**Supplementary Digital Information**

1. **Materials and Methods**

***Participants***

A total of 1,421 participants were included in the study: 673 patients with BPD and 748 controls. The patients were recruited at four German academic institutions: Department of Psychosomatic Medicine, Central Institute of Mental Health, Mannheim (252); Department of Psychiatry and Psychotherapy, University Medical Center Mainz (214); Department of Psychiatry, Charité, Berlin (179); Department of Psychiatry, Ludwig Maximilians University Munich (28). Patients were included if the following criteria were met: age ranging from 16 to 65, Central European ancestry, lifetime diagnosis of BPD (according to DSM-IV). 748 unscreened controls were recruited via blood donation in the area of Mannheim.

***Clinical assessment***

Diagnoses of BPD criteria (for DSM-IV) were established from clinical interviews. At the Central Institute of Mental Health assessment of BPD criteria was based on the German versions of the IPDE Loranger. The three other centers used the SCID-II to assess DSM-IV criteria of BPD First. In all of the centers the diagnostic interviews were carried out by experienced and trained raters.

In all centers, diagnoses of bipolar disorders were assessed with clinical interviews. While different diagnostic interviews were used across the study sites (SCID-I, ([8](#_ENREF_8)); MINI, ([9](#_ENREF_9)); DIA-X, ([10](#_ENREF_10))), all were carried out by experienced and trained raters.

**Table S1. Demographic characteristics**

|  |  |  |
| --- | --- | --- |
|  | **Cases (n = 673)** | **Controls**  **(n = 748)** |
| Age (Mean ± standard deviation) | 29.8 ± 8.7 | 44.5 ± 12.7 |
| Gender (% female) | 90.9% | 55% |

at-Test; bFisher’s exact test.

**Table S1b: Gender distribution of patient samples per study site:**

|  |  |  |
| --- | --- | --- |
| Study site | Males | Females |
| Mannheim | 0.4% | 99.6% |
| Mainz | 21.0% | 79.0% |
| Munich | 0.0% | 100.0% |
| Berlin | 8.4% | 91.6% |

***Genotyping***

Individuals with call rates of >90% had been filtered out prior to the present analyses. Markers were filtered using the following criteria: call rate > 0.9; minor allele frequency > 0.01; conformance with Hardy-Weinberg-Equilibrium (p>0.001). Finally, genotyping quality was assessed via visual inspection of the clusterplots of selected SNPs. After quality control, the final sample comprised 673 BPD cases and 748 controls. All five SNPs of interest obtained call rates of > 0.99. No evidence of differential missingness was obtained for any of the six markers.

**2. Results**

**BPD and comorbid BD**

A total of n=31 cases met diagnostic criteria for bipolar disorders (4.6 %). Following the exclusion of BPD cases with co-morbid BD, the p-value increased (preduced sample=0.062). However, this increase was most likely due to the decreased sample size rather than the exclusion of patients with mania, as indicated by a Monte-Carlo approach which randomly excluded 31 cases 10,000 times.

A formal test of heterogeneity of effects in the two genders obtained a marginally significant result of p=0.07 rs1006737. Although this result did not fulfill our stringent criteria for significance, it was marginally significant and thus suggestive of a sex difference.

**Table S2A: Results in female subsample**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SNP**a | **Gene** | **Minor allele** | **genotype counts cases** | **genotype counts controls** | **ORb (95%-CIc)** | **P-Value (2-tailed)** |
| **rs10994336** | ANK3 | T | 1/74/536 | 2/42/367 | 1.12 (0.77–1.63) | 0.56 |
| **rs10994397** | ANK3 | T | 2/76/533 | 2/44/365 | 1.13 (0.78–1.63) | 0.52 |
| **rs12576775** | ODZ4 | G | 16/166/427 | 14/104/291 | 1.01 (0.79–1.28) | 0.94 |
| **rs1006737**d | CACNA1C | A | 73/262/276 | 34/162/215 | 1.29 (1.06–1.56) | **0.01** |
| **rs4765913**d | CACNA1C | A | 33/202/376 | 7/128/276 | 1.34 (1.07–1.69) | **0.01** |

aSNP

**b**OR = odds ratio

cCI = confidence interval

dMarkers ar in LD (r²=0.46, D’=0.90)

**Table S2B: Results in male subsample**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SNP**a | **Gene** | **Minor allele** | **genotype counts cases** | **genotype counts controls** | **ORb (95%-CIc)** | **P-Value (2-tailed)** |
| **rs10994336** | ANK3 | T | 0/12/50 | 1/34/302 | 1.90 (0.96–3.76) | 0.06 |
| **rs10994397** | ANK3 | T | 0/13/49 | 1/38/298 | 1.86 (0.96–3.58) | 0.06 |
| **rs12576775** | ODZ4 | G | 0/14/48 | 12/87/238 | 0.65 (0.36–1.17) | 0.15 |
| **rs1006737**d | CACNA1C | A | 4/26/32 | 29/152/156 | 0.83 (0.54–1.28) | 0.39 |
| **rs4765913**d | CACNA1C | A | 1/24/37 | 11/124/202 | 0.96 (0.60–1.53) | 0.86 |

aSNP

**b**OR = odds ratio

cCI = confidence interval

dMarkers ar in LD (r²=0.46, D’=0.90)

**3. References**

1. First MB, Spitzer RL, Robert L, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York: Biometrics Research, New York State Psychiatric Institute; 2002.

2. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008;40(9):1056-8. Epub 2008/08/20.

3. Liu Y, Blackwood DH, Caesar S, de Geus EJ, Farmer A, Ferreira MA, et al. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry. 2011;16(1):2-4. Epub 2010/03/31.

4. Psychiatric GCBDWG. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011;43(10):977-83. Epub 2011/09/20.

5. Cichon S, Muhleisen TW, Degenhardt FA, Mattheisen M, Miro X, Strohmaier J, et al. Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. Am J Hum Genet. 2011;88(3):372-81. Epub 2011/03/01.

6. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57.

7. Wittchen H-U, Pfister H. DIA-X Interview. Swets & Zeitlinger: Frankfurt. 1997.