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Evidence of association between brain-derived neurotrophic factor (*BDNF*) gene and bipolar disorder

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Abstract

Objective—Brain-derived neurotrophic factor (*BDNF*) plays an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons throughout adulthood. There is growing evidence suggesting that *BDNF* is involved in the pathophysiology of mood disorders.

Methods—Ten SNPs across the *BDNF* gene were genotyped in a sample of 1,749 Caucasian Americans from 250 multiplex bipolar families. Family-based association analysis was employed with three hierarchical bipolar disorder models to test for association between SNPs in *BDNF* and the risk for bipolar disorder. In addition, an exploratory analysis was performed to test for an association of the SNPs in *BDNF* and the phenotypes of rapid cycling and episode frequency.

Results—Evidence of association ($p < 0.05$) was found with several of the SNPs using multiple models of bipolar disorder; one of these SNPs also showed evidence of association ($p < 0.05$) with rapid cycling.

Conclusion—These results provide further evidence that variation in *BDNF* affects the risk for bipolar disorder.

Keywords

brain-derived neurotrophic factor; bipolar disorder; association study; single nucleotide polymorphism

Introduction

While family, twin, and adoption studies have provided strong evidence for a significant genetic component in bipolar disorder (Craddock and Jones, 1999), it is clear that multiple genes must contribute to disease susceptibility (McGuffin and Katz, 1989; Gershon, 1990). Brain-derived neurotrophic factor (*BDNF*), which belongs to the neurotrophin family, plays an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons throughout adulthood (Schinder, 2000; Huang and Reichardt, 2001). There is growing convergent evidence suggesting that *BDNF* is involved in the pathophysiology of mood disorders and in the mechanism of action of therapeutic agents (Sheline *et al.*, 1996, 2003; Chen *et al.*, 2001; Fukumoto *et al.*, 2001; Duman, 2002; Karege *et al.*, 2002; Nestler, 2002; Shirayama *et al.*, 2002; Coyle *et al.*, 2003; Shimizu *et al.*, 2003; Chen *et al.*, 2004; Ogden *et al.*, 2004).

Several human studies have shown that serum BDNF levels were decreased in patients with major depressive disorder when compared with the control group (Karege *et al.*, 2002; Shimizu *et al.*, 2002). Increased levels of BDNF immunoreactivity were found in postmortem hippocampal tissue among antidepressant treated bipolar patients, compared with antidepressant untreated bipolar subjects (Chen, *et al.*, 2001). Neuroimaging studies suggested that decreased BDNF levels might account for structural brain changes in bipolar patients (Sheline *et al.*, 1996, 2003; Manji, *et al.*, 2001).

Studies in animal models have suggested that *BDNF* expression might be a downstream target of antidepressant treatments and that *BDNF* might provide protection against stress-induced neuronal damage (Duman, 2002; Nestler *et al.*, 2002; Coyle *et al.*, 2003). In animal models of depression, an antidepressant-like effect was produced by the infusion of BDNF into the rat midbrain (Siuciak *et al.*, 1997; Shirayama *et al.*, 2002). The level of BDNF mRNA in the rat hippocampus was increased by electroconvulsive seizures, and the down-regulation of BDNF mRNA was blocked by the chronic administration of electroconvulsive seizures (Lindeforts, *et al.*, 1995; Nibuya *et al.*, 1995). Chronic administration of lithium or valproate increased *BDNF* expression in rat brain (Fukumoto *et al.*, 2001). *BDNF* ablation affects the reactivity of the serotonergic system to the stress hormone corticosterone (Hensler *et al.*, 2007).

Two family studies of bipolar disorder have reported linkage to chromosome 11p13, where *BDNF* is located (Detera-Wadleigh *et al.*, 1999; McInnes *et al.*, 1996). Significant association of bipolar disorder with polymorphic markers genotyped in *BDNF* has been reported in two family based studies (Neves-Pereira *et al.*, 2002; Sklar *et al.*, 2002). Both studies genotyped the Val66Met polymorphism (rs6265) and reported over-transmission of the common Val66 allele to individuals with bipolar disorder. This finding was confirmed in a case-control study of unrelated subjects from the NIMH Genetics Initiative (Lohoff *et al.*, 2005). Further evidence of association of the Val66Met polymorphism was reported in three small childhood-onset samples: two using a family-based design (Geller *et al.*, 2004; Strauss, 2005) and one employing a case-control approach (Strauss *et al.*, 2004). In addition to the Val66Met polymorphism, Strauss *et al.* found significant evidence of association between bipolar disorder and four other *BDNF* SNPs (Strauss, 2005). A novel microsatellite polymorphism, which is

located about 1.0 kb upstream of the translation initiation site of the *BDNF* gene, was reported to confer susceptibility to bipolar disorder (Okada *et al.*, 2006). In contrast to these positive findings, a number of groups have failed to replicate the association of *BDNF* with the risk of bipolar disorder (Hong *et al.*, 2003; Nakata *et al.*, 2003; Kunugi *et al.*, 2004; Oswald *et al.*, 2004; Skibinska *et al.*, 2004; Neves-Pereira *et al.*, 2005; Green *et al.*, 2006; Liu *et al.*, 2007; Kanazawa *et al.*, 2007). Several investigators also studied the association between *BDNF* and rapid-cycling: Muller *et al.* found several markers across *BDNF*, including the Val66Met polymorphism, were significantly associated with both bipolar disorder and rapid-cycling (Muller *et al.*, 2006); Green and colleagues did not find evidence of association between bipolar disorder and the Val66Met polymorphism, but their study of a subset of bipolar subjects with rapid cycling showed significant association with this missense polymorphism (Green *et al.*, 2006).

Most association studies of bipolar disorder have limited their analyses of *BDNF* polymorphisms to a single marker: the Val66Met polymorphism (Geller *et al.*, 2004; Green *et al.*, 2006; Kunugi *et al.*, 2004; Skibinska *et al.*, 2004; Lohoff *et al.*, 2005). The sample sizes for most studies were relatively small. To ensure a rigorous evaluation of the role of *BDNF* in bipolar disorder susceptibility, the present study has analyzed a large sample of American Caucasian multiplex bipolar disorder families. Ten single nucleotide polymorphisms (SNPs) that spanned *BDNF*, including Val66Met, were genotyped, and family-based association analysis was employed. Using this rigorous approach, we found that several *BDNF* SNPs were associated with the risk for bipolar disorder.

Materials and Methods

Sample

Multiplex families with bipolar disorder were recruited at 10 centers across the United States: Indiana University (with a satellite site at University of Louisville), Johns Hopkins University, the NIMH Intramural Research Program, Rush-Presbyterian Medical Center in Chicago, University of California at Irvine, University of California at San Diego, University of Chicago, University of Iowa, University of Pennsylvania, and Washington University in St. Louis. All participating sites' institutional review boards approved this study. All subjects received a personal assessment with the Diagnostic Interview for Genetic Studies (DIGS) by a trained interviewer. Medical records were sought for any subject with a history of mental health treatment. First-degree relatives of each proband were interviewed as well with the DIGS and the FIGS (family interview for genetic studies). Pedigree extension through affecteds was carried out as much as possible given resources available to the sites. Each participant was diagnosed by a best estimate procedure involving two senior clinicians reviewing all available information and agreeing on all Axis I diagnoses. A third clinician tiebreaker was consulted when consensus was not reached (about 1–2% of cases). All affected subjects were at least 16 years of age. The ascertainment and assessment of the study participants were previously described (NIMH Genetics Initiative Bipolar Group, 1997).

A whole genome screen was completed in 644 families consisting of 2,909 individuals (Edenberg *et al.*, 1997; Detera-Wadleigh *et al.*, 1997; Rice *et al.*, 1997; Stine *et al.*, 1997; Foroud *et al.*, 2000; Dick *et al.*, 2003; Willour *et al.*, 2003; Zandi *et al.*, 2003). Each family was carefully examined for its informativeness for family-based association study. A total of 250 multiplex families, consisting of 1,749 individuals (771 males, 978 females), were selected for genotyping based on two criteria: all family members were European American; and DNA was available from both parents for at least one affected individual in each family. This selection not only provided a more ethnically homogeneous sample, but also maximized its power for a family-based test of association.

Phenotype Definitions

A set of three hierarchical disease definitions were used in the statistical analysis for bipolar disorder. Model 1 was the narrowest disease definition and included as affected only those individuals meeting criteria for either bipolar I or schizoaffective bipolar disorders (657 affected). Model 2 included as affected individuals meeting criteria for model 1, plus individuals diagnosed with bipolar II disorder (785 affected). Model 3 was the broadest disease definition and included as affected all individuals meeting criteria for models 1 and 2, plus individuals with recurrent unipolar depression (950 affected). We considered two models for our definition of unaffected individuals. In the first, we used very liberal criteria: for each hierarchical disease model, an unaffected individual was defined as anyone who was not affected under that model (Model 1: 1,053 unaffected; Model 2: 925 unaffected; Model 3: 760 unaffected). In the second, more conservative definition, we did not consider anyone to be unaffected; rather, the individuals who did not meet criteria for being affected were classified as unknown.

Rapid cycling was defined as the occurrence of four or more distinct episodes of depression and mania or hypomania within twelve months. The rapid cycling variable met DSM-IV criteria. Episode frequency was defined as the total number of distinct episodes suffered by the bipolar patient divided by the total number of years since the first episode occurred.

SNP genotyping

BDNF is located on chr11p13 (Maisonpierre, *et al.*, 1991) and is approximately 67 kb in size (NM_170731). SNPs across *BDNF* (Figure 1) were selected from public databases, such as dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>) and HapMap (<http://www.hapmap.org/>). Tag SNPs were chosen within the CEU population of the HapMap database ($r^2 = 0.8$, $MAF \geq 0.05$). The Val66Met polymorphism (rs6265) was among the genotyped SNPs. SNP genotyping was performed using a modified single-nucleotide extension reaction, with allele detection by mass spectrometry (Sequenom MassArray system, Sequenom, San Diego, CA). To determine allele frequencies and to test the assays, SNPs were genotyped in a set of 40 unrelated Caucasian individuals obtained from Coriell and examined for deviations from Hardy-Weinberg equilibrium. SNPs with minor allele frequencies greater than 0.10 were preferentially genotyped in the study sample; all SNPs were in Hardy-Weinberg equilibrium. All genotypic data on the subjects were checked for Mendelian inheritance errors using the program PEDCHECK (O'Connell and Weeks, 1998). Marker allele frequencies and heterozygosities were estimated using the USERM13 (Boehnke, 1991) option of the MENDEL linkage computer program. Deviation from Hardy-Weinberg equilibrium was assessed for each SNP using Haploview (Barret, *et al.*, 2005). The genotyped SNPs in *BDNF*, along with their chromosomal positions and minor allele frequencies, are shown in Table 1.

Statistical analyses

Linkage disequilibrium (LD) was evaluated between the SNPs using the program Haploview (Barret, *et al.*, 2005). The extent of LD was evaluated using Lewontin's standardized disequilibrium coefficient (D') and delta-squared (r^2). The program Tagger (de Bakker *et al.*, 2005) was used to examine how well the genotyped SNPs captured information from the ungenotyped SNPs. The Haploview program was also used to examine the haplotype block structures, where the blocks were defined using the criteria proposed by Gabriel (Gabriel, *et al.*, 2002; Reich, *et al.*, 2001).

Family-based association was performed for each of the genotyped SNPs using the three hierarchical bipolar disorder models. The pedigree disequilibrium test (PDT; Martin *et al.*, 2000) implemented in the UNPHASED package (Dudbridge, 2003) was used to test SNPs for their association with bipolar disorder. The PDT utilizes data from all available trios in a family,

as well as discordant sibships. Evidence for association is assessed based on the overtransmission of a particular allele to affected individuals, and the greater frequency of that particular allele in affected individuals than in their unaffected siblings. In the liberal definition of unaffected, the PDT statistic would include both concordant and discordant transmissions. When using the conservative definition of unaffected, the PDT statistic would only include transmissions to affected individuals. In all analyses, the “average-PDT” statistic, which averages the association statistic across all families, was used to test for association between the SNPs and bipolar disorder (Martin *et al.*, 2000).

There were only 24 families in our sample with at least one member having the rapid cycling phenotype. As a result, there was no power to perform family-based association analyses. Therefore, a case-control approach was taken by selecting one rapid cycling case from each of the 24 families. A control was defined as a subject with bipolar disorder who did not have rapid cycling and one such subject was randomly selected from each of the remaining 226 families. The Pearson Chi-square test was performed to test for an association between the *BDNF* SNPs and the rapid cycling diagnosis.

Exploratory analyses were also performed on the phenotype of episode frequency. From each family, the bipolar subject with the greatest episode frequency was selected for analysis. Due to the skewness of the distribution, the distribution was dichotomized. Those patients in the top 1/3 of the distribution (83 subjects) were classified as having high episode frequency. Those patients in the bottom 1/3 of the distribution (83 patients) were classified as having low episode frequency. The Pearson Chi-square test was used to test for an association between episode frequency classification and *BDNF* SNP genotype.

Results

Ten SNPs were genotyped across *BDNF*. The pairwise LD among adjacent SNPs was high ($D' > 0.98$) and all the SNPs fell into a single haplotype block (Figure 2). To determine whether these SNPs adequately assessed the variation within *BDNF*, the program Tagger (de Bakker *et al.*, 2005) was used to examine how well the genotyped SNPs capture information from ungenotyped SNPs. Eight of the ten genotyped SNPs were in the HapMap database and could be assessed; these 8 SNPs captured 77.3% of all HapMap alleles (of $MAF \geq 0.05$) at $r^2 > 0.8$, and 88.6% alleles at $r^2 > 0.5$; the mean r^2 was 0.86. Two SNPs were not included in HapMap and therefore could not be assessed; therefore, these numbers underestimate the coverage of *BDNF*.

Initial PDT analyses employing a liberal definition of unaffected detected some evidence of association ($p < 0.03$) with two SNPs (rs1519480 and rs7127507) in *BDNF* across all three hierarchical bipolar disorder models. However, when PDT analyses were performed using the conservative definition of unaffected, much stronger evidence of association ($p < 0.005$) with these two SNPs was observed using the narrowest disease model (Table 1). Two additional SNPs (rs2030324 and rs2883187) provided evidence of association ($p < 0.05$) when the two narrower models of disease were employed, and one more SNP (rs12273363) provided evidence only for the narrowest model.

Several of the SNPs between rs1519480 and rs7127507 did not provide evidence of association using any of the three disease models. To better understand how a gene that appeared to be in a single block based on D' estimates of LD could have such a pattern of association, we reviewed the pattern of LD using the r^2 statistic. As shown in Figure 3, an unusual pattern of LD was identified. The two SNPs with the greatest evidence of association with bipolar disorder, rs1519480 and rs7127507, were in very high LD with each other ($r^2 = 0.88$), but had little evidence of LD with the SNPs between them ($r^2 < 0.14$). The intervening SNPs were in

high LD with each other ($r^2 > 0.87$) and with the SNP flanking rs7127507 ($r^2 > 0.87$). The genotypes at rs1519480 and rs7127507 were 97% concordant. Data from HapMap were reviewed and these two SNPs are in nearly absolute LD in that dataset as well.

SNP rs7127507 was also found to be associated with the phenotype of rapid cycling ($p < 0.05$; genotype counts in controls: CC:CT:TT=25:87:98; genotype counts in rapid cycling patients: CC:CT:TT=6:5:8). No other SNP provided evidence of association with rapid cycling. The previously reported Val66Met polymorphism (rs6265) was not significantly associated with either bipolar disorder or rapid cycling; there was a trend ($p=0.06$) toward an overtransmission of the common Val allele using the broadest bipolar disorder model. None of the SNPs were associated with episode frequency.

Discussion

This study presents a thorough evaluation of the evidence for association between bipolar disorder and the *BDNF* gene. We found several SNPs showing evidence of association with bipolar disorder. However, when we use the same phenotypic definition as Sklar and colleagues (Sklar *et al.*, 2002), our results with SNP rs6265 using Model 1 are consistent with the previous report ($p=0.40$, T/U=654/644, where T=transmissions from heterozygous parent to affected offspring, U=non-transmissions). The study of Sklar *et al.*, employed about 25% of the same subjects used in this study. We also analyzed the data by excluding the first 97 families ascertained trios from which were included in a previous report (Sklar *et al.*, 2002). The same LD structure and a similar pattern of significant association results were obtained in this sample independent of the Sklar study. SNPs rs1519480 and rs7127507 were still significant across all three hierarchical bipolar disorder models ($p < 0.05$); rs2030324 and rs2883187 still showed evidence of association ($p < 0.05$) in the two narrower disease models.

It is not clear how best to define unaffected persons in multiplex pedigrees for bipolar disorder. Onset of bipolar disorder can occur throughout the life span; however, the median age of onset for the first major mood episode is about 20. Some authors report multiple peaks in age of onset data, with a subgroup of patients having their first episode in the 30's or later (Leboyer *et al.*, 2005; Lin *et al.*, 2006). It is also clear that bipolar illness represents the extreme endpoint of a spectrum of mood instability, and that minor variants may not come to clinical attention (Angst, 1998; Akiskal and Pinto, 1999). In this context it is not unreasonable to define only affected individuals and regard undiagnosed persons as having an unknown affected status. The fact that *BDNF* produced more significant evidence for association in this model may suggest that our family database includes a number of persons with subclinical bipolar phenotypes carrying *BDNF* "risk" variants, who detracted from the association evidence when they were classed as unaffected.

It is interesting to see that SNP rs7127507 is significantly associated with both bipolar disorder and rapid cycling in our study. Muller and colleagues also reported that several markers on the gene *BDNF* had significant association with both bipolar disorder and rapid cycling, and suggested that their significant findings on bipolar disorder were mainly driven by the rapid cycling patients (Muller *et al.*, 2006). Since we have a relatively small number of rapid cycling patients in our sample, and there is only one SNP associated with rapid cycling, we plan to collect more rapid cycling cases to confirm this observation.

Although we have performed the association tests for 10 SNPs, all these SNPs are in high LD, and fall in one haplotype block, as indicated in Figure 2; therefore, it would not be appropriate to correct for 10 tests, since these SNPs are highly correlated. However, since we employed three different nested phenotype definitions and two nested definitions of unaffected individuals (i.e., 6 models in total), an overly conservative Bonferroni correction was applied

to our results, Both SNP rs1519480 and rs7127507 are still significantly associated with bipolar disorder after this correction ($P < 0.05$). Since there is only one phenotype model for rapid cycling and these analyses were exploratory, we did not perform any statistical correction to that association result.

Many previous studies have focused on the missense polymorphism Val66Met (rs6265) (Geller *et al.*, 2004; Kunugi *et al.*, 2004; Neves-Pereira *et al.*, 2002; Skibinska *et al.*, 2004; Lohoff *et al.*, 2005; Green *et al.*, 2006; Liu *et al.*, 2007; Kanazawa *et al.*, 2007). Neves-Pereira *et al.* (2002) reported a significant association (p -value=0.00064) using 283 trios. Lohoff *et al.* (2005) performed a case-control (621 BPI cases vs. 998 controls) study and reported the Val allele was significantly increased in BPI patients when compared to the controls. Among their 621 BPI cases, 213 were used in this study, which accounts for 12% of this sample. Sklar *et al.* (2002) found a marginally significant overtransmission of the Val allele to the bipolar proband (p -value=0.04) in their Hopkins sample (136 trios); however, this finding was not confirmed when they employed 189 trios from the NIMH bipolar initiative (p -value=0.09), which accounted for about 25% of our sample. They also did not find significant association in their UK sample (p -value=0.24) with a sample 145 trios. There are also a number of case-control studies which have failed to replicate the association of bipolar disorder with *BDNF* (Hong *et al.*, 2003; Nakata *et al.*, 2003; Kunugi *et al.*, 2004; Oswald *et al.*, 2004; Skibinska *et al.*, 2004; Neves-Pereira *et al.*, 2005; Green *et al.*, 2006; Liu *et al.*, 2007). These conflicting reports could be due to the use of differing study designs, variable ancestry of the samples, and the wide range of sample sizes which directly affect the power of the samples to detect association.

Two of the SNPs providing evidence of association with bipolar disorder, rs1519480 and rs12273363, are located in highly conserved regions when compared with other vertebrate genomes in the 17-way Vertebrate MultiAlignment (UCSC Genome Browser, v. 141). This suggests that these two markers may play some important functional role. None of the SNPs genotyped in this study was on or near the alternative splicing sites that give rise to 5 known transcription isoforms of *BDNF* (www.ncbi.nlm.nih.gov). Therefore, the three significantly associated markers, rs7127507, rs2030324, and rs2883187, in the intronic region of the gene may play some other functional role(s) than alternative splicing. Such mechanisms are yet to be discovered. Interestingly, in two recently published genome-wide association studies (Baum *et al.*, 2007; The Wellcome Trust Case Control Consortium, 2007), four additional SNPs in this intronic region (rs16917234, rs12291186, rs11030108, rs12291063) were found to be significantly associated with bipolar disorder in three independent datasets: NIMH, German and Wellcome Trust Case Control Consortium (Personal communication with Dr. Francis McMahon for the NIMH and German datasets). These four SNPs are shown in Figure 1. In contrast with the inconsistent reports on the Val66Met polymorphism, the cumulative evidence of association in the intron region suggests that mRNA processing, stability and *BDNF* expression levels play a role in the susceptibility for bipolar disorder.

The current study has several strengths. First, we employed a sample of 250 multiplex, well-characterized bipolar disorder families, with 402 trios in model 1, 471 trios in model 2 and 522 trios in model 3. Second, analyses were performed in a single ethnic group (European Americans). Third, we employed family-based tests of association on bipolar disorder, which minimize the effects of potential population stratification. Fourth, the most significant association analyses used only affected individuals. While this limits the informativeness of the PDT analysis by eliminating the contribution of discordant sib pairs, we have reduced the possible effects of erroneous subject classification. Fifth, 10 SNPs were genotyped across *BDNF*, with high LD between the SNPs. This ensured good coverage of the gene and maximized our power to detect association anywhere in *BDNF*.

In summary, we have found evidence of association between bipolar disorder and SNPs in *BDNF*, including SNPs near both ends of this gene. The evidence provided by us in this paper supports a role for *BDNF* as a pathophysiologic factor in mood disorders.

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Figure 1. *BDNF* gene structure and SNP location

The *BDNF* gene structure is drawn based on the transcript NM_170731 (encoding isoform b), with five alternative forms shown above: NM_170732 (isoform a), NM_170733 (isoform a), NM_001709 (isoform a), NM_170734 (isoform c), NM_170735 (isoform a), in order from bottom to top; other splicing forms have also been reported. SNP positions are shown below. Exons are numbered and indicated in black, the untranslated regions in dark gray and introns as light gray bars connecting the 2 exons. The direction of transcription of all isoforms is right to left, as indicated by the horizontal arrow. The SNPs which demonstrated significant association with bipolar disorder are underlined. The SNPs showing evolutionary conservation are indicated by asterisks. Four SNPs showing nominal significance ($p < 0.05$) in recent GWAS studies are in italics and boxed (Personal communication with Dr. Francis McMahon; Baum et al., 2007; The Wellcome Trust Case Control Consortium, 2007). The size of the gene is scaled by a 2 kb bar at lower right.

Figure 2.

Pairwise linkage disequilibrium (D') between the SNPs genotyped in *BDNF*. Empty boxes indicate SNPs are in complete LD ($D'=1$), dark grey boxes are in high linkage disequilibrium.

Figure 3. Pairwise linkage disequilibrium (r^2) between the SNPs genotyped in *BDNF*. Color scheme: white ($r^2=0$), shades of grey ($0 < r^2 < 1$), black ($r^2=1$).

Table 1
BDNF SNPs: chromosome position, minor allele frequency and association with bipolar disorder

SNP #	SNP	Position ^a	Location [†]	MAP ^b	Average PDT ^c		
					Model 1	Model 2	Model 3
1	rs1519480	27,632,288	downstream	0.30	0.005	0.02	0.03
2	rs6265	27,636,492	exon 2/val66met	0.21	0.40	0.26	0.06
3	rs11030104	27,641,093	intron 1	0.22	0.78	0.87	0.35
4	rs7103411	27,656,701	intron 1	0.23	0.64	0.69	0.27
5	rs7127507	27,671,460	intron 1	0.32	0.002	0.009	0.009
6	rs988748	27,681,321	intron 1	0.23	0.55	0.58	0.21
7	rs2030324	27,683,491	intron 1	0.47	0.02	0.04	0.16
8	rs7934165	27,688,559	intron 1	0.49	0.12	0.24	0.58
9	rs2883187	27,697,668	intron 1	0.47	0.02	0.04	0.14
10	rs12273363	27,701,435	upstream	0.20	0.05	0.12	0.10

^a Positions along Chromosome 11 are based on dbSNP build 125/human genome build 34.1.

[†] Position within or near gene

^b Minor allele frequency in European Americans in this study

^c P-value of Average PDT statistic for association between the SNPs and bipolar disorder. Significantly associated SNPs are shown in bold. Analyses are reported for the narrow definition of unaffected in which everyone who is not affected is classified as unknown rather than unaffected.