Review Article

Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder

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Juvenile bipolar disorder (JBD) has been a subject of significant research and debate. Phenotypic differences between JBD and adult-onset bipolar disorder have led researchers to question whether or not similar neuropathologic mechanisms will be found. While much is known about the genetic and environmental contributions to the adult-onset phenotype, less is known about their contributions to JBD. Here, we review family, twin, adoption, and molecular genetic studies of JBD. Behavioral genetic data suggest both genetic and environmental contributions to JBD, while molecular genetic studies find linkage to age of onset of bipolar disorder to chromosomes 12p, 14q, and 15q. Additionally, changes associated with symptom age of onset have been recently reported in the brain-derived neurotrophic factor (BDNF) and glycogen synthase kinase 3-beta (GSK3-beta) genes. We contend that further progress in discovering the precise genetic and environmental contributions to JBD may depend on advances in phenotypic refinement, an increased appreciation of comorbid conditions, and more investigation of the longitudinal course of the disorder.

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The existence, prevalence and proper taxonomic designation of juvenile bipolar disorder (JBD) has been the focus of considerable debate (1–5). Fueling this confusion is the lack of knowledge regarding the pathogenesis of JBD, despite the fact that bipolar disorder in adults is one of the best characterized and studied of all psychiatric disorders (6). One reason for the relative lack of data about JBD may be the intense disagreement about how best to describe children and adolescents with significant hyperactivity, with aggressive out of control behavior, and affective instability including manic-like behaviors that cycle rapidly over the course of a day. Definitional artifact makes it difficult to discern whether these symptoms are best described as 'manic behaviors' or 'severe hyperactivity of attention-deficit hyperactivity disorder (ADHD)', especially due to the difficulty establishing discrete episodes of mood disruption. Moreover, it has been suggested that the high likelihood of transition from pediatric major depressive disorder (MDD) to bipolar disorder makes them difficult to separate (7). The interface between ADHD and JBD is a complex one, and as a result leads to a great deal of debate on how to best conceptualize children with these symptom domains. Despite these diagnostic difficulties, a growing body of literature suggests that the diagnosis of bipolar disorder in youth is valid in at least some cases (2–5, 8). The cluster of symptoms that occur in children share many, but not all, of the characteristics of late-onset bipolar affective disorder (6), and some modifications of DSM criteria for pediatric populations (2, 9) have been proposed (10). For a complete review of the

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debate surrounding the definition of the clinical phenotypes for juvenile mania, please see a recent discussion by Leibenluft et al. (11).

Because clinical features alone are insufficient to clarify nosologic questions, it is useful to examine other sources of external validation such as follow-up studies, laboratory measures, and genetic studies (12, 13). Genetic studies of JBD can yield important insights into the etiology and pathophysiology of the disorder (14). In addition, findings can be compared with those in adult-onset bipolar disorder in an effort to clarify the continuities and discontinuities between the two conditions. If JBD is closely linked with the adult-onset form, then, like adult-onset bipolar disorder, it should run in families and be highly heritable. Here, we briefly review what is known about genetic and environmental contributions to adult-onset bipolar disorder before turning to major findings in JBD from family, twin, adoption, and molecular genetic studies.

Family studies of bipolar disorder

The family study is often the first exploration into whether a particular disorder is heritable. These studies typically examine the family of a patient with bipolar disorder (an affected proband) and compare them with family members of a patient without bipolar disorder (an unaffected proband). If bipolar disorder has a familial component, the proportion of bipolar disorder in the family members of the affected proband is expected to be higher than the proportion in family members of an unaffected proband. It would be exceedingly unlikely that genetics would contribute to a trait if that trait did not run in families. However, the finding that a trait runs in the families does not necessarily mean that the trait is due to genetic influence. Other factors can contribute to familiality such as a common or shared environment within the family. Consequently, family studies inform the possibility of heritability, but do not allow for estimation of the magnitude of genetic effects.

Family studies conducted from 1929 to 1954 did not distinguish between major depression and bipolar disorder (i.e., at the time, the term 'manic-depression' was used to encompass both disorders). They also did not routinely assess psychiatric comorbidity. Prevalence estimates from these early studies ranged from 3.2% to 23.4%, with a mean of 14.6%, among parents of affected individuals, and ranged from 2.7% to 23.0%, with a mean of 10.9%, among siblings of probands, in comparison with a general population estimate of 0.7% (0.4–1.7%). These data thus provided early evidence for familial transmission of the disorder.

As diagnosis has become more systematized with the onset of the DSM criteria, more methodological rigor has been applied to family studies of bipolar disorder. Whereas earlier studies did not distinguish between mood disorders and/or psychotic disorders in general, studies since 1982 have concentrated on separating unipolar and bipolar depression along with psychotic and non-psychotic mood disorders. It is possible that bipolar disorder may have been associated with familiality only through its association with schizoaffective disorder or MDD. The preponderance of evidence is that adult-onset bipolar disorder has clear familiality. Gershon et al. (15) examined first-degree relatives of bipolar, depressed and control subjects in a double-blind, controlled study, finding a prevalence of bipolar disorder of 4.5% among relatives of bipolar patients, compared with 1.5% among relatives of depressed patients, and 0.0% among relatives of controls. Both the 16.6% prevalence of depression among relatives of depressed patients and the 14.0% prevalence of depression among relatives of bipolar patients were nearly three times the risk observed in the control group. Subsequent studies have found similar results (16–21). Reviews by Tsuang and Faraone (22) and Smoller and Finn (23) show markedly greater risk of bipolar disorder among relatives of bipolar probands compared with relatives of controls. Smoller and Finn (23) estimated a 10-fold risk of bipolar disorder in first-degree relatives of bipolar probands compared with control families. Multiple studies have also shown an increase in unipolar depression in bipolar probands, but not the reverse (16–21).

Family studies of juvenile bipolar disorder

An association between the age of onset of bipolar disorder in a proband and increased risk of bipolar disorder in family members has been noted (24, 25). These studies stratified their samples by age but did not specifically ascertain probands on the basis of early-onset disorder. Others have looked specifically at early-onset probands to demonstrate that relatives of pediatric onset bipolar patients were more likely to have bipolar disorder than were relatives of later-onset probands (26, 27). Strober et al. (28) found elevated rates of both bipolar disorder and major depression in first-degree relatives of all bipolar patients, but a higher prevalence of bipolarity in relatives of pediatric bipolar cases (29.4%) compared with older-onset cases (7.4%). In addition, adolescent probands with childhood onset had significantly

increased aggregation of bipolar I disorder in first-degree relatives and a poorer response to lithium compared with those with later onset (28). Neuman et al. (26) observed a similar pattern, in which relatives of earlier-onset bipolar patients (before age 21) were more than twice as likely to have bipolar disorder than were relatives of later-onset patients. MacKinnon et al. (29) provided evidence that rapid switching of mood was associated with earlier onset of illness and inferred that rapid switching of mood may be the mediating factor to earlier findings of increased familiality in JBD.

The question of the mode of inheritance has been investigated by two segregation analysis studies. Noting the absence of twin studies to calculate the heritability of early-onset JBD, these segregation analyses suggested that the transmission of early-onset bipolar disorder was not purely environmental and was more consistent with non-Mendelian major-gene inheritance with a polygenic component while the best model for the late-onset probands was a multifactorial model (30, 31). While an important step prior to using linkage study methods to investigate genes associated with bipolar disorder, segregation analysis studies in bipolar disorder are often difficult to interpret, given that they are very sensitive to the phenotype used. Moreover, sample size and ascertainment strategies can markedly change the models that are fit using this technique (32).

In summary, family studies and segregation analyses show clear familiality of early-onset bipolar disorder at levels that may exceed those of late-onset bipolar disorder. Furthermore, this familiality of the disorder appeared from initial studies to be due to at least some genetic influence. These findings have led some authors to suggest a greater genetic role in early-onset cases, and to regard them as more genetically homogeneous (23, 25).

Other diseases, such as breast cancer and Alzheimer's disease, offer precedents for such phenomena. In both cases, earlier-onset forms appear to be caused by fewer genes with higher penetrance than the late-onset forms (33, 34). Early-onset forms of breast cancer and Alzheimer's disease confer higher risk for relatives than do late-onset forms, similar to the increased risk experienced by relatives of patients with early-onset bipolar disorder. The increased severity and worse prognosis of early-onset bipolar disorder, as evidenced by its chronicity, resistance to mood-stabilizers, and higher rate of psychotic symptoms (1, 5, 9, 35–38) appears to be mirrored by early-onset breast cancer. Early-onset breast cancer is considered more severe due to an increased incidence of bilateral disease (39) and poorer prognosis.

Overview of twin studies of bipolar disorder

Once a trait is determined to be heritable and presumed to be genetically influenced, a next step is to estimate the genetic and environmental contributions from a population of twins. Because twins share a common environment while also sharing either all of their genes [identical or monozygotic twins (MZ)] or half of their genes [fraternal or dizygotic twins (DZ)], one can compare the rate of a disorder between monozygotic twins and dizygotic twins as a first test for genetic contributions. This tendency is often summarized by concordance rates and through estimates of genetic heritability. Bertelsen et al. (40), using twins identified through the Danish Psychiatric Twin Register, found a concordance rate of 0.67 for bipolar disorder in MZ twins, a more than threefold increase above the 0.20 rate in DZ twins, and estimated the heritability of bipolar disorder to be 0.59. Using structural equation modeling, one can examine twin data sets more thoroughly to explore the contributions of genetic, common environmental, and unique environmental factors (41, 42). These methods have been applied to adult-onset or mixed samples of twins with bipolar disorder. Tsuang and Faraone reviewed six twin studies of bipolar disorder (22). In total, these studies assigned about 60% of the variance to genetic factors, 30–40% of the variance to common environmental factors, and 10% to unique environmental factors, although these early studies often did not distinguish between bipolar illness and other episodic disorders of mood like unipolar depression (22). In later work, Kendler et al. (43) showed that genetics contributed to about 79% of the variance while unique environmental components accounted for the remaining 21%. More recent twin studies examining the liability for bipolar disorder have found evidence for even greater genetic influence of between 85% (44) and 93% (45). The lack of common or shared environmental influence in the most recent studies (which selected for only bipolar disorder and no other affective disorder) suggests that the finding of common environmental influences found previously may have been due to the inclusion of other types of affective illness in those samples (46).

Twin studies of juvenile bipolar disorder

There have been no twin studies of childhood bipolar disorder published in the literature to our knowledge, with the exception of one study

currently under review (47). To look specifically at the transmission of childhood bipolar disorder, Hudziak et al. (47) used specific profiles from the Child Behavior Checklist (CBCL; 48) as a proxy for JBD. Elevation on three of the subscales of the CBCL (Attention Problems, Aggressive Behavior, and Anxious/Depressed) has been shown to be an accurate and reliable (49–51) indicator of JBD (52), to the point where it can potentially be used as a screening tool for JBD (53). This is likely because the symptom overlap of JBD with the subscale overlap of the CBCL scales is so robust that children without elevations on these subscales who are diagnosed with JBD are the exception rather than the rule. The study examined maternal report CBCL data for 5418, 3562, and 1971 Dutch twin pairs at ages 7, 10, and 12 years – a much larger and younger sample than previous twin studies. Depending on age and sex, we showed genetic contributions of 54–68%, common environmental contributions of 18–30%, and unique environmental contributions of 14–17%. The common environmental contributions, which have been found to be minimal in other childhood conditions such as ADHD (54) were higher in girls than in boys. In boys, the common environmental contributions were found mainly for younger children (47). This finding suggests some discontinuities between early- and late-onset bipolar disorder. More specifically, evidence of a shared environmental component in JBD, especially in the young, suggests the possibility of moderating shared environmental factors in the expression of this phenotype that may be more evident in early-onset compared with late-onset cases, although this work has yet to be replicated.

There are preliminary data on the use of latent class analysis (LCA) to further understand the phenotype of JBD and its use in a twin design to show heritability of JBD. Althoff et al. examined over 6000 male and female Dutch twins using the CBCL. One latent class included subjects with the CBCL-JBD phenotype, which comprises about 1% of the sample, along with another 3–4% of the sample that showed lower levels of aggression and affective dysregulation. This latent class showed higher odds ratios between MZ and DZ twins (suggesting a genetic contribution to the phenotype). This suggests that the LCA measure encompasses a spectrum of mood-dysregulated aggression. Intriguingly, the mood-dysregulated latent class was the only class that had significant elevations on the suicidal items (no. 18 and no. 91) of the CBCL (55). The analysis found other subgroups manifesting combinations of inattentive, aggressive, and anxious-depressed symptoms. As these other sub-groups have not been given the level of individual scrutiny accorded the CBCL-JBD phenotype, the presence of these other groups may contribute to some of the variability in the JBD diagnosis.

Adoption studies of bipolar disorder

Adoption studies are used in psychiatric genetics to further expand the examination of genetic and environmental contributions to psychiatric disorders. Because a child moved into an adoptive home will have an environmental, but not a genetic, manipulation, one can examine the resemblance of the children to their biological parents and to their adoptive parents. These studies, however, tend to be difficult to arrange and give rise to a number of confounds that are not present in twin or family studies (56).

There have been few adoption studies of any mood disorder. Mendlewicz and Rainer (57) showed that the biological parents of bipolar adoptees showed a higher prevalence of psychiatric illness than the adopted parents. Similarly, rates of bipolar disorder in biological and adoptive parents of Danish patients who were hospitalized for bipolar disorder have been compared (58). The biological relatives were six times more likely to have completed suicide, had an eightfold increase in major depression, and a 15-fold increase in alcoholism compared with adoptive relatives. This study bolstered the Belgian evidence for genetic factors in familial transmission of mood disorder risk.

Adoption studies of juvenile bipolar disorder

No adoption studies of pediatric bipolar disorder have yet been published.

Molecular genetic studies of bipolar disorder

While twin and adoption studies can give strong indications for genetic influence, they do not tell an examiner *which* specific genes may be implicated. To accomplish this objective, molecular genetic studies of two main types are used. Linkage studies scan the whole genome to help identify chromosomal locations of interest. Candidate gene studies are used to examine the association between a disorder and an identified polymorphism in a particular gene.

Molecular genetic studies of bipolar disorder have proliferated in the last decade (59), and their results have been extensively reviewed (60–66).

Like most neuropsychiatric conditions, bipolar disorder is thought to be a genetically complex disease caused by a combination of many genes with perhaps more than one variant of each gene increasing the risk for the disorder. It seems likely that a full understanding of the etiology of the disorder will require documentation of gene–gene interactions, gene–environment interactions and correlations, and epigenetic effects.

Several chromosomal loci identified through linkage analysis also appear to harbor susceptibility genes for bipolar disorder. Many of these loci were examined in two large meta-analyses of bipolar disorder. Badner and Gershon (67) used the Multiple Scan Probability technique on published studies up until 2001. They found evidence for susceptibility loci on 13q and 22q for bipolar disorder. Segurado et al. (68), using a genome scan meta-analysis approach, including unpublished data, and excluding smaller studies, found that no region achieved genome-wide significance but that the most significant regions were chromosomes 9p, 10q, and 14q.

Subsequently, other genome-wide scans have found areas of interest at 18q22 (69, 70) and 20p12 (71). A much larger genome scan of 250 multiplex families from the NIMH study showed peaks at 17q, as well as at 6q (72). More recently, the area at chromosome 6q22 has sparked particular interest. This locus was one of the two strongest findings reported by Dick et al. (72), with a LOD score of 3.61. It was identified again by Pato et al. (73), and was further validated by a follow-up study using DNA microarray analysis (74). Both the Pato and Middleton papers reported a similarly strong locus at 11p11 as well. The complete list of candidate loci identified through whole-genome scanning and linkage analysis is beyond the scope of this paper, and a fairly recent review of the topic is available (75).

Several genes have been repeatedly implicated as contributing to bipolar disorder etiology. In particular, findings for the genes which code for catechol-*O*-methyltransferase (COMT), monoamine oxidase (MAOA), the dopamine transporter (76), the G72/G30 gene (77), and the serotonin transporter (SLC6A4) have been variably reported (60, 78). Craddock et al. (60), however, performed a meta-analysis of eight separate studies of the serotonin transporter from 11 different samples and found little overall evidence to support a role for this polymorphism in the susceptibility to adult bipolar disorder. This has been updated in two recent meta-analyses. Cho et al. (79) found weak but statistically significant evidence for two 5-HTT polymorphisms [the 17 base pair variable-number tandem repeat (VNTR) and the 44 base pair insertion/deletion in the promoter region (44-bp polymorphism)]. Lasky-Su et al. (80), using a slightly more restrictive sampling of the literature found no evidence for the 17-bp VNTR but did find a weak association for the 44-bp polymorphism and bipolar disorder. The gene coding for brain-derived neurotrophic factor (BDNF) has also been implicated by several studies of bipolar adults (62, 81, 82) and youth (83).

Molecular genetic studies of juvenile bipolar disorder

Of the studies listed above, few have included age at onset as a covariate and even fewer have specifically investigated onset prior to age 15 (8). What studies that do exist in JBD have not uniformly supported findings in adults. For example, Geller and Cook found no evidence to support the associations found in adult-onset patients with genes for COMT, the dopamine transporter gene or the short/long polymorphism of the promoter region of the gene encoding the serotonin transporter (HTT) (84, 85). The latter association was reported by Ospina-Duque et al. (86) and this discrepancy itself is similar to the variable findings reported for adult-onset bipolar disorder. Failure to find association in early-onset samples may simply reflect insufficient statistical power to detect a small effect in a small sample; however, an alternative conclusion may relate to a difference in the genetic etiologies of early- and late-onset bipolar disorders.

One candidate gene that has been suggested is the dopamine D2 receptor (DRD2) gene in early-onset bipolar disorder patients who also had disorganized symptoms (87). Additionally, as noted above, a polymorphism in the BDNF gene, Val66Met (i.e., where alternative alleles lead to the substitution of valine for methionine in the BDNF molecule) showed a significant association with JBD in a sample of 53 parent-juvenile proband trios, where the mean age of probands was 10.7 years (83). Because the gene that codes for BDNF has been implicated in the liability for adult-onset bipolar disorder (82), this finding could be consistent with at least some shared etiology between adult- and juvenile-onset forms of the illness. However, this is one small study. To date, there has been no definitive evidence of a specific gene implicated in both JBD and adult BD.

Another genetic variant which has also been associated with age of onset in a sample of 185 Italian adult bipolar probands (88) is a single nucleotide polymorphism (T/T genotype for a T/C) in the glycogen synthase kinase 3-beta (GSK 3-beta) gene.

The authors point out that, as GSK3-beta is involved in circadian cycling in *Drosophila*, there may be some utility in investigating genes involved in molecular clocks as endophenotypes.

Further evidence for genetic influence on the age at symptom onset came from Faraone et al. (89) genetic linkage study, which found age of onset of mania to be significantly heritable, and linked to loci on chromosomes 12p (marker D12S1292), 14q (marker GATA31B), and 15q (marker GATA50C). These findings need to be replicated, but may offer a first glimpse of the promise of methodologies involving whole-genome scanning and advanced linkage analysis techniques in the search for susceptibility genes which affect the age of onset of bipolar disorder.

Another area of relevant effort has focused on phenotypic anticipation in bipolar disorder (90). Phenotypic anticipation refers to the increasing disease severity and earlier age of onset seen in some illnesses as through successive generations. Links between the phenomenon of anticipation and the existence of expanding trinucleotide-repeat (TNR) sequences have been reported in other disorders such as Huntington's disease (91), fragile-X syndrome (92), spinal and bulbar muscular atrophy (93), and myotonic dystrophy (94). It should be noted, however, that studies of genetic anticipation are limited by ascertainment bias based on severity of disease and with preferential bias of ascertainment of families with simultaneous onset in parent and offspring. Moreover, fertility biases may affect psychiatric disorders with earlier-affected individuals being less likely to produce offspring. With these limitations in mind, Vincent et al. (95) found some supportive evidence for a repeat-expansion mechanism in pediatric bipolar disorder, but the data were derived from a mixed patient sample composed of individuals with schizophrenia, bipolar disorder, juvenile-onset depression, and borderline personality disorder. Interestingly from another study, examination of a specific CAG/CTG repeat polymorphism (coding for polyglutamine tracts) within the Expanded Repeat Domain 1 on chromosome 17 actually revealed a higher prevalence of low-repeat alleles among patients with pediatric onset of bipolar disorder (96), but the significance of this difference did not withstand corrections for multiple testing. In contrast, Schurhoff et al. (97) found no evidence for genetic anticipation in a limited sample of individuals with adolescent-onset bipolar disorder. This conclusion was based on the absence of protein products containing expanded polyglutamine tracts, rather than the absence of expanded nucleotide sequence repeats. Currently, though presently unresolved, an appreciable contribution to risk through polyglutamine tract expansion seems unlikely (98).

Genetic studies of the comorbidity of juvenile bipolar disorder

Patients with bipolar disorder are frequently diagnosed with comorbid psychiatric conditions. One of the most frequent, especially among pediatric-onset cases of bipolar disorder, is ADHD. There is most likely a familial and genetic basis for this co-occurrence (35, 99–103). Furthermore, risk for the two disorders is bi-directional: ADHD is approximately three times more common in offspring of a bipolar parent than in children of normal control subjects, and bipolar disorder is twice as common in the relatives of ADHD probands than in the relatives of control children (35). A series of family studies has been conducted examining the patterns of comorbidity between bipolar disorder and ADHD. Faraone et al. (100) found the rate of ADHD among relatives of probands with comorbid bipolar disorder and ADHD to be 22%, in comparison with 15% among family member of ADHD probands and 3% in family members of control subjects. In a related study, Wozniak et al. (104) showed that children with ADHD and JBD had high rates of both JBD and ADHD in their first-degree relatives. Furthermore, the rate of pure bipolar disorder (i.e., bipolar disorder without ADHD) is not increased in relatives of ADHD/bipolar probands or in those of ADHD probands (35, 100, 101). The relatives of control subjects did not show any comorbidity between bipolar disorder and ADHD, and only 2% of relatives of ADHD probands had this combination of conditions. However, some evidence for cosegregation of the two disorders was seen in the 12% prevalence of ADHD/bipolar disorder comorbidity among relatives of probands with both disorders. The age at onset of bipolar disorder in relatives of comorbid probands (11 years) was less than half that of bipolar relatives of ADHD probands (24 years), adding evidence for a more severe, genetically based form of the disorder. This finding has been replicated by the same group in two additional family study samples (100, 104). Researchers have used these findings to bolster their conclusion that JBD is not simply a manifestation of extreme ADHD, but is instead a separate nosologic entity. Due to the low prevalence of pure bipolar disorder among relative groups, however, some of these examinations may have lacked sufficient statistical power to be considered definitive. Moreover, the majority of published family studies comparing rates of

comorbidity between JBD and ADHD have used samples of JBD children who were ascertained through clinics. This may lead to ascertainment bias and a higher rate of comorbidity between JBD and other disorders than may be seen if the samples were ascertained through general population sampling.

These data are relevant to an understanding of the expression of JBD in that they may speak of the various symptom dimensions that are reflected in commonalities with ADHD. New tools available to researchers have the potential to remove many of the presuppositions about bipolar disease mechanisms and etiology related to specific candidate genes. For example, the COMT gene has been reported to be associated primarily with the hyperactive-impulsive type of ADHD (105) rather than with other subtypes. Similarly, the dopamine transporter gene is reportedly more strongly associated with hyperactive-impulsive symptoms (106). This raises the possibility that these genes may be associated with hyperactive-impulsive symptoms in both ADHD and JBD. The discovery of reliable endophenotypic markers of illness (as was done in schizophrenia with P50 gating deficits) (107) or empirically derived subtypes of bipolar disorder (70) could drastically help researchers maximally harness the vast potential of these emerging technologies (108).

Conclusions and future directions

Advances in family, twin, and molecular genetic studies are providing a better understanding of the relative contributions of genes and environment to JBD. Evidence from all sources has consistently demonstrated familial aggregation and genetic transmission of bipolar disorder, with less disease risk attributable to shared and unique environmental experiences. These studies have also shown that early-onset of the disorder confers a greater familial risk to relatives of perhaps a more severe form of illness. Relatively little is known about genetic transmission in families having juvenile-onset cases, although the picture of genetic transmission of the adult illness is nearly as unclear. Family, twin, and adoption studies continue to be needed that specifically look at juvenile cases. Similarly, more genome-wide scans are needed that specifically examine JBD as the phenotype of analysis, or at least include age of onset in the analytic model.

Molecular genetic studies of early-onset bipolarity are just beginning to yield results, and all findings reported in the preceding sections require substantial replication. However, there may be utility in pursuing such research in earnest, whether for the elucidation of early-onset etiology, or for a more general understanding of bipolar disorder. As suggested by Todd et al. (30), if early-onset illness is an integral part of the bipolar spectrum, it may be the most useful bipolar subtype in identifying genes that influence risk for all cases of the illness because it may be a more genetically influenced condition. Early-onset forms of disease should produce stronger genetic 'signals' in linkage and association studies due to reduced genetic heterogeneity, greater penetrance of risk alleles, or both. Such cases may also have a higher genetic loading of risk alleles (i.e., they possess a greater number of the critical alleles of risk genes), facilitating detection of one or more risk genes out of the many that may exist. Studies of other early-onset disease forms, including Alzheimer's disease (109, 110) and diabetes mellitus (111), have proven extremely useful in identifying genetic contributors to those conditions. The studies to date suggest that there is likely a similar or possibly lower heritability in the early-onset form of the illness, making this possibility less clear for bipolar disorder. But lower heritability will not compromise the search for genes if JBD is more genetically homogeneous than adult-onset BD. If fewer genes mediate JBD, their individual effect sizes may be larger than the individual effects of genes for adult-onset BD despite the latter's greater overall heritability. Because JBD shows a higher shared and unique environmental component, if these components can be formally characterized, the search for $G \times E$ interactions may be more fruitful in the early-onset form of the disorder.

Alternatively, early-onset bipolar disorder may be etiologically separate from the adult-onset form. Preliminary evidence to date suggests the presence of at least some discontinuities between JBD and its adult-onset counterpart. Twin studies suggest a greater role for shared environmental factors, while molecular genetic studies in JBD have often failed to replicate associations found in adult samples. If this is indeed the case, the etiology of early-onset bipolar disorder may consist of altogether different genes, gene–gene, or gene–environment interactions, than the more typical adult-onset illness. Regardless, pediatric bipolar disorder etiology must be considered in the context of a general bipolar phenotype that is complex and comorbid with many other disorders including conduct disorder, anxiety disorders, substance use disorders, and ADHD (2, 9, 112–118). Future genetic studies must address the breadth of the phenotype, its discrimination from other disorders, increased clarity in nosologic subtyping, and its continuity with bipolar disorder in adulthood.

An additional area for future study must be a concentration on G × E interactions. In 2005 the idea is clearly not 'nature versus nurture' but 'nature and nurture and how they interact.' Recent discoveries have shown that the interaction between the serotonin transporter gene and the trauma affecting the likelihood of MDD (119) that can be present in childhood can be reduced by the presence of positive social support (120). Thus far there have been no studies of specific G × E interactions with JBD, although it seems probable that these will be uncovered with time. Mood disorders in childhood, especially MDD, have been demonstrated to be highly associated with bipolar disorder in adulthood (7). Because there are G × E interactions at play in the onset of MDD in childhood, one can assume that these interactions will be important in JBD as well. Perhaps one of the reasons that such high additive genetic effects have been found in JBD is that they are covering a G × E interaction. It has been speculated that one possible mechanism of such a G × E interaction leading to mania has been hypermethylation of DNA affecting synaptogenesis (121). However, if we follow the protocol for identification of G × E interactions specified by Moffit et al. (122), more work needs to be done to identify possible environmental pathogens and to demonstrate their association with JBD before the G × E exploration will be fruitful.

Similar to other psychiatric disorders, it seems likely to us that the involvement of many genes, each contributing some liability, can affect and be affected by many environments to generate a range of phenotypes that fall under the name 'JBD'. However, the evidence for this type of G × E interaction for JBD is still lacking. Consideration of possible risk environments and identification of a more cogent constellation of phenotypes may be the next hurdles toward improvement of understanding of the pathology of this disorder.

There is evidence from ADHD, pervasive developmental disorder, and obsessive-compulsive disorder that similar phenotypic refinement using alternate classification techniques (123–126) rather than strict DSM approaches may lead to new candidate genes (127). This process has started with JBD and there is reason for cautious optimism about this approach (55).

Rigorous longitudinal data are also in critical need. There remains a great lack of clarity as to how many early-onset bipolar disorder patients will maintain their illness into adulthood and in what form, develop comorbid conditions, or for that matter, will see their symptoms remit altogether. Therefore, tracking long-term outcome (e.g., beyond 2 years of onset) of juvenile-onset bipolar disorder patients would be a useful method of clarifying the phenotypic complexities of the disorder. Such studies are only now being undertaken (128). Most importantly, twin, adoption, and longitudinal studies of JBD which have the capability of incorporating the complex nature of the disorder, should be considered a top priority in order to further understanding of this often debilitating condition.

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