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Early onset bipolar disorder: possible linkage to chromosome 9q34

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Objectives: Bipolar disorder (BD) is characterized by manic and depressive states that onset at various times in life. Research shows that early onset forms of BD are associated with a stronger genetic loading for the illness. We hypothesized that using age at onset to look at subsets of BD families in a genetic linkage analysis would prove useful in separating etiologically homogeneous BD sub-groups and subsequently identifying genetic susceptibility regions.

Methods: We used the wave-I National Institute of Mental Health (NIMH) Genetics Initiative BD sample, which includes 540 individuals from 97 families with BD, in an ordered-subsets linkage analysis with age at onset of mania as the subset-identifying covariate. This analysis was performed using GENEHUNTER-PLUS followed by the ordered-subsets analysis program. This program generates empirical p-values for the subset with the largest LOD score to determine whether this value was significantly higher than the baseline LOD score using all families.

Results: Three chromosomal regions resulted in LOD scores above 2.0: 2.21 (6q25), 3.21 (9q34), and 2.16 (20q11). The largest increase in LOD score was observed on chromosome 9q34 between markers D9S290 and D9S915 in the subset of 58 families that had mania onset before age 20. Families with a minimal mania onset less than 20 years had a significantly greater number of psychiatric comorbidities (p = 0.02) and a marginal increase in depressive symptoms (p = 0.10).

Conclusions: Further investigation into chromosomal region 9q34 is necessary to determine whether this region may harbor a gene specific to families with a minimal age at onset of less than 20.

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Although bipolar disorder (BD) has a strong genetic basis and some regions of the genome have been repeatedly implicated in risk for the illness in individual linkage studies, the specific genes involved in its etiology remain unknown (1, 2). In part, this stems from the variability of the results of the majority of linkage studies; thus, while some studies have found overlapping evidence for linkage at a particular chromosomal region (3, 4), there are no such loci that have been identified in all or even a majority of studies. In fact, even after the results of more than 11 independent genome-wide linkage scans of BD were pooled by different methods of meta-analysis (5, 6), discrepant findings of linked chromosomal regions emerged. Although some prime candidate loci for BD, such as chromosomes 13q and 22q, are now being pursued in fine-mapping efforts (7), such variability indicates that the disorder is not likely to be easily mapped onto discrete loci.

The variability observed in gene-finding efforts for BD may reflect the clinical complexity and heterogeneity of the disorder. For example, individuals with BD differ markedly in illness severity and duration, rates of personal and familial suicidality

and mood disorder, and extent of concomitant substance abuse and neuropsychiatric abnormalities. In addition, BD may be incorrectly identified as major depression, schizophrenia, or schizoaffective disorder in as many as 10% of cases (8). Such complexity creates classification problems that can restrict the power of genetic studies of the condition.

Some of this phenotypic heterogeneity may be due to pleiotropy, i.e., multiple effects of a single set of BD genes; alternatively, such complexity could be due to underlying etiologic heterogeneity, where different causal paths to the illness exist in the population. Segregation studies have supported the latter concept by providing evidence for autosomal dominant transmission of the illness in some families and multifactorial polygenic segregation in others (9–13). The inherent phenotypic and causal heterogeneity of this illness – now recognized as limiting factors in the search for risk genes – have recently been the subject of attempts to delimit sub-classes of the illness to facilitate targeting more homogeneous and informative phenotypes for genetic study. Thus, the potentially greater etiologic homogeneity of a BD sub-group delineated based on the grounds of phenotypic similarity may strengthen the observed genetic effects more and render them more easily recognizable.

The age at onset of BD has been considered as one potentially useful variable for constructing homogeneous groups of patients (14, 15), as this characteristic correlates with several clinical features that may make it useful for resolving the clinical heterogeneity of the illness. For example, an early age at onset has been associated with a chronic course and a poorer response to mood stabilizers, while a later age at onset is linked to more severe abnormal thought content (16). Age at onset may also be a useful marker of the degree of genetic contribution to disease development. For example, Grigorouio-Serbanescu et al. (17) found that different modes of transmission best fit the segregation of early and late-onset BD, with early-onset forms best explained by passage of a non-Mendelian major gene with a polygenic component and late-onset forms showing multifactorial inheritance. Early-onset cases also show comorbidity and co-familial transmission with attention-deficit/hyperactivity and conduct disorders (ADHD) (18–21).

Because age at onset is both familial (22) and heritable (23), it is reasonable to use linkage analysis to detect genes that regulate this trait in bipolar families. In our previous work, we determined that the age at onset of mania – but not depression – in BD families was significantly heritable, and was possibly linked to three chromosomal loci on chromosomes 12p, 14q, and 15q (14). This approach provided some support for the notion that features of BD could be used to identify genetic loci contributing to the variability of the overall disease phenotype. In the present analysis, we have extended this approach. The previous study in this sample was devised to identify quantitative trait loci that regulate the age at onset of mania in BD; however, the present study was designed to use the knowledge that age at onset was a marker for genetic loading for the illness to divide the sample of families into those with higher genetic load (evidenced by a relatively early age at onset in the family) and those with a lower genetic load (with consequently later age at onset). It was thus hypothesized that the genetic linkage signal in the highly loaded families with an earlier age at onset would be greater at some loci than in the entire sample of BD families.

Methods

Subjects

In wave-I of the National Institute of Mental Health (NIMH) Genetics Initiative for Bipolar Disorder, probands meeting DSM-III-R criteria for bipolar disorder I (BDI) were systematically ascertained by screening consecutive patients at psychiatric hospitals near Indiana University, Johns Hopkins University, the NIMH Intramural Research Program, and Washington University as part of the NIMH Human Genetics Initiative (http://www-srb.nimh.nih.gov/gi.html). Families with at least one first-degree relative with a DSM-III-R diagnosis of BDI or schizoaffective disorder, bipolar type (SA/BP), were retained for further examination. Families were excluded if both parents had either BDI or SA/BP. The sample consisted of 540 genotyped individuals in 97 families with 232 BDI, 32 SA/BP, 72 BDII, and 88 unipolar depressed individuals. A genome scan of these families with three qualitative traits for affection has been published elsewhere (24–27). We accessed the genotypes and clinical data through the NIMH Center for Genetic Studies (http://zork.wustl.edu/nimh/).

Genotyping, allele frequencies, and maps

Genotyping methods for this sample have been described elsewhere in detail. In summary, allele frequencies were initially created using the program, USER13 (28) and marker distances were generated using the Kosambi mapping function and the computer program, CRIMAP. Genetic

maps were then compared to existing genetic databases (29) and genotypes were examined for Mendelian inconsistencies. In total, there were 319 markers spaced at an average of 10 cM apart throughout the genome.

Ordered subsets analyses

Ordered subsets analysis (OSA) can be used to find evidence for genetic linkage in a heterogeneous sample by identifying a more homogeneous subset. OSA identifies the family subset that maximizes the LOD score through the use of a covariate that rank orders families. In this analysis, the minimal age at onset of mania in each family was used as the covariate. Age at onset of mania was obtained through the Diagnostic Interview for Genetic Studies (DIGS) (8, 30). The DIGS includes a mania/hypomania section that quantifies the mania status of subjects. In this section, each participant was asked two questions about the age at onset of mania; the first question asked for the age at onset of any manic episode and the second question asked for the age at onset of the first manic episode that could not be attributed to medical illness, medications, or substance abuse. We used the second question in our analyses because this eliminated mania episodes due to non-genetic factors; however, the correlation between the two variables was significant ($r^2 = 0.62$, p < 0.0001). Using the latter question excluded 23 subjects who reported at least one manic episode but no 'clean' episodes. For each family, the minimal age at mania onset reported by a family member was used as the family covariate value.

GENEHUNTER-PLUS was initially used to calculate multipoint nonparametric LOD scores in affected relative pairs using the allele-sharing method. In this analysis, individuals diagnosed with either BDI or SA/BP were considered affected. This narrowly defined affection status corresponds to model I in the initial published findings of these data. Due to analysis constraints by chromosome, as few as 94 of the 97 BD pedigrees, with 259 affected and 261 unaffected individuals, were included in the analysis. The nonparametric LOD scores were then input to the computer program, OSA. Details of the OSA program can be found elsewhere (31, 32). In brief, the OSA program identifies significant increases in the nonparametric LOD score when a subset of the families is used in the analysis. This subset was identified through the covariate, minimal age at onset of mania. Families were first ranked according to the earliest age at mania onset in the family. Families with the same age at onset

were considered tied and analyzed as a group. Beginning with the earliest age at onset families, total multipoint LOD scores were calculated by summing the family LOD scores. The subset was then expanded to include families with the second earliest onset age and overall multipoint LOD scores were recalculated. This process was repeated by continually expanding the subset size until all of the families are included in the final subset. The subset that produces the largest LOD score for that chromosome was then selected and an empirical p-value was calculated via permutation testing to determine if the observed LOD score was significantly higher than the baseline LOD score using all families. Therefore, the p-value in this case refers to change in LOD score using the subset identified through OSA compared with the initial LOD score using the entire sample. This p-value does not address the issue of whether the overall finding is significant. A significant result would therefore suggest that a particular subset of individuals in the sample is more strongly linked to the specified chromosomal region than the sample as a whole.

In this analysis, we were only interested in an ascending rank ordering of the covariate. That is, we were interested in looking only at subsets that begin with the earliest onset families and gradually increase the subsets by including families with greater ages at mania onset. This was our primary interest because of the research indicating that earlier ages of mania onset are associated with greater genetic loading (33, 34). Mania onset, not depression onset, was of particular interest because clinically, it is a more clearly defined event than depression onset. Therefore, there is less chance for misdiagnosis with mania onset compared with the onset of depression. In addition, our previous work has found the age at onset of mania – but not depression – to be significantly heritable in this sample (14).

Adjustment for multiple testing using the false discovery rate (FDR)

The OSA program only adjusts for multiple testing on each chromosome. Therefore, to adjust for multiple testing over all 22 chromosomes, we used the FDR method developed by Benjamini and Hochberg (35). The primary focus of this method is not to control the overall error rate, but to control the proportion of false-positive results among the significant findings. The methodology behind the FDR employs a *q*-value that is an analog to the p-value in that it provides each observation with it own level of significance. A *q*-value can be interpreted as the expected proportion of false-

positives among all observations as or more extreme. Advantages of using the FDR are that it is more powerful than several alternatives (e.g., Bonferroni), it is versatile, and the overall type-I error rate can be preserved by specifying the value of FDR. In this study, we will set the FDR = 0.05.

Clinical differences in age at onset groupings

The age at mania onset that resulted in largest LOD score was noted. Families with an age at onset less than or equal to that value were compared with families whose minimal onset was greater than that value on several clinical variables. Generalized estimating equations (GEE) with an exchangeable covariance matrix were used to compare the two groups on: (i) the total number of DSM-III-R psychiatric comorbidities; and (ii) five standard factor scores previously generated from BD symptoms. Formerly, a principal components factor analysis followed by an orthogonal varimax rotation was performed on a total of 29 psychiatric signs and symptoms relevant to BD that were derived from data in the DIGS. This resulted in five factors that explained 90.1% of the variance. The factors reflected: (i) depressed state; (ii) psychosis; (iii) sleep disturbances; (iv) psychomotor acceleration; and (v) irritable or euphoric mania. All five factors were highly non-normal and therefore a rank transformation was used before employing these variables in the GEE analysis. In both statistical models an affection status covariate, where BDI and SA/BP were considered affected, was also included.

Results

A summary of the subsets that maximized the LOD score is included in Table 1. Three chromosomal regions resulted in LOD scores above 2.0: 2.21 (6q25), 3.21 (9q34), and 2.16 (20q11). A statistically significant increase in LOD score was observed on chromosome 9q34 between markers D9S290 and D9S915. The baseline LOD was 1.31 compared with a LOD of 3.2 (p = 0.017) in the subset of 58 families that had mania onset before age 20. This p-value describes the strength of the relationship between minimal age at onset and the linkage information for the given subset of families. The average age at mania onset was 14.6 for the identifying subset while the average mania onset for those families not included in this group was 25.2. After adjusting for the tests on all 22 chromosomes, the q-value at this region was calculated to be 0.37, indicating that the increase in LOD score is not significantly different than what was observed in the entire sample. Once multiple testing was accounted for, there were no chromosomal regions that resulted in a significant increase in LOD score with a subset of BD families. Therefore, we conclude that no particular subset is more strongly linked to any chromosomal region than the entire sample as a whole. It is

Table 1. Results by chromosome from ordered subsets analysis

Chromosome	cM	Subset LOD	Baseline LOD	p-value	q-value	No. families in subset	Proportion of families
1	271	1.31	1.31	0.63	0.70	12	0.13
2	0	1.16	1.13	0.34	0.70	22	0.23
3	24	0.79	0.77	0.48	0.70	36	0.38
4	28	0.79	0.65	0.84	0.87	18	0.19
5	203	1.20	1.18	0.35	0.70	22	0.23
6	193	2.21	0.79	0.12	0.61	36	0.38
7	128	0.56	0.56	0.87	0.87	12	0.13
8	60	1.29	1.29	0.14	0.61	12	0.13
9	115	3.21	1.91	0.02	0.37	58	0.62
10	49	1.76	0.16	0.54	0.70	87	0.92
11	0	0.50	0.50	0.62	0.70	4	0.04
12	119	1.24	1.06	0.14	0.61	12	0.13
13	46	1.21	0.58	0.48	0.70	71	0.76
14	90	1.35	0.51	0.41	0.70	84	0.88
15	87	1.12	0.90	0.61	0.70	29	0.31
16	35	1.48	0.95	0.11	0.61	29	0.31
17	111	1.53	0.24	0.54	0.70	84	0.89
18	79	1.14	1.01	0.39	0.70	12	0.13
19	71	0.65	0.33	0.64	0.70	18	0.19
20	103	2.16	0.24	0.31	0.70	86	0.91
21	35	1.23	1.17	0.20	0.70	4	0.04
22	21	1.24	1.24	0.25	0.70	12	0.13

important to note that this p-value does not address the issue of whether any of the findings are significant overall.

The largest LOD score on chromosome 9 was generated using a subset of families who had mania onset before the age of 20. Using this cutoff, the GEE analysis found a significantly greater number of comorbidities among those families with the younger minimal age at mania onset (p = 0.03). Of the standardized factor scores, depressed state was marginally significant (p = 0.10), while psychosis (p = 0.85), sleep disturbances (p = 0.18), psycho-motor acceleration (p = 0.68), and type of mania (p = 0.34) were not significantly different between the two age-at-onset classes. When only the affected family members were compared on the depressed state factor, the difference was statistically significant (p = 0.05). Families with earlier mania onset had a marginally stronger depressed state than families who onset later. This factor includes measures of depression, loss of interest, inhibited thought, inadequacy, feelings of guilt, fatigue, psychomotor inhibition, activity change, appetite change, weight change, and suicide.

Discussion

Our work suggests that the chromosomal region 9q34 may contain genes that influence BD in families. This locus yielded a strongly suggestive LOD score within the younger age-at-onset families, however the increase in this LOD score over what was initially observed in the entire sample was not significant after correcting for multiple comparisons across the genome (q = 0.37). Nevertheless, this analysis identifies chromosome 9q34 as a potentially promising region for harboring BD risk genes, especially for younger-onset forms of the illness. Further studies of this region, including attempts to replicate the current patterns of linkage at this locus, should be pursued.

Previously, this sample reported a peak LOD score on chromosome 9q32, which is proximal to this finding (27). This chromosomal region has not been implicated for BD in either of the two published meta-analyses. A rank-based meta-analysis on 18 genome scans found a promising – but not statistically significant – result on the p arm of chromosome 9 (36). Another recent meta-analysis that used 1128 affected individuals from 11 studies found the strongest evidence for linkage on chromosomes 13q and 22q. Recently, Venken et al. (37) reported linkage to 9q31.1-q34.1 for affective disorders using a 2 cM linkage scan in an isolated Swedish population. The strongest result in the OSA analysis replicates this finding, although our

analysis suggests that this region is linked in families where the children onset with mania early.

The present study identifies an early-onset class as families with a minimal mania onset less than 20. This may prove useful in gene identification, as early age of onset cases have consistently been associated with a stronger genetic loading. Pauls et al. (33) studied age at onset of BD as a possible factor linked to genetic loading and found increased lifetime rates of BD in first-degree relatives of individuals who onset by age 12 compared with those who onset afterwards. Rice et al. found similar results in an analysis of 187 families of bipolar patients from the NIMH Collaborative Program. Relatives of BD probands with early onset were found to have a greater risk for BD than relatives of probands with late onset (34). Tsuang and Faraone (38) reviewed 16 family studies and concluded that the rates of mood disorders were greater in families of early-onset BD probands compared with those who onset later. Thus, a growing body of evidence suggests that early-onset BD is associated with stronger familial aggregation. Therefore, families with pediatric BD cases may be a useful group to target for gene identification. Because early-onset families have a stronger genetic loading than later-onset families, the region identified on chromosome 9 may be identifying an area that is unique to early-onset families. This study lacks the power to investigate this hypothesis thoroughly. Although not currently available, a future study that ascertains juvenile-onset mania probands could more powerfully examine this hypothesis. In addition, this analysis has markers at an average of 10 cM throughout the chromosome; therefore, it is premature to identify any particular gene that may be responsible for the observed LOD score. After a replication study, future fine-mapping efforts in this region may be worthwhile to help identify genes with polymorphisms responsible for this finding.

Although disagreement about early-onset BD exists, a growing body of literature suggests that a BD diagnosis is appropriate in children with severe affective dysregulation (15, 39). The clinical picture of this group is not typical of most BD adults. Adult-onset mania often manifests with euphoria while pediatric-onset mania typically manifests with severe, relentless irritability and/or aggression that is often so violent that other individuals are threatened (40). In addition, the course of pediatric mania tends to be chronic and continuous rather than periodic, which is common in adult BD. These individuals do not respond well to mood stabilizing medicine and have high comorbidity with ADHD (15, 19, 40, 41). Although the pediatric-onset

description of BD is not the dominant form observed in adults, McElroy et al. (42) estimated that this clinical description is observed in approximately one-third of adult cases, suggesting that a BD diagnosis is not unreasonable in these children. With these established clinical pictures, one would expect that families with mania onset at less than 20 years would be clinically different from families with older ages of mania onset, particularly in regard to the type of mania manifestation (irritable versus euphoric). Our findings from this study do not find this difference when using the standardized factor score that differentiates type of mania (p = 0.29). This is likely a result of low power; we only had standardized factor scores on 154 individuals from the 97 BD families. Despite low power, there is modest evidence that there is a distinct difference in depressive state among families with at least one person with early onset compared to those with no early onset individuals. As expected, the early onset families exhibited a more severe depressive state. Previous research has found the depressive state factor to be heritable (43). The observed increase in this heritable trait suggests that early onset mania families may have a greater genetic loading – and therefore possibly more genes – for depressive state. Our study also found a larger number of total psychiatric comorbidities: on average, early onset families had more psychiatric comorbidities than late-onset families (2.8 versus 2.4 comorbid diagnoses, p = 0.04). This finding extends beyond the current hypothesis that early-onset individuals are likely to have more psychopathology and suggests that not only early-onset individuals, but also family members of these individuals, have more psychopathology than families with no early-onset individuals.

This analysis also builds on our previous work with this data set, where we used the logarithm of the age at mania onset as a quantitative trait in a genetic linkage analysis and found three loci with LOD scores near or above 3.0 at 12p, 14q, and 15q (43). It may initially seem surprising that the results from this analysis do not identify the same linkage peaks as in the previous analysis; however, after interpreting the results more carefully, it is evident that these analyses identify distinctly different things. The three previously reported linkage peaks can be interpreted as regions where individuals who onset with mania at similar times have more identity by descent (IBD) allele sharing than what is expected by chance. Thus the linkage at these loci is to age at onset as a trait itself and not to either those individuals who onset early or late. In this analysis our approach and the interpretation is distinctly different. Here we are stratifying the sample based on the age at which someone onsets with mania and we perform linkage analysis on the stratified sub-groups where the quantitative trait of interest is affection status. Therefore, when an elevated LOD score is observed, it can be interpreted that there is excessive IBD allele sharing among those affected with BD in the sibling pairs that onset by a specified age. Because these two analyses are reporting conceptually different things, the results from these two reports should not necessarily be expected to overlap. Together, these studies suggest that age at onset is a biologically meaningful feature of BD that is useful in clarifying the heterogeneity of the disorder.

There are several limitations to this study that should be considered. First, although the sample size in this study is moderate, the power to detect genes with small effects remains limited by this sample size. This is more of a problem when OSA is employed, as this methodology only uses a subset of the data. By reducing the sample size we are reducing the power and increasing the chance of obtaining a spurious finding. Second, we did not account for other forms of genetic heterogeneity that could exist in this sample. Third, we only considered a narrow definition of BD, including only BD type I and schizoaffective disorder, bipolar type individuals, resulting in less specific phenotype definitions.

In conclusion, the present study has identified one chromosomal region at 9q34 that may harbor a gene specific to families with a minimal age at onset of less than 20. This gene appears distinct from those that influence susceptibility to the disorder among all families. Before this chromosomal region can be identified as harboring genes specific to early onset of mania families, these findings are in need of replication using pedigrees with juvenile mania-onset individuals as probands. After such a study, fine mapping of promising chromosomal regions can be conducted to identify polymorphisms responsible for the elevated LOD score.

Acknowledgements

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