated the existence of a genetic predisposition for BP disorder. Monozygotic twins are concordant for BP illness (including UP diagnoses) ≈65% of the time, but dizygotic twins show a concordance rate of ≈14% *(see Table I)*. The heritability of BP illness may be as high as 80%.

Modern twin studies,[15-18] conducted with operationalized diagnostic criteria, validated semistructured interviews, and blinded assessments also describe significantly greater monozygotic (MZ) twin concordance. The MZ twin concordance rate (≈65%) indicates decreased penetrance of inherited susceptibility or the presence of phenocopies (nongenetic cases). Among MZ twin pairs concordant for mood disorder, when one twin has a BP diagnosis, UP illness is present among 20% of the ill cotwins.[13,14] This suggests that BP and UP syndromes share some common genetic susceptibility factors. This may have clinical relevance, in that it provides a heuristic model to support the use of lithium for prophylaxis of recurrent UP illness.[19]

Family studies of BP illness show that a spectrum of mood disorders is found among the first-degree relatives of BP probands: BP I, BP II with major depression (hypomania and recurrent UP illness in the same person), schizoaffective disorders, and recurrent unipolar depression.[20-29]

Mendlewicz and Rainer[30] reported a controlled adoption study of BP probands, including a control group of probands with poliomyelitis. The biological relatives of the BP probands had a 31% risk for BP or UP disorders, as opposed to 2% in the relatives of the control probands. The risk for affective disorder in biological relatives of adopted BP patients was similar to the risk in relatives of BP patients who were not adopted away (26%). Adoptive relatives do not show increased risk compared to relatives of control probands.

Wender et al[31] and Cadoret[32] studied UP and BP probands. Although evidence for genetic susceptibility was found, *adoptive* relatives of affective probands had a tendency to excess affective illness themselves, compared with the adoptive relatives of controls. Von Knorring et al[33] did not find concordance in psychopathology between adoptees and bio-

Study	Monozygotic twins		Dizygotic twins	
	Concordant pairs/Concordance		Concordant pairs/Concordance	
	Total pairs	%	Total pairs	%
Luxemberger,[8] 1930	3/4	75.0	0/13	0.0
Rosanoff et al,[9] 1935	16/23	69.6	11/67	16.4
Slater,[10] 1953	4/7	57.1	4/17	23.5
Kallman,[11] 1954	25/27	92.6	13/55	23.6
Harvald and Hauge,[12] 1975	10/15	66.7	2/40	5.0
Allen et al,[13] 1974	5/15	33.3	0/34	0.0
Bertelsen et al,[14] 1977	32/55	58.3	9/52	17.3
Total	**95/146**	**65.0**	**39/278**	**14.0**

TABLE I. Concordance rates for affective illness in monozygotic and dizygotic twins. Data not corrected for age. Diagnoses include both bipolar and unipolar illness.

logical relatives when examining the records of 56 adoptees with UP disorders. Heritable factors may be more evident in BP syndromes than in UP disorders.

The twin, adoption, and family studies have provided impetus to systematic searches of the human genome for BP susceptibility loci, using multiplex BP kindreds and microsatellite genotypes in linkage analyses.[34] These reports are reviewed below.

Bipolar molecular linkage studies—general considerations

The human genome consists of ≈3.3 billion base pairs of DNA. A strand of DNA consists of a sugar (deoxyribose) phosphate backbone, each sugar bonded to one of four nucleotides in a linear manner. The linear sequence of the nucleotides (guanine [G], cytosine [C], thymine [T], and adenine [A]) is the genetic code. DNA is naturally found as a double helix, in which two complementary (in terms of nucleotide sequence) strands are intertwined. The DNA is organized into 22 pairs of autosomal chromosomes, numbered according to physical size, and a pair of sex chromosomes, X and Y. Each chromosome is constituted by two complementary strands of DNA, in double helix conformation. Physical distance along the chromosomes can be expressed in terms of base pairs. Alternatively, distance can be expressed in terms of centiMorgans (cM), reflecting the frequency of recombination. One cM is ≈one million base pairs (bp) of DNA.

Molecular linkage studies of BP disorder have been conducted using highly polymorphic DNA markers, termed microsatellites.[34] These DNA sequences differ in length among individuals because they contain a variable number of a simple repetitive sequence (usually consisting of 2, 3, or 4 nucleotides). The most common repetitive sequence in microsatellites is CA, although GATA and others are frequently encountered. Many of these microsatellites have 10 or more sizes, each different size constituting an allele that can be traced through a family to determine if the allele segregates with illness. Consider the following kindred, in which father has BP disorder and mother is unaffected. At some anonymous DNA marker, father has alleles 1,2; mother has alleles 3,4. It can be seen that allele 1 is transmitted with illness and allele 2 is transmitted to the unaffected children. The probability that father will transmit allele 1 to each child is 50%. A LOD (logarithm of odds of linkage) score statistic assesses the probability that, *within a family*, cosegregation of illness and a marker allele has occurred randomly, versus the probability that the cosegregation of illness and a marker allele has occurred because the marker allele is located near a disease gene on the same chromosome, such that the two are transmitted together more often than expected by chance (=50%).

LOD score calculations require specification of the disease allele frequency in the population, the mode of inheritance (dominant or recessive or some intermediate model), and the penetrance. If the mode of inheritance is misspecified, then the LOD score may not detect linkage when it is present.[35] For BP disorders, of course, none of these parameters are known. In practice, investigators usually calculate LOD scores under dominant and recessive models of inheritance with reduced penetrance. A LOD score numerical value of 3 occurs 1 to 2 times randomly whenever the entire genome is searched for linkage.[36]

Another useful statistic in complex trait analysis is the affected sibling pair (ASP) calculation. This statistic relies on the fact that pairs of siblings will share 50% of their alleles randomly. The distribution of this allele sharing randomly assumes the following pattern:

Number of alleles shared:	0	1	2
Percentage of all sibling pairs:	25%	50%	25%

Pairs of affected siblings will tend to share alleles to a greater extent when the DNA marker alleles are located near a disease gene that contributes to the illness in the affected siblings pairs. Consider the affected siblings in the pedigree diagram above. Four affected sibling pairs share 1 allele and 2 pairs share 2 alleles, but none share 0 alleles. This skewing of the expected random distribution of allele sharing towards greater sharing is consistent with the hypothesis that the DNA marker is located near a BP susceptibility gene (ie, linkage is present). This method can be extended to all pairs of affected relatives.[37-39] These statistics do not require specification of the mode of inheritance, penetrance, or disease allele frequency, as is necessary for the LOD score method. Because these affected relative statistics do not require specification of these parameters, they are often described as *nonparametric* methods.

In genetic linkage studies of complex traits, validity is conferred only by demonstrating the underlying DNA sequence variants that explain the linkage statistics or through independent confirmation of the original linkage report in a second group of pedigrees. Statistical guidelines for judging validity of linkage reports in complex disorders have been suggested.[36,40] These guidelines suggest thresholds for an ini-

tial report of "significant" linkage (LOD score ≈3.6 or nominal $P \approx 0.00002$) and for confirmation (LOD score =1.2 or $P \approx 0.01$). These guidelines should limit false positives to less than 5%. It should be remembered that these guidelines refer to analysis of a single phenotypic definition (eg, BP I and BP II disorders). If multiple (overlapping) phenotypes are analyzed, some statistical adjustments for multiple hypothesis testing may be necessary.

An associated critical issue is the power of a confirmation study to detect the effect size initially described. Effect sizes are often expressed as the increased relative risk[41] due to a specific genetic locus.[42] This increased relative risk refers to the ratio of the risk to a BP proband's relative (eg, sibling) to develop the disorder divided by the risk for the general population. For BP disorder, family studies suggest that the relative risk for siblings is increased by a factor of ≈8 to 9 (see Gershon et al,[20] for example). Because BP disorder is almost certainly an oligogenic syndrome, in which at least several loci contribute to the increased relative risk, locus-specific relative risk (the increased risk due to a single locus) is expected to be much less than 9. For complex traits, such as hypertension, diabetes, and BP disorder, loci that increase risk by factors greater than 2 are unusual. One such locus is near the HLA locus for insulin-dependent diabetes mellitus (relative risk ≈3),[43] another is the apolipoprotein E locus in late-onset Alzheimer's disease.[44]

If three loci of equal effect size are used in an interactive multiplicative model to explain the increased relative risk in BP disorder (each locus increases relative risk by ≈2), then these three hypothetical interactive loci explain most of the relative risk ($2 \times 2 \times 2 = 8$). Thus, loci that increase risk for BP disorder will have minor to moderate effects. Substantial sample sizes are required to detect such loci of minor effect. As Hauser and Boehnke[45] have shown, ≈400 affected sibling pairs are needed to have >95% power to detect initially (LOD >3) loci which increase risk by a factor of 2, while 200 pairs are needed to have >95% power to provide confirmation ($P \leq 0.01$) of a previously detected locus.

Review of bipolar molecular linkage studies

Molecular methods have been used in BP linkage studies to localize susceptibility genes. A linkage study of Old Order Amish pedigrees described evidence (LOD score >4.0) for a BP locus on 11p15,[46] but this evidence has been weakened by failure to confirm the finding in numerous other pedigrees[47-54] and by evaluation of newly ascertained individuals in the original pedigree.[55] However, this hypothesis (that a BP susceptibility gene exists on the tip of the short arm of chromosome 11) remains viable and interesting. The LOD score in the original Old Order Amish pedigree 110 is ≈2.0, and similar weakly positive LOD scores are reported for this region by other investigators.[56,57] Furthermore, several reports have described evidence for association of tyrosine hydroxylase (located in 11p15) with BP disorder,[58-64] although other groups have not confirmed this observation.[65-74] The existence of an 11p15 locus of small effect on risk for BP illness remains a tenable hypothesis.

Xq28 was reported linked to BP illness in studies employing clinically-assessed color blindness and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[75-81] Molecular studies have not confirmed these "pre–molecular reports."[54,82-85] The linkage to color blindness and G6PD deficiency in the most recent positive report[78] was not confirmed in those same pedigrees by molecular methods employing relevant Xq28 DNA markers.[86] There is no published molecular linkage study consistent with an Xq28 BP susceptibility locus.

The complex inheritance of BP illness and the failure of multiple genome-wide scans to detect major gene effects indicate that BP susceptibility loci represent small to moderate effects. Novel statistical methods to detect loci of small effect[38,39,87] and development of dense highly polymorphic marker maps[88,89] have provided the necessary tools to conduct the large-scale, definitive studies.

Suarez et al[90] simulated initial detection of linkage, and subsequent independent confirmation of the originally detected locus, in a complex disease caused in part by six equally frequent independent (unlinked) disease loci. A larger sample size is necessary and an extended waiting period is likely for confirmation of a previously detected locus. This is intuitively reasonable, because of sampling variation. Independent pedigree samples might detect one of the other five loci, as opposed to the one locus initially detected. This simulation study[90] suggests that universal agreement regarding BP linkage studies will not occur. If two or more independent investigators find significant evidence for linkage in independent series of pedigrees, it is reasonable to assume validity.[36,91] It is reassuring to note that several groups have reported putative BP susceptibility loci that have been confirmed independently. This suggests that genetic dissection of BP disorders will proceed from established linkages, as has been the case with Alzheimer's disease.[44]

Berrettini et al[92,93] reported significant evidence for a BP susceptibility locus on chromosome 18 using affected sibling pair (ASP) and affected pedigree member (APM) methods

(P=10^{-4}-10^{-5}), obtained in 22 Caucasian kindreds of European ancestry. Independent confirmation of this finding was reported by Stine et al[94] and others as noted in *Table II*. Evidence for linkage appears to be more prominent in those families with paternally transmitted illness.[94-97]

Wildenauer et al[98,99] studied 59 multiplex German and Israeli schizophrenia pedigrees, in which there were only two BP cases. Their analyses involved a broad affection status model in which 23 recurrent UP cases were included. When these data were analyzed by a multipoint identical-by-descent (IBD) statistic, the maximum LOD score was 3.2 at D18S53.[98] Wildenauer et al[99] also describe linkage disequilibrium (P≈0.0001) with the 124 bp allele of a microsatellite in the Golf gene, a candidate gene in 18p11.2. This region of 18p may contain a gene that increases risk for psychotic disorders of varying syndromal form. The possibility that BP and schizophrenic disorders might share some of the same susceptibility factors is consistent with family studies of schizophrenia, which report an increased risk for schizoaffective and unipolar disorders among the first-degree relatives of schizophrenic probands.[29,100] Similarly, increased risks for schizoaffective and UP disorders are found among the first-degree relatives of BP probands, compared to first-degree relatives of controls.[20,24,29] Further, Kendler et al[101] found increased risk for schizophrenia among the relatives of individuals with psychotic affective illness.

Table II summarizes nominal significance levels for statistical analysis of marker genotypes located in a ≈10-cM region of chromosome 18p11. Results are presented for a narrow phenotypic definition in which only BPI was affected[96,97] or for a broader definition.[93,94,102]

If the locus described by Berrettini et al[92,93] increases risk for BP disorder by a factor of ≈2, simulations indicate that ≈200 affected sibling pairs are required to have >90% power to detect it[103] at a significance level (LOD >1.2 or P<0.01) adequate for confirmation.[36] Various authors[104-110] have studied samples from European, Icelandic, and North American populations, and found no evidence for confirmation of linkage on 18p, but these sample sizes did not exceed 100 affected sibling pairs in any one study. However, the 18p BP locus has not been confirmed in the National Institutes of Mental Health (NIMH) Collaborative Study[111] in which an adequate sample size was evaluated.

Genetic Analysis Workshop 10[112] allowed statistical geneticists to analyze data from Berrettini et al,[93] Nothen et al,[96] Stine et al,[94] Knowles et al,[97] and Kalsi et al.[104] Results of several different analyses were consistent with the existence of a BP susceptibility gene. For example, Lin and Bale[113] analyzed the entire data set of 382 affected sibling pairs (defined under a broad affection status model) using a multipoint nonparametric method. At D18S37, for 382 affected sibling pairs excess allele sharing (58%) was evident, with P=2.8×10^{-8}. Stine et al[94] also reported evidence for linkage to a distinct and separate region, 18q21-2. This 18q linkage was supported by the LOD score method (LOD is 3.51 for D18S41) and the ASP method (P=0.00002 at D18S41) in paternal pedigrees. In an extension of this work, McMahon et al[109] provided additional evidence for linkage to 18q21-2 in 30 new BP kindreds. This locus may have been detected by Freimer et al[114] and McInnes et al[115] who studied Costa Rican BP kindreds. McInnes et al[115] described evidence for increased allele sharing at some of the same markers identified by McMahon et al.[109] For example, at D18S55, McMahon et al[109] reported a nonparametric LOD score of 2.2, while McInnes et al[115] at this same marker report a maximum likelihood estimate of the LOD score as 1.67.

Straub et al[116] described linkage of BP illness to 21q21, near the phosphofructokinase locus. An extended BP pedigree with a LOD score of 3.41 was reported from a series of 57 BP kindreds; further, the APM method yielded evidence for linkage (P<0.0003 for PFKL). A confirmatory report has been described from a two-locus analysis of genotypic data from 21q21 and 11p15.5 in a study by Gurling et al.[56] This 21q21 BP susceptibility locus has been confirmed by Detera-Wadleigh et al,[117] who employed multipoint ASP analyses (P<0.001). Confirmation has been recorded by the NIMH Genetics Initiative collaborative study of BP disorder.[111] Thus, there are three independent confirmatory studies of this BP susceptibility locus.

Xq26, including the coagulation factor IX (F9) locus is a third region of interest regarding BP susceptibility loci. The F9 locus was identified as a region of interest by Mendlewicz et al.[118] A number of supportive reports followed.[119-122] However, these reports involved either a single or a few DNA markers with low polymorphism content or clinically assessed F9 deficiency as markers in single kindreds. Pekkarinen et al[123] reported evidence for BP linkage (a LOD score of 3.54 at DXS994) by using multiple microsatellite DNA markers in the region near HPRT, which is ≈10 cM centromeric to F9, in a single large Finnish pedigree. This finding probably represents a confirmation of the previous reported F9 linkage. Confirmatory affected sibling pair data have also been published for Xq26 markers in an analysis of affected sisters.[54]

Blackwood et al[124] reported on a single large Scottish kindred which showed linkage (LOD 4.1 at D4S394) to 4p DNA

Study	DNA marker (distance in cM)					
	D18S53 (2)	S37 (2)	S453 (2)	S40 (3)	S45	MP*
Berrettini et al,[93] 1997	0.04	0.01	0.06	0.0046	0.002	0.00008
Stine et al,[94] 1995	0.02	0.0003	NR†	0.02	NS‡	NR
Nothen et al,[96] 1998§	0.03	0.005	0.002	0.005	NR	0.0004
Knowles et al,[97] 1998	0.001	0.08	0.50	NR	0.0003	NS
Wildenauer et al,[99] 1997‖	0.0001	0.0056	0.078	0.038	NR	0.0006

TABLE II. Linkage results (*P* values) for bipolar disorder and 18p11 DNA markers. *MP = multipoint; †NR = not reported; ‡NS= not significant; §results for paternal kindreds; ‖schizophrenia probands.

markers, near the α_{2C} adrenergic and D_5 dopaminergic receptor genes. They found weakly positive LOD scores in several smaller kindreds of the same ethnic origins. They found no mutations in the dopamine receptor gene. Confirmation of the 4p locus has been noted by Nothen et al,[125] in which increased allele-sharing was noted at D4S394 (*P*=0.0009).

Ginns et al[126] conducted a genomic scan of multiple kindreds from the Old Order Amish community near Lancaster, Pennsylvania. This group reports modest evidence for BP susceptibility loci on chromosomes 6 (LOD=2.5 at D6S7), 13 (at D13S1), and 15 (at D15S45). Confirmation of these loci has not been reported.

Kelsoe et al[127] reported some evidence for a BP susceptibility locus on chromosome 5p15.5, near the dopamine transporter locus, in North American and Icelandic kindreds. In an affected sibling pair analysis, at D5S392, *P*=0.0008. This report, which did not reach statistical criteria for significant linkage (Lander and Kruglyak[36]), requires confirmation.

Ewald et al[128] reported evidence for a BP susceptibility locus on 16p13 in two Danish kindreds. Assuming a recessive mode of inheritance, a two-point LOD score of 2.52 was found for marker D16S510, and a three-point LOD score of 2.65. Support for this 16p13 locus had been described, in a preliminary publication,[129] but Ewald et al's report[128] did not describe evidence for significant linkage. Thus, this locus must be studied in greater detail.

Lachman et al[130] described limited evidence for a BP susceptibility locus on chromosome 22, near the velocardiofacial syndrome locus. This region has been implicated in risk for schizophrenia,[98,131] and modest supportive evidence for linkage to BP disorder has been reported.[129] This region deserves further study.

Anticipation is the term used to define an observation that a familial disorder occurs with earlier age-at-onset and/or increasing severity among younger generations, compared to older generations. Anticipation occurs in several neurodegenerative diseases, including Huntington's disease, fragile X, myotonic dystrophy, spinocerebellar ataxias, and others. The molecular explanation for anticipation in these disorders involves unstable intragenic trinucleotide repeats, which expand in subsequent generations, giving rise to increasing levels of gene disruption and thus to earlier age-at-onset and increasingly severe phenotype in younger generations.[132]

Evidence for anticipation has been reported in several family studies of BP illness,[3,133-135] but some authors suggest that there is intractable ascertainment bias.[136,137] Individuals with earlier age-at-onset BP disorder may have reduced capacity to reproduce, so parents with such early-onset disorders may be underrepresented in the general population. Individuals with familial BP disorder may come to treatment earlier than those with sporadic disease, such that less severe mood disorder episodes are detected medically, and an earlier age-at-onset is defined. Such individuals (by virtue of their familiarity with mood disorder symptoms) may be more likely to report minor mood disturbance in terms of "diagnosable syndromes." Some evidence for anticipation in BP disorder comes from extensive studies of multiplex BP families for linkage studies. These linkage studies select for earlier age-at-onset cases, because preference is given to densely-affected kindreds. Among broader cultural factors possibly underlying the evidence for anticipation, if stigma concerning mood disorders is less among younger affected persons (compared to older individuals), then younger cohorts might describe their experiences more easily in terms of a diagnosable mood disorder, since denial (due to stigma) is less prevalent among the younger cohorts. These potential confounding factors make detection of anticipation in BP disorder difficult.

The hypothesis that anticipation in BP disorder reflects causative expanding trinucleotide CTG repeat sequences has generated genomic searches for such sequences,[138-141]

using the repeat expansion detection method.[142] Increased lengths of CTG repeats were thus noted in BP disorders, especially among those with familial disease. However, not all studies have reported this difference,[143] and no report shows transmission of an expanding repeat within BP families, the definitive evidence. Furthermore, greater than 90% of the expanded CTG repeats detected by the repeat expansion detection method[142] are from two apparently nonpathogenic unstable CTG repeats on 17q and 18q21.[144] The hypothesis that unstable trinucleotide repeats represent BP susceptibility factors deserves continued study. ❑

Estudios de enlace molecular en los trastornos bipolares

Los estudios de enlace han definido al menos cinco locus de susceptibilidad a los trastornos bipolares (BP) que cumplen con las directrices estándard para la identificación inicial y la confirmación subsecuente. Dichos locus, localizados en 18p11, 18q22, 21q21, 4p16 y Xq26, son blancos para las investigaciones genéticas en candidatos bipolares. La disección molecular de las secuencias expresadas para estas regiones parece producir alelos específicos para la susceptibilidad BP en la mayoría de los casos. Con toda probabilidad, estos alelos de susceptibilidad BP se encuentran presentes en la población general pero, individualmente, no son ni necesarios ni suficientes para la expresión del síndrome. En la actualidad, parece lógico considerar los modelos oligogénicos aditivos o multiplicativos que involucran varios locus de susceptibilidad. Se espera que estos genes de susceptibilidad BP permitirán aumentar la comprensión de los diferentes misterios que rodean dichos trastornos, incluyendo la respuesta a los fármacos, los patrones cíclicos, la edad de aparición y las formas de transmisión.

Etudes des liaisons génétiques dans le trouble bipolaire

L'étude des liaisons génétiques dans le trouble bipolaire a abouti à la définition d'au moins cinq loci de susceptibilité, situés en 18p11, 18q22, 21q21, 4p16 et Xq26, répondant aux critères standard d'identification initiale puis de confirmation. C'est sur ces loci que portent les recherches pour préciser la structure des gènes mis en cause dans le trouble bipolaire. L'analyse moléculaire des séquences exprimées de ces loci devrait probablement le plus souvent permettre de déterminer des allèles de susceptibilité spécifiques des troubles bipolaires. Selon toute probabilité, la présence de ces allèles se révèlera très fréquente dans la population générale et ne sera ni nécessaire ni suffisante sur un plan individuel pour susciter des manifestations de la maladie. Il semble plus raisonnable pour l'instant d'envisager l'hypothèse de modèles impliquant des loci de susceptibilité dans lesquels plusieurs gènes s'associent de façon additive ou multiplicative. On peut espérer que la détermination de ces gènes de susceptibilité des troubles bipolaires permettra de mieux comprendre un certain nombre de points restés obscurs à propos de cette pathologie, en particulier en ce qui concerne la réponse thérapeutique, le type d'évolution cyclique, l'âge de début et les modes de transmission.

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