Bipolar Disorder increasingly features in the literature. This is an excellent and comprehensive article although somewhat technical on the ongoing research to determine the cause, course, and treatment for BD. FYI

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Bipolar Disorders Expert Column Series
Bipolar Disorders and Genetics: Clinical Implications of High Heritability

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Basic Genetics and Heritability of Bipolar Disorder

The high heritability of bipolar disorder (BD) has been well documented through familial incidence, twin, and adoption studies.[1] For example, the concordance rate of BD in monozygotic twins (indicating the chance that if one twin has BD, so will the other) is between 40% and 70%. Despite general acceptance that BD is therefore a disorder with a strong *genetic* basis, no specific gene has been identified as the one "bipolar gene." Nevertheless, linkage studies have implicated the involvement of several chromosomal regions in BD, including 4p16, 12q23-q24, 16p13, 21q22, and Xq24-q26. Chromosome 18 has also been an area of high focus, with up to 3 possible regions implicated.[1,2] Recent areas of interest have included chromosome 6q[3] as well as the G-protein receptor kinase 3 gene, located at 22q12.[4] There are also data suggesting that relatively common polymorphisms of genes coding for the serotonin transporter protein and brain-derived neurotrophic growth factor may contribute somewhat to the development of BD. Because of these variable findings in very different chromosomal regions, it is likely that BD is caused by the presence of multiple genes conferring susceptibility to BD when combined with psychosocial stressors (see below). Thus, inheritance of a specific set of these genes could lead to one phenotypic presentation of the disorder, whereas a different set of genes would lead to a slightly different clinical presentation within the bipolar spectrum of illness.

Genes may also contribute to the age at onset of BD and a phenomenon called genetic anticipation. Anticipation refers to the phenomenon of an illness occurring in successive generations with earlier ages of onset and/or increasing severity. In a recent study using registry data of bipolar subjects, age at onset of first illness episode was examined in 2 successive cohorts: subjects born from 1900 through 1939 and from 1940 through 1959.

The median age at onset of the first episode of bipolar illness was lower by 4.5 years in subjects born during or after 1940. The proportion of subjects with bipolar disorder presenting with a prepubertal onset was also significantly higher in the later birth-year cohort, thus supporting the notion of genetic anticipation.[5]

Some research results have suggested that unstable trinucleotide repeats (eg, CAG), which are transmitted in greater lengths to successive generations, may be the biological basis of genetic anticipation.[6] For example, an increase in mean CAG repeat length was associated with a diagnosis of BD[7,8] and with anticipation of BD in a few studies of families with BD.[9,10] However, there have been no replications of these studies and several negative reports.[11-14] Furthermore, these repeat sequences have not been successfully linked to meaningful gene regions.

Methodologic limitations such as the phenotypic heterogeneity of BD and reliance of retrospective reports of onset and severity of bipolar symptoms may be partially responsible for the difficulty in isolating gene regions consistently associated with BD and replicating positive findings. Longitudinal, prospective studies examining parents with BD and the genetics and phenomenology of their high-risk offspring might help address such limitations.

Epidemiologic and phenomenologic studies of bipolar offspring also support the high heritability of BD. A meta-analysis of studies conducted before 1997 found bipolar offspring to be at 2.7 times higher risk for developing any psychiatric disorder, and at 4 times higher risk for developing a mood disorder, than children of parents without psychiatric illness.[15] Recent cross-sectional studies have reported about 50% of bipolar offspring meet criteria for at least one DSM-IV psychiatric disorder.[16-18] In these studies, the presence of a bipolar spectrum disorder (bipolar I, II, and cyclothymia) ranged from 14% to 50%. However, one study from The Netherlands found a much lower incidence (2.8%) of BD in bipolar offspring.[19] The authors suggest that a much lower use of antidepressants and stimulants to treat children in European countries might account for this discrepant finding. Of note, this study still identified a 27% incidence of mood disorders in these offspring, raising the possibility that these symptomatic offspring might still be in early phases of the illness. It therefore seems important to identify which children may truly be in the prodromal stages of BD.

Early Detection of Bipolar Disorder

Retrospective studies of adults with BD help provide insight into the early expression of BD. Thirty-one percent of adults enrolled in a BD support group reported the onset of significant mood symptoms before the age of 15 years and 17% before the age of 10 years.[20] More recently, it has been reported that up to 65% of adults with BD had an initial mood episode before age 18 years, with 28% occurring before age 12 years.[21] In another study of adults with BD hospitalized for their first psychotic episode, 67% reported a childhood onset of psychiatric disturbances, with 21% reporting specific

disruptive-behavioral disorders.[22] Although retrospective in nature, these studies suggest that development of BD *usually* begins in childhood, with either disruptive behavior disorders or mood episodes as initial presentations of BD.

Attention-deficit/hyperactivity disorder (ADHD) specifically has been proposed as a common initial presentation of BD, especially early-onset BD. In studies conducted since 1988, approximately 27% of bipolar offspring have met criteria for ADHD or significant behavioral or attention problems.[23] These findings, in conjunction with the high comorbidity of ADHD and BD in childhood,[24] have led to the suggestion that ADHD in children with strong family histories of BD may be the first sign of a developing BD. Furthermore, family studies of probands with ADHD and BD suggest this comorbidity represents a familial type of early-onset bipolar disorder.[24,25] In one study of bipolar offspring, 7 of 8 offspring with BD had met criteria for ADHD before obtaining a diagnosis of BD.[16] Furthermore, parents with BD who had retrospectively reported a history of ADHD during their own childhood were more likely to have children diagnosed with BD compared with bipolar parents without a history of ADHD, supporting the concept of ADHD as one initial presentation of a familial early-onset BD.

As many children with ADHD, even those with familial loading for BD, would likely *not* develop this disorder, biological markers associated with BD would help identify those at high risk for developing the illness. Although no such markers have been identified in adults or children, there exists promising ongoing work in the fields of neuroimaging and genetics research. Volumetric magnetic resonance imaging (MRI) studies suggest that patients with BD may have prefrontal, temporal, cerebellar, ventricular, and deeper structural (striatum and amygdala) volume changes, as well as white matter abnormalities as indicated by white matter hyperintensities.[26] Adults and children with BD have been found to have lower prefrontal concentrations of n-acetylaspartate, an indirect marker of neuronal density.[27] Positron emission tomography and functional MRI studies of patients with BD have implicated the prefrontal cortex, limbic structures, striatum, and thalamus in the neuropathophysiology of BD.[28] Euthymic children with familial BD have also been reported to have overactivation of prefrontal and limbic brain areas in response to cognitive and affective tasks, suggesting overactivation as a possible marker of pediatric-onset BD.[29]

Further neuroimaging investigations of bipolar offspring are necessary to establish whether these abnormalities exist prior to the onset of the illness. If so, these markers could identify those at highest risk for BD development, who may then be candidates for preventive interventions.

Early Intervention Studies

In addition to the presence of early psychopathology, psychosocial stressors such as dysfunctional family environments, stressful life events, and ineffective coping strategies may also interact with genetic predispositions to induce the full expression of BD in high-

risk individuals.[30] These stressors may effect neurobiological change that not only leads to mood episodes but may also create vulnerability to future, more frequent episodes. This concept of kindling in BD suggests that early identification and intervention are essential to not only lessen future morbidity in individuals with BD, but to possibly prevent full illness onset.[23]

It has been hypothesized that medications that have been effective in treating patients with BD, such as mood stabilizers and antipsychotics, may also halt or reverse the full development of the illness in high-risk subjects. In a study of bipolar offspring with mood and/or disruptive behavioral disorders, but not bipolar I or II disorder, 79% of 24 offspring improved clinically after a 12-week open trial of divalproex monotherapy.[31] Although improvements were seen in mood symptoms and overall functioning, the prophylactic utility of divalproex or other medications in preventing the full expression of BD needs to be examined through longitudinal studies lasting years rather than weeks.

As psychosocial stressors likely interact with biological predispositions to induce illness expression, early interventions aimed at improving dysfunctional family communication and coping skills and educating at-risk families about early signs of BD may prevent full expression of BD in the at-risk child.[23] Though never tested for its prophylactic utility, family-focused therapy (FFT) has been shown to reduce relapse rates, enhance stabilization of mood symptoms, improve medication compliance, and decrease stressful family interactions in adults with BD.[32] It is currently being applied to adolescents with BD. Studies of psychosocial strategies such as group cognitive therapy and family psychoeducation in offspring of depressed parents also reduce depressive symptoms and problematic behaviors of the offspring.[33,34] Thus, it is hoped that psychosocial and psychotherapeutic interventions such as FFT and cognitive therapy will be studied in high-risk populations to determine their efficacy in preventing the full expression of BD. These studies should aim not only to develop and examine the efficacy of psychosocial interventions, but also to identify the mediating pathways most effective for prevention.

Conclusion

Although the high rates of heritability of BD have been widely accepted, much work remains to be done in gaining a more exact understanding of the mechanisms involved. Given that BD is being increasingly diagnosed in children and adolescents, it has become imperative to understand the genetic basis, identify potential biological markers, and identify early stages of this debilitating illness. Such knowledge will not only inform the development of more effective treatment interventions, but also help identify, and perhaps prevent, the onset of BD in at-risk individuals.

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