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A Controlled Family Study of Children with DSM-IV Bipolar-I Disorder and Psychiatric Comorbidity

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Abstract

Objective—To estimate the spectrum of familial risk for psychopathology in first degree relatives of children with unabridged DSM-IV Bipolar-I Disorder (BP-I).

Methods—We conducted a blinded, controlled family study using structured diagnostic interviews of 157 children with BP-I probands (N=487 1st degree relatives), 162 ADHD (without BP-I) probands (N=511 1st degree relatives), and 136 healthy control (without ADHD or BP-I) probands (N=411 1st degree relatives).

Results—The morbid risk (MR) of BP-I disorder in relatives of BP-I probands (MR=0.18) was increased 4-fold (95%CI=2.3-6.9, p<0.001) over the risk to relatives of control probands (MR=0.05) and 3.5-fold (95%CI=2.1-5.8, p<0.001) over the risk to relatives of ADHD probands (MR=0.06). In addition, relatives of children with BP-I disorder had high rates of psychosis, major depression, multiple anxiety disorders, substance use disorders, ADHD, and antisocial disorders compared with relatives of Control probands. Only the effect for antisocial disorders lost significance after accounted for by the corresponding diagnosis in the proband. Familial rates of ADHD did not differ between ADHD and BP-I probands.

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Conclusions—Our results document an increased familial risk for BP-I disorder in relatives of pediatric probands with DSM-IV BP-I disorder. Relatives of probands with BP-I disorder were also at increased risk for other psychiatric disorders frequently associated with pediatric BP-I disorder. These results support the validity of the diagnosis of BP-I in children as defined by DSM-IV. More work is needed to better understand the nature of the association between these disorders in probands and relatives.

Introduction

A converging body of evidence indicates that a sizeable minority of children and adolescents in clinic and research settings satisfy DSM-IV diagnostic criteria for bipolar disorder (Mick *et al.*, 2003, Perlis *et al.*, 2004). This literature also documents that pediatric bipolar disorder is extremely morbid and commonly associated with significant functional impairment in multiple domains including increased risks for psychiatric hospitalization, antisocial behaviors, addictions, and suicidal ideation (Biederman *et al.*, 2004, Birmaher *et al.*, 2006, Geller *et al.*, 2000a, Wozniak *et al.*, 1995a). In parallel to pediatric studies, an emerging literature in adults documents that as many as 65% of adults with bipolar disorder have an onset of their disorder in childhood and adolescence, indicating that onset in childhood and adolescent is a common feature of this disorder (Perlis *et al.*, 2004). Despite these compelling findings, questions remain as to the validity of pediatric bipolar disorder.

A cornerstone of establishing the validity of a psychiatric disorder is demonstrating that relatives of diagnosed individuals (i.e. the proband) are at an increased risk for the same disorder (Robins and Guze, 1970). That bipolar disorder in adults is highly familial has been known since the middle of the 20th century (Faraone *et al.*, 2003, Tsuang and Faraone, 1990). In a recent review, Craddock et al (Craddock and Forty, 2006) estimated the risk for bipolar disorder in the siblings of adult probands to be 5-10% and that the heritability of the disorder ranges from 0.80-0.90. In contrast to a rich literature on family studies of adult bipolar disorder, a much more limited literature exists on the familiality of pediatric bipolar disorder. In an uncontrolled study, Dwyer et al (Dwyer and Delong, 1985) showed an excess of bipolar disorder in the relatives of 20 outpatient children with DSM-III diagnosed bipolar disorder. The excess risk for bipolar disorder in 1st degree relatives was replicated in subsequent family studies of child probands with DSM-III (Kutcher and Marton, 1991, Neuman *et al.*, 1997, Strober *et al.*, 1988), DSM-IIIR (Wozniak *et al.*, 1995b), and DSM-IV bipolar disorder (Brotman *et al.*, 2007, Findling *et al.*, 2001, Geller *et al.*, 2006, Wilens *et al.*, 2007) that reported ranges of bipolar disorder in relatives of pediatric bipolar disorder probands ranging from 12%-35% with the risk of unipolar depression ranging from 15%-42%.

However, despite their clear contributions, the existing family studies of pediatric bipolar disorder suffer from several methodological limitations. Three studies relied on family history methods rather than directly interviewing relatives and half of the available studies examined only parents or adult relatives (Brotman *et al.*, 2007, Findling *et al.*, 2001, Kutcher and Marton, 1991, Neuman *et al.*, 1997, Strober *et al.*, 1988, Wilens *et al.*, 2007). Of the four studies utilizing DSM-IV criteria, two (Brotman *et al.*, 2007, Geller *et al.*, 2006) restricted recruitment of probands to children meeting a “narrow” phenotype (Leibenluft *et al.*, 2003) excluding other children who may have otherwise fully met DSM-IV bipolar-I disorder.

Furthermore, despite the fact that high rates of psychiatric comorbidity have been consistently reported in youth with bipolar disorder the extant literature on family studies of pediatric bipolar disorder probands has seldom systematically assessed other psychiatric disorders beyond mood disorders and those studies that did, did not account for a potential

impact of psychiatric comorbidity in probands on the risk of psychiatric morbidity in relatives.

The main aim of the present study was to re-evaluate the familiality of pediatric bipolar I (BP-I) disorder attending to the limitations of the extant literature using a large family study sample. To this end, we conducted a familial risk analysis comparing structured diagnostic interview derived data from all first degree relatives of pediatric probands with DSM-IV BP-I disorder attending to psychiatric comorbidity in probands and relatives. Comparisons were made with findings in first degree relatives of probands with ADHD and control probands without BP-I or ADHD. We hypothesized that first degree relatives of probands with pediatric BP-I would be at increased risk for BP-I compared to relatives of ADHD probands and non-BP, non-ADHD control probands. Additionally, based upon patterns of psychiatric comorbidity in children with BP-I (Brotman *et al.*, 2007, Findling *et al.*, 2001, Geller *et al.*, 2000b, Mick *et al.*, 2003, Wozniak *et al.*, 1995b) we also hypothesized that relatives of pediatric BP-I probands would be at increased risk for disruptive behavior disorders, anxiety disorders, addictive disorders and psychosis. To the best of our knowledge this study represents one of the largest and most comprehensive family studies of pediatric bipolar disorder.

Methods

Subjects

Families were recruited and assessed at the Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital. Probands were recruited for studies of bipolar probands 6-17 years of age of both genders, (Wozniak, 2005) ADHD or non-ADHD control probands 6-17 years of age of both sexes, (Biederman *et al.*, 1992, Biederman *et al.*, 1999, Biederman *et al.*, 2006a, Biederman *et al.*, 2006b) All studies were sampled from the same source population and used the same assessment methodology regardless of the disorder used to classify subjects as cases. All study procedures were reviewed and approved by the subcommittee for human subjects of our institution. All subjects' parents or guardians signed written informed consent forms and children older than 7 years of age signed written assent forms.

We recruited 157 BP-I probands and their 4871st degree relatives for the family study pediatric bipolar disorder. From 522 families participating in our case-control ADHD family studies we randomly selected 162 non-bipolar ADHD (511 1st degree relatives) and 136 non-bipolar non-ADHD control probands (411 1st degree relatives) so that the age and gender distribution was similar to that of the BP-I probands. ADHD probands with comorbid bipolar disorder were not included in the present analyses.

Ascertainment Methods

Potential BP-I probands were ascertained from our clinical service, referrals from local clinicians or self-referral in response to advertisements. To avoid biasing our sample toward familial cases of bipolar disorder, all probands were ascertained blind to the diagnostic status of their relatives. Subjects were administered a phone screen reviewing symptoms of DSM-IV BP-I and, if criteria were met, were scheduled for a face-to-face structured diagnostic interview (described below). In addition to the structured diagnostic interview it is the routine for the PI (JW) to perform a clinical interview that includes both the proband and his or her parents in order to confirm the diagnosis of bipolar disorder using the KSADS mania module, and we make every effort to ensure that this interview occurs with every proband. We have published data on the convergence of these clinical interviews with our structure interview diagnosis on the first 69 cases. We report 97% agreement between the

structured interview and clinical diagnosis in this analysis of 69 children. (Wozniak *et al.*, 2003)

As previously reported (Biederman *et al.*, 1992, Biederman *et al.*, 1999, Wozniak *et al.*, 2005) ADHD cases were identified from either a major academic medical center, where we selected ADHD subjects from referrals to pediatric psychopharmacology program and from a major Health Maintenance Organization (HMO), in which ADHD subjects were selected from pediatric clinic outpatients. Controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the bipolar probands with the exception that we queried about ADHD (and not bipolar disorder) in the initial telephone screening and each proband was not assessed clinically.

Diagnostic Procedures

Psychiatric assessments of subjects younger than 18 years were made with the KSADS-E (Epidemiologic Version) (Orvaschel, 1994) and assessments of adult family members were made with the Structured Clinical Interview for DSM-IV (SCID) (First *et al.*, 1997) supplemented with modules from the KSADS-E to cover childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either reporter resulted in a positive diagnosis.

Interviews with both the KSADS and the SCID were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of classroom instruction of interview mechanics, diagnostic criteria and coding algorithms. They also observed interviews by experienced raters and clinicians and were observed while conducting interviews during the final training period. In addition all diagnoses were reviewed by a sign-off committee of experienced board certified child and adolescent psychiatrists or clinical psychologists. The committee members were blind to the subjects' ascertainment group, ascertainment site, and data collected from other family members. We computed kappa coefficients of agreement by having experienced clinicians diagnose subjects from audio taped interviews made by the assessment staff. Based on 500 interviews, the median kappa coefficient between raters and clinicians was 0.99 and for individual diagnoses was: ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (.95), substance use disorder (1.0), and tics/Tourette's (0.89). The median agreement between individual clinicians and the clinical review committee chaired by the PI was 0.87 and for individual diagnoses was: ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (.80), panic (.77), substance use disorder (1.0), and tics/ Tourette's (0.68).

Children were diagnosed with BP-I disorder according to DSM-IV criteria. The DSM-IV requires subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive or irritable mood lasting at least one week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. To ensure that the B criterion symptoms were concurrent with A criterion mood disturbance, subjects were directed to focus on the worst or most impairing episode of mood disturbance while being assessed for the presence of the confirmatory B criterion symptoms. That is, the subject was asked to consider the time during which the screen was at its worst for the purposes of determining whether the remaining symptoms were also evident at the same time as the screening item.Also recorded was the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. Any subject meeting criteria for

BP-II or BP-NOS was not included in this study. To gauge a distinct episode our interviewers ask for 'a distinct period (of at least one week) of extreme and persistently elevated, expansive or irritable mood' and further require that the irritability endorsed in this module is 'super' and 'extreme.'

Statistical Analysis

We analyzed censored time-to-failure data (i.e. onset of disorder if the disorder is present or age at interview if the disorder was not present) with survival analysis methods to weight the contribution of each family member by their age at assessment. This is necessary because we assessed both child and adult relatives and the simple prevalence of disorder in relatives may under-estimate the true risk since children have not yet progressed through the entire window of risk. Thus, we report estimates of morbid risk (MR) calculated from Kaplan-Meier cumulative failure function.

Hazards ratios (HR) and their 95% confidence intervals were estimated from Cox proportional hazard models to test for differences between groups of relatives. To estimate the independent risk of additional psychiatric morbidity in relatives, congruent proband comorbidity was included in family risk models. For example, in estimating the relative increase in familial risk of anxiety, we modeled the risk of anxiety in relatives as a function of group status (BP-I, ADHD, and Control), comorbid anxiety in proband, and any other confounders of interest.

To account for non-independence within families, we adjusted variance estimates of these Cox models with Huber's (Huber, 1967) formula as implemented in Stata (Rogers, 1993) to produce p-values that are robust to distributional assumptions. Other demographic data (e.g. age, sex, etc) were analyzed with one-way analysis of variance or Pearson's $\chi 2$ test. All statistical tests were 2-tailed and any p-values <0.05 were considered statistically significant.

Results

Demographic and clinical characteristics of the sample are presented in Table 1. Eighty percent of the BP-I probands are male.There were small but statistically significant differences in the ethnic and socio-economic backgrounds of the families. The control had had higher SES and the BP-I families had more ethnic diversity. Accordingly, all subsequent tests were adjusted for SES and race. There were no differences in the age or sex of the BP-I, ADHD, and control probands (by design, see methods above). The BP-I probands were more impaired than both ADHD and control children according to past and current global assessment of functioning (GAF) score (Table 1). There were no meaningful demographic characteristics differences between the parents or siblings of the BP-I, ADHD, and control probands, but relatives of BP-I probands were more impaired according to both lifetime and current GAF scores than the relatives of both the ADHD and control relatives.

The clinical presentation of BP-I disorder in probands was characterized by early onset (5.8±3.4 years), rapid cycling (22.4±61.6 episodes) and a chronic course (3.6±3.3 years in duration). As shown in Table 2, BP-I in probands was predominantly mixed with co-occurring depression (N=131, 83%) and probands with BP-I were at increased risk of multiple (≥2) anxiety disorders, disruptive behavior disorders, and substance use disorder relative to both the ADHD and control probands. Although statistical comparisons could not be made between these groups for ADHD or psychosis due to the inclusion/exclusion criteria of the ADHD family studies, both of these disorders were overrepresented in BP-I probands.

The age-dependant cumulative morbid risk of BP-I disorder in relatives is illustrated in Figures 1 and 2. The risk of BP-I disorder in relatives of BP-I probands was statistically significantly higher compared with the relatives of both the ADHD (Hazard Ratio (HR)=3.1 (1.8-5.5); p<0.0001) and the healthy control probands (HR=3.3; (1.9-5.5); p<0.0001). In contrast, the relatives of ADHD probands were not at increased risk of BP-I compared with relatives of control probands (HR=1.0; (0.5-1.9); p=0.9). In this context, the HR indexes the relative risk for a disorder in the relative given the proband diagnoses. For example, the HR for BP-I in relatives of BP-I vs relatives of ADHD probands was 3.6, which means that there was an, age corrected 3.6 fold increase of BP-I among the relatives of BP-I probands compared with relatives of ADHD probands. Controlling for psychiatric comorbidity in probands (ODD, conduct disorder, major depression, multiple anxiety disorders, and substance use disorder) did not impact the statistical significance or magnitude of the hazards ratios comparing the relatives of BP-I probands with relatives of ADHD (corrected HR=3.8 (1.9-7.6, p<0.0001) or control (corrected HR=4.0 (1.6-10.1, p<0.0001) probands.

The morbid risk of additional psychiatric disorders in the 1st degree relatives of BP-I, ADHD, and control probands are presented in Table 3. Relatives of BP-I probands were at increased risk of psychosis, major depression, multiple anxiety disorders, substance use disorders, ADHD, Oppositional Defiant Disorder (ODD) and antisocial (Conduct Disorder [CD] or Antisocial Personality Disorder [ASPD]) compared with relatives of Control probands. In addition, in comparison with relatives of ADHD probands, relatives of BP-I probands were also at increased risk of major depression, multiple anxiety disorders, substance use disorders and ODD (Table 3). However, in models adjusting for the same psychiatric comorbidity in probands, the relatives of BP-I probands were no longer at increased risk for ODD nor for CD/ASPD compared with relatives of Control probands, nor for ODD and CD/ASPD compared with relatives of ADHD probands (all p's >0.05). Thus, BP-I in probands was independently associated with major depression, multiple anxiety disorders substance use disorders and ADHD in comparison with controls. Relatives of BP-I probands were at statistically significant increased risk of psychosis, multiple anxiety disorders and substance use disorder compared with relatives of ADHD probands independently of the psychiatric comorbidity with these disorders in probands.

To determine if our findings of familial transmission were moderated by age, we augmented our statistical models by adding the interaction of age (12 and under vs. older) by proband group. We found no statistically significant interactions, which indicates that the magnitude of familial transmission was not moderated by age group.

Discussion

Particular strengths of this study include its large sample size, the comprehensive scope of psychopathology examined in both probands and relatives, and the use of both psychopathological (ADHD) and healthy control comparison groups. By assessing a wide range of psychiatric conditions in these data we could adjust for psychiatric comorbidity in probands when estimating the familiality of BP-I in their first degree relatives and estimate the familial risk of additional psychiatric disorders in relatives of BP-I child probands, also while adjusting for psychiatric comorbidity in the probands. The diagnosis of pediatric bipolar disorder continues to confound clinicians and researchers with questions remaining as to its validity. Following the logic of Robins and Guze (Robins and Guze, 1970), family studies provide data external to the clinical picture, that can support the validity of a diagnosis. Our study is unique in several ways: 1) is the largest family study of this disorder; 2) it includes a psychopathological control group; 3) it ascertains subjects based on un-modified DSM criteria; 4) is the first to focus on the familiality of additional psychopathological conditions in relatives.

In our sample 80% of the bipolar I probands are male. This is consistent with previous reports of male preponderance by Geller et al (Geller *et al.*, 2008) 67%, Findling (Findling *et al.*, 2001) 71.1%, and Luckenbaugh (Luckenbaugh *et al.*, 2009) 70%. Only Birmaher et al (Birmaher *et al.*, 2009) found a nearly equal gender representation for Bipolar I subjects of 53.5%.

The significantly elevated morbid risk of BP-I in relatives was not appreciably changed after controlling for psychiatric comorbidity in probands. This was so despite the high rates of comorbid ADHD, oppositional defiant disorder, major depression, and anxiety disorders in children with BP-I disorder, as has been previously documented by several research groups (Brotman *et al.*, 2007, Findling *et al.*, 2001, Geller *et al.*, 2000b, Mick *et al.*, 2003, Wozniak and Biederman, 1995, Wozniak *et al.*, 1995a). Moreover, the similar magnitude and statistical significance of the corrected and uncorrected hazard ratios suggests that comorbidity in probands had little impact on the familiality of BP-I disorder. This finding cannot be explained by any theory that posits BP-I disorder in children to be an epiphenomenon of another disorder.

Although relatives of BP-I probands were at increased risk for major depression compared with relatives of controls, the risk for major depression was not distinguishable between relatives of BP-I and relatives of ADHD probands. These results are consistent with previous studies (Brotman *et al.*, 2007, Geller *et al.*, 2006, Kutcher and Marton, 1991, Wozniak *et al.*, 1995a, Wozniak *et al.*, 1995b). Based on our previous work examining the nature of the association between ADHD and major depression, similarities in the risk for major depression between ADHD and BP-I families could be explained by research suggesting that ADHD and major depression may share familial risk factors (Biederman *et al.*, 2008, Biederman *et al.*, 1998, Faraone and Biederman, 1997).

Our findings that the elevated rates of antisocial disorders in relatives of BP-I probands was accounted by these disorders in the proband is consistent with findings reported by Wozniak et al (Wozniak *et al.*, 2001). These investigators also found that the relatives of BP-I in probands were not at increased risk for antisocial disorders after accounting for this comorbidity in probands.

The association between BP-I and ADHD in families has been the subject of prior investigation. Rende et al (Rende *et al.*, 2007) reported that 33% of children with BP-I disorder had a family history of ADHD and, although the morbid risk of ADHD was not specifically estimated, Geller et al (Geller *et al.*, 2006) found that relatives with ADHD, of child bipolar probands, were at increased risk for bipolar disorder. The familial relationship between ADHD and BP-I observed in these studies of BP-I probands (Geller *et al.*, 2006, Rende *et al.*, 2007) is consistent with our previous family studies of ADHD and BP-I (Faraone *et al.*, 1997, Faraone *et al.*, 2001, Wozniak *et al.*, 1995b). That these disorders may also share familial risk factors could explain the association of the dopamine transporter gene with both bipolar disorder (Greenwood *et al.*, 2006, Mick *et al.*, 2007) and ADHD (Asherson *et al.*, 2007, Brookes *et al.*, 2006a, Brookes *et al.*, 2006b). More work is needed with larger samples of non-ADHD BP-I probands and their relatives to fully parse the familiality of ADHD and pediatric BP-I.

Our finding of increased familial risks for substance use disorders and anxiety disorders in relatives of pediatric BP-I probands is consistent with the literature (Brotman *et al.*, 2007, Dwyer and Delong, 1985, Strober *et al.*, 1988). Wozniak et al (Wozniak *et al.*, 2002) also found an excess of anxiety disorders in relatives of pediatric bipolar probands but only among those of probands who also suffered from anxiety disorders. Similarly, prior work has shown an excess of substance use disorders in child BP-I probands and their relatives

(Biederman *et al.*, 2000a, Biederman *et al.*, 2000b). The consistency of the familial risk for psychopathology in our study with that of the extant literature is particularly noteworthy considering the variability in study methodology (i.e. ascertainment criteria, sample size, study design) and suggests that the familiality of pediatric BP-I disorder may be as highly reproducible as it is for adult BP-I disorder (Tsuang and Faraone, 1990).

Our findings should be considered in the context of methodological limitations. Despite the large sample size, full stratification by psychiatric comorbidity would have resulted in cells with small sample size (e.g., 24 non-ADHD BP-I probands). For our structured interviews, both the KSADS and the SCID, we use extensively trained interviewers with undergraduate degrees in psychology, rather than clinician raters. Although we did not administer structured diagnostic interviews directly to children younger than 12 years of age, a clinical diagnosis of BP-I in probands was corroborated by clinical assessment by an expert clinician prior to study inclusion (Wozniak *et al.*, 2003). Also, we did not concurrently enroll comparison families but relied instead upon existing samples of ADHD and non-ADHD families. However, because all subjects were recruited from the same catchment area using the same ascertainment schema and research assessments, it is unlikely that the sample definition accounts for the findings presented here. Finally, because this sample was clinically referred and primarily Caucasian, these results may not generalize to non-referred children or to families of other ethnicities.

With these considerations in mind, we report that relatives of pediatric probands with DSM-IV defined BP-I disorder were at significantly increased risk for BP-I disorder compared with relatives of both ADHD and control probands. In addition, we found that pediatric BP-I disorder was associated with an increased familial risk of syndrome-congruent psychiatric comorbidity such as of major depression, substance use disorder, anxiety disorders and psychosis. High rates of antisocial disorders were noted among the relatives of BP-I probands who also suffered from these comorbidities. These results are consistent with the literature documenting the familiality of pediatric bipolar disorder and suggest that of DSM-IV BP-I disorder diagnostic criteria applied to children is a valid clinical entity worthy of further clinical and scientific attention. While the familial component of the Robins and Guze (1970) criteria for a valid psychiatric condition may have been met, prospective follow-up studies, genetic association studies, and neuroimaging studies are needed to further characterize the prognostic course and neurobiological underpinnings and causes of DSM-IV defined pediatric bipolar disorder.

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References

Asherson P, Brookes K, Franke B, Chen W, Gill M, Ebstein RP, Buitelaar J, Banaschewski T, Sonuga-Barke E, Eisenberg J, Manor I, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Faraone SV. Confirmation that a specific haplotype of the dopamine transporter gene is associated with combined-type ADHD. American Journal of Psychiatry. 2007; 164:674–7. [PubMed: 17403983]

Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, Cote M, Faraone SV. New insights into the comorbidity between ADHD and major depression in adolescent and young adult

females. Journal of the American Academy of Child and Adolescent Psychiatry. 2008; 47:426–34. [PubMed: 18388760]

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, Ugaglia K, Jellinek MS, Steingard R, Spencer T, Norman D, Kolodny R, Kraus I, Perrin J, Keller MB, Tsuang MT. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. Archives of General Psychiatry. 1992; 49:728–38. [PubMed: 1514878]

Biederman J, Faraone SV, Mick E, Williamson S, Wilens TE, Spencer TJ, Weber W, Jetton J, Kraus I, Pert J, Zallen B. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. Journal of the American Academy of Child and Adolescent Psychiatry. 1999; 38:966–975. [PubMed: 10434488]

Biederman J, Faraone SV, Monuteaux MC, Feighner JA. Patterns of alcohol and drug use in adolescents can be predicted by parental substance use disorders. Pediatrics. 2000a; 106:792–7. [PubMed: 11015524]

Biederman J, Faraone SV, Wozniak J, Monuteaux MC. Parsing the association between bipolar, conduct, and substance use disorders: a familial risk analysis. Biological Psychiatry. 2000b; 48:1037–44. [PubMed: 11094136]

Biederman J, Mick E, Faraone S. Depression in attention deficit hyperactivity disorder (ADHD) children: “True” depression or demoralization. Journal of Affective Disorders. 1998; 47:113–122. [PubMed: 9476751]

Biederman J, Mick E, Faraone SV, Van Patten S, Burback M, Wozniak J. A Prospective Follow Up Study of Pediatric Bipolar Disorder in boys with attention deficit/hyperactivity disorder. Journal of Affective Disorders. 2004; 82S:S17–S23. [PubMed: 15571786]

Biederman J, Monuteaux M, Mick E, Spencer T, Wilens T, Klein K, Price JE, Faraone SV. Psychopathology in females with attention-deficit/hyperactivity disorder: A controlled, five-year prospective study. Biological Psychiatry. 2006a; 60:1098–105. [PubMed: 16712802]

Biederman J, Monuteaux M, Mick E, Spencer T, Wilens T, Silva J, Snyder L, Faraone SV. Young Adult Outcome of Attention Deficit Hyperactivity Disorder: A Controlled 10 year Prospective Follow-Up Study. Psychological Medicine. 2006b; 36:167–179. [PubMed: 16420713]

Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Houck P, Ha W, Iyengar S, Kim E, Yen S, Hower H, Esposito-Smythers C, Goldstein T, Ryan N, Keller M. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. American Journal of Psychiatry. 2009; 166:795–804. [PubMed: 19448190]

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Clinical course of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry. 2006; 63:175–83. [PubMed: 16461861]

Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, Aneey R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, Campbell D, Knight J, Andreou P, Altink M, Arnold R, Boer F, Buschgens C, Butler L, Christiansen H, Feldman L, Fleischman K, Fliers E, Howe-Forbes R, Goldfarb A, Heise A, Gabriels I, Korn-Lubetzki I, Marco R, Medad S, Minderaa R, Mulas F, Muller U, Mulligan A, Rabin K, Rommelse N, Sethna V, Sorohan J, Uebel H, Psychogiou L, Weeks A, Barrett R, Craig I, Banaschewski T, Sonuga-Barke E, Eisenberg J, Kuntsi J, Manor I, McGuffin P, Miranda A, Oades RD, Plomin R, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Taylor E, Thompson M, Faraone SV, Asherson P, Johansson L. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Molecular Psychiatry. 2006a

Brookes KJ, Mill J, Guindalini C, Curran S, Xu X, Knight J, Chen CK, Huang YS, Sethna V, Taylor E, Chen W, Breen G, Asherson P. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. Archives of General Psychiatry. 2006b; 63:74–81. [PubMed: 16389200]

Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, Towbin KE, Pine DS, McMahon FJ, Leibenluft E. Parental diagnoses in youth with narrow phenotype bipolar disorder or

severe mood dysregulation. American Journal of Psychiatry. 2007; 164:1238–41. [PubMed: 17671287]

Craddock N, Forty L. Genetics of affective (mood) disorders. European Journal of Human Genetics. 2006; 14:660–8. [PubMed: 16721402]

Dwyer J, Delong R. A family history study of twenty probands with childhood manic-depressive illness. Journal of the American Academy of Child and Adolescent Psychiatry. 1985; 26:176–180. [PubMed: 3584013]

Faraone S, Glatt S, Tsuang M. The genetics of pediatric onset bipolar disorder. Biological Psychiatry. 2003; 53:970–977. [PubMed: 12788242]

Faraone SV, Biederman J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? Journal of Nervous and Mental Disease. 1997; 185:533–541. [PubMed: 9307614]

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? Journal of the American Academy of Child and Adolescent Psychiatry. 1997; 36:1378–87. discussion 1387-90. [PubMed: 9334551]

Faraone SV, Biederman J, Monuteaux MC. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? Journal of Affective Disorders. 2001; 64:19–26. [PubMed: 11292516]

Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disorders. 2001; 3:202–210. [PubMed: 11552959]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). American Psychiatric Press; Washington, DC: 1997.

Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. Journal of the American Academy of Child and Adolescent Psychiatry. 2000a; 39:1543–8. [PubMed: 11128332]

Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Archives of General Psychiatry. 2008; 65:1125–33. [PubMed: 18838629]

Geller B, Tillman R, Bolhofner K, Zimerman B, Strauss NA, Kaufmann P. Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. Archives of General Psychiatry. 2006; 63:1130–8. [PubMed: 17015815]

Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, Soutullo CA. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology. 2000b; 10:157–64. [PubMed: 11052405]

Greenwood TA, Schork NJ, Eskin E, Kelsoe JR. Identification of additional variants within the human dopamine transporter gene provides further evidence for an association with bipolar disorder in two independent samples. Molecular Psychiatry. 2006; 11:125–33. 115. [PubMed: 16261167]

Huber, PJ. The behavior of maximum likelihood estimates under non-standard conditions; Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability; 1967; p. 221-233.

Kutcher S, Marton P. Affective disorders in first-degree relatives of adolescent onset bipolars, unipolars, and normal controls. Journal of the American Academy of Child and Adolescent Psychiatry. 1991; 30:75–78. [PubMed: 2005067]

Leibenluft E, Charney D, Towbin K, Bhangoo R, Pine D. Defining clinical phenotypes of juvenile mania. American Journal of Psychiatry. 2003; 160:430–7. [PubMed: 12611821]

Luckenbaugh DA, Findling RL, Leverich GS, Pizzarello SM, Post RM. Earliest symptoms discriminating juvenile-onset bipolar illness from ADHD. Bipolar Disord. 2009; 11:441–51. [PubMed: 19500097]

Mick E, Biederman J, Faraone S, Murray K, Wozniak J. Defining a Developmental Subtype of Bipolar Disorder in a Sample of Non-Referred Adults by Age-At-Onset. Journal of Child and Adolescent Psychopharmacology. 2003; 13:453–462. [PubMed: 14977458]

Mick, E.; Kim, J.; Biederman, J.; Wozniak, J.; Wilens, T.; Smoller, J.; Spencer, T.; McGrath, C.; Sklar, P.; Faraone, S. Family based association study of SLC6A3 in pediatric bipolar disorder; NIMH Collaborative Pediatric Bipolar Disorder Conference; Washington, DC. 2007; 5U13MH064077

Neuman R, Geller B, Rice J, Todd R. Increased prevalence and earlier onset of mood disoders among relatives of prepubertal versus adult probands. Journal of the American Academy of Child and Adolescent Psychiatry. 1997; 36:466–473. [PubMed: 9100420]

Orvaschel, H. Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version. Nova Southeastern University, Center for Psychological Studies; Ft. Lauderdale: 1994.

Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry. 2004; 55:875–81. [PubMed: 15110730]

Rende R, Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Childhood-onset bipolar disorder: Evidence for increased familial loading of psychiatric illness. J Am Acad Child Adolesc Psychiatry. 2007; 46:197–204. [PubMed: 17242623]

Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. American Journal of Psychiatry. 1970; 126:983–987. [PubMed: 5409569]

Rogers W. Regression standard errors in clustered samples. Stata Technical Bulletin. 1993; 13:19–23.

Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R. A family study of bipolar I disorder in adolescence: Early onset of symptoms linked to increased familial loading and lithium resistance. Journal of Affective Disorders. 1988; 15:255–268. [PubMed: 2975298]

Tsuang, MT.; Faraone, SV. The Genetics of Mood Disorders. The John Hopkins University Press; Baltimore: 1990.

Wilens T, Biederman J, Adamson JJ, Monuteaux M, Henin A, Sgambati S, Santry A, Faraone SV. Association of bipolar and substance use disorders in parents of adolescents with bipolar disorder. Biological Psychiatry. 2007; 62:129–34. [PubMed: 17481590]

Wozniak J. Recognizing and managing bipolar disorder in children. J Clin Psychiatry. 2005; 66(Suppl 1):18–23. [PubMed: 15693748]

Wozniak J, Biederman J. Childhood mania exists (and coexists) with ADHD. American Society of Clinical Psychopharmacology Progress Notes. 1995; 6:4–5.

Wozniak J, Biederman J, Faraone SV, Blier H, Monuteaux MC. Heterogeneity of childhood conduct disorder: further evidence of a subtype of conduct disorder linked to bipolar disorder. Journal of Affective Disorders. 2001; 64:121–31. [PubMed: 11313079]

Wozniak J, Biederman J, Kiely K, Ablon S, Faraone S, Mundy E, Mennin D. Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. Journal of the American Academy of Child and Adolescent Psychiatry. 1995a; 34:867–876. [PubMed: 7649957]

Wozniak J, Biederman J, Kwon A, Mick E, Faraone SV, Orlovsky K, Schnare L, Cargol C, Van Grondelle A. How cardinal are cardinal symptoms in pediatric bipolar disorder?: An examination of clinical correlates. Biological Psychiatry. 2005; 58:583–588. [PubMed: 16197929]

Wozniak J, Biederman J, Monuteaux MC, Richards J, Faraone SV. Parsing the comorbidity between bipolar disorder and anxiety disorders: a familial risk analysis. J Child Adolesc Psychopharmacol. 2002; 12:101–11. [PubMed: 12188979]

Wozniak J, Biederman J, Mundy E, Mennin D, Faraone SV. A pilot family study of childhood-onset mania. Journal of the American Academy of Child and Adolescent Psychiatry. 1995b; 34:1577–1583. [PubMed: 8543528]

Wozniak J, Monuteaux M, Richards J, L. K,E, Faraone SV, Biederman J. Convergence between structured diagnostic interviews and clinical assessment on the diagnosis of pediatric-onset mania. Biol Psychiatry. 2003; 53:938–44. [PubMed: 12788238]

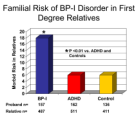

Figure 1.
Familial risk of bipolar-I (BP-I) disorder in first-degree relatives. ADHD, attention deficit hyperactivity disorder.

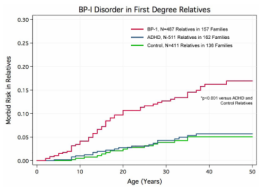

Figure 2.
Bipolar-I (BP-I) disorder in first-degree relatives.

Table 1

Clinical and Demographic Characteristics

	BP-I Families	ADHD Families	Control Families	Statistic
Total	**N=644**	**N=673**	**N=547**	
SES	1.8±0.9 [a]	1.8±0.9 [a]	1.6±0.8	F(2,451)=5.3, p=0.005
Race/Ethnicity				
Caucasian	594(92) [a,b]	667 (99)	536 (98)	$\chi 2(6)=56.7$, p<0.001
African-Am.	32 (5)	6 (1)	7 (1)	
More than 1	12 (2)	0 (0)	0 (0)	
Unknown	6 (1)	0 (0)	4 (1)	
Probands	**N=157**	**N=162**	**N=136**	
Age (y)	10.5±3.2	10.6±3.0	10.7±3.0	F(2,452)=0.2,p=0.8
Sex (m)	125 (80)	121 (75)	99 (73)	$\chi 2(2)=2.1$, p=0.3
Past GAF	40.6±5.9 [a,b]	50.7±7.3 [a]	70.5±8.5	F(2,452)=630.7,p<0.001
Current GAF	46.2±6.3 [a,b]	57.4±8.2 [a]	73.3±7.3	F(2.452)=505.0, p<0.001
Parents	**N=301**	**N=323**	**N=269**	
Age (y)	42.3±6.6	41.3±6.4	41.6±5.8	F(2,884)=2.0,p=0.1
Sex (m)	144 (48)	161 (50)	133 (49)	$\chi 2(2)=0.3$, p=0.9
Past GAF	52.2±9.7 [a,b]	56.9±12.6 [a]	63.5±12.4	F(2,875)=65.9, p<0.001
Current GAF	63.4±7.8 [a,b]	68.5±9.5 [a]	72.9±7.9	F(2,834)=85.5, p<0.001
Siblings	**N=186**	**N=188**	**N=142**	
Age (y)	11.6±5.5 [b]	13.7±5.8	12.9±5.1	F(2,511)=7.2,p=0.001
Sex (m)	98 (51)	103 (55)	74 (52)	$\chi 2(2)=0.8$, p=0.7
Past GAF	57.7±9.4 [a,b]	61.8±12.0 [a]	65.9±10.7	F(2,504)=23.3, p<0.001
Current GAF	62.6±7.7 [a,b]	67.9±10.8 [a]	71.1±8.4	F(2,503)=35.9, p<0.001

SES - Socioeconomic status; GAF Global Assessment of Function

[a] p<0.05 vs. Control

[b] p<0.05 vs. ADHD

Table 2

Psychiatric Comorbidity in Proband Children

	BP-I N=157	ADHD N=162	Control N=136	Statistic
	N (%)	N (%)	N (%)	
Psychosis	51 (33)	*	*	-
Major Depression	131 (83) *a,b*	61 (37) *a*	10 (7)	$\chi 2(2)=175.5$, $p<0.001$
Multiple (2) Anxiety Disorders	100 (64) *a,b*	43 (27) *a*	6 (4)	$\chi 2(2)=120.7$, $p<0.001$
ADHD	133 (85)	*	*	-
Oppositional Defiant Disorder	141 (90) *a,b*	87 (54) *a*	8 (6)	$\chi 2(2)=205.9$, $p<0.001$
Conduct Disorder	80 (51) *a,b*	24 (15) *a*	2 (2)	$\chi 2(2)=109.9$, $p<0.001$
Substance (alcohol or Drug) Use Disorder (abuse or Dependence)	18 (12) *a,b*	5 (3)	1 (1)	$\chi 2(2)=19.2$, $p<0.001$

a $p<0.05$ vs. Controls

b $p<0.05$ vs. ADHD.

* Potential probands with psychosis were excluded during ascertainment of ADHD and Control families.

Table 3

Psychiatric Morbidity in 1st Degree Relatives of Pediatric BPD, ADHD and Control Probands

	BP-I N=487	ADHD N=511	Control N=411
	MR (95% CI)	MR (95% CI)	MR (95% CI)
Psychosis	0.07 (0.05-0.11)[b,c]	0.01 (0.005-0.03)	-
Major Depression	0.49 (0.44-0.55)[a,b,c]	0.39 (0.34-0.45)[a,c]	0.22 (0.18-0.27)
Multiple (2) Anxiety Disorders	0.38 (0.32-0.44)[a,b,c,d]	0.19 (0.15-0.23)[a]	0.13 (0.10-0.18)
Substance (alcohol or Drug) Use Disorder (abuse or Dependence)	0.57 (0.52-0.63)[a,b,c,d]	0.40 (0.35-0.46)	0.28 (0.23-0.33)
ADHD	0.23 (0.19-0.27)a[a,c]	0.20 (0.17-0.24)[a,c]	0.07 (0.04-0.09)
Oppositional Defiant Disorder	0.21 (0.17-0.25)[a,b]	0.12 (0.09-0.16)[a]	0.07 (0.05-0.10
Conduct Disorder/Antisocial Personality Disorder	0.17 (0.13-0.21)[a]	0.16 (0.12-0.20)[a]	0.06 (0.04-0.10)

MR =Morbid RiskHR (95% CI) = hazard ratio (95% confidence interval) All results corrected for Family SES and race.

[a] p<0.05 vs Controls relatives

[b] p<0.05 vs ADHD relatives

[c] p<0.05 vs Controls relatives after correcting for concordant psychiatric comorbidity in the proband after correcting for concordant psychiatric comorbidity in the proband (e.g., the analysis of ADHD in the relatives was corrected for the presence of ADHD in the proband)

[d] p<0.05 vs ADHD relatives; after correcting for concordant psychiatric comorbidity in the proband