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Chromosome 9: linkage for borderline personality disorder features
Marijn A. Distel\textsuperscript{a,}\textsuperscript{*}, Jouke-Jan Hottenga\textsuperscript{a,}\textsuperscript{*}, Timothy J. Trull\textsuperscript{b} and Dorret I. Boomsma\textsuperscript{a}

Objective A large-scale twin study implicated genetic influences on borderline personality disorder (BPD) features, with a heritability estimate of 42%. To date, no genome-wide linkage study has been conducted to identify the genomic region(s) containing the quantitative trait loci that influence the manifestation of BPD features.

Methods We conducted a family-based linkage study using Merlin regress. The participating families were drawn from the community-based Netherlands Twin Register. The sample consisted of 711 sibling pairs with phenotype and genotype data, and 561 additional parents with genotype data. BPD features were assessed on a quantitative scale.

Results Evidence for linkage was found on chromosomes 1, 4, 9, and 18. The highest linkage peak was found on chromosome 9p at marker D9S286 with a logarithm of odds score of 3.548 (empirical \(P = 0.0001\)).

Conclusion To our knowledge, this is the first linkage study on BPD features and shows that chromosome 9 is the richest candidate for genes influencing BPD.

Introduction Borderline personality disorder (BPD) is characterized by emotional lability, impulsivity, interpersonal difficulties, identity disturbances, and cognitive impairments (American Psychiatric Association, 2000). BPD is often comorbid with other personality and mood disorders and is associated with poor short-term treatment outcomes (Skodol \textit{et al.}, 2002a). Individuals with BPD are well represented in treatment settings, accounting for 10% of all outpatients and 15–20% of all inpatients (Skodol \textit{et al.}, 2002b). BPD is associated with a number of negative outcomes, including suicidal behavior, frequent emergency room admissions, substance abuse, impaired occupational functioning, and poor quality of interpersonal relationships. Recent estimates from the US general population suggest that approximately 1% of adults meet diagnostic criteria for this disorder. BPD is equally prevalent among men and women and is more likely to be diagnosed in early adulthood (Lenzenweger \textit{et al.}, 2007).

A recent, multinational, large-scale twin study implicated genetic influence on BPD features, with a heritability estimate of 42% (Distel \textit{et al.}, 2008). A study into the genetic covariance structure among the four main features of BPD suggested that a single genetic factor underlies most of the genetic variance in BPD symptoms (Distel \textit{et al.}, 2007a), and this is the optimal case for the goal of this study: to conduct a genome-wide linkage analysis to help identify chromosomal regions that may harbor the gene(s) that influence the development of BPD. To date, we know of no linkage study that has been conducted to help identify the genomic region(s) that contain the quantitative trait loci that influence the manifestation of BPD features.

Methods Participants This study is part of an ongoing study on health and lifestyle in twin families registered with the Netherlands Twin Register (Boomsma \textit{et al.}, 2006a). Surveys on health and lifestyle were sent to the twin families every 2–3 years. For this study, data from the seventh survey, which was sent in 2004–2005, were used. Details on response rate and demographic characteristics of the sample have been described elsewhere (Distel \textit{et al.}, 2007b, 2008).
Survey data from 5234 twins and siblings were available of whom a subsample was also invited to provide DNA through buccal swab or whole blood (Boomsma et al., 2000, 2006b; Middeldorp et al., 2006). Phenotype and genotype data were available for 1032 siblings from 505 nuclear twin families of which 10 families were also related at a second degree (and analyzed as such). There were 300 dizygotic male twins and brothers and 510 dizygotic female twins and sisters (in total 711 sibling pairs). There were 87 families consisting of at least one sibling plus a monozygotic twin pair and two families with only a monozygotic twin pair. Monozygotic twin status was specified in Merlin and phenotype and genotype data from both monozygotic twins were included in the analysis. Monozygotic twin pairs do not provide information for linkage, but data from monozygotic twins give information on the total genetic contribution to trait variance. To estimate identity by descent, genotype data from 561 additional parents were included. All participants gave their informed consent and the study was approved by the appropriate ethical committees.

For receiver operating character (ROC) analysis, Personality Assessment Inventory-Borderline Features scale (PAI-BOR) data were collected from an independent sample of 62 BPD outpatients and a control group of 45 psychiatric participants without BPD but with current major depressive disorder (MDD) or dysthymia (DYS). All patient data were obtained from an ongoing experience sampling study of affective instability (Trull et al., 2008). After diagnostic interviewing to establish eligibility for the study, patients completed the PAI-BOR and other questionnaires before starting the experiencesampling phase of the study. Psychiatric diagnoses were established with Axis I and Axis II interviews, and reliability of the assigned diagnoses was checked by independent raters who reviewed audiotapes of a random sample of the 14 participants. Agreement was excellent for a diagnosis of MDD/DYS ($\kappa = 1.0$), a diagnosis of BPD ($\kappa = 0.85$), and the number of BPD symptoms present (intraclass correlation coefficient = 0.96).

For the entire sample of patients, the average age of participants was 33.69 (SD = 11.73), and the majority of participants were women (86.9%), white non-Hispanic (87.9%), single/divorced/separated (67.3%), and reported a family income of $25,000 or less (72.0%). Fifty percent of the sample reported being currently employed full or part time. Most participants reported at least one previous psychiatric hospitalization (52.3%).

**Measures**

BPD features were measured by the PAI-BOR (Morey, 1991, 2003). PAI-BOR items tap features of severe personality pathology that are clinically associated with BPD. The PAI-BOR consists of 24 items that are rated on a 4-point scale (0 to 3; false, slightly true, mainly true, very true). The items consist of statements concerning, for example, stability of mood and affects, emotionally responsiveness, anger control, self-image, feelings of emptiness, intense and unstable relationships, loneliness, impulsivity, self-harm, and recklessness. Several studies have supported the reliability and the validity of total PAI-BOR scores in indexing the degree to which BPD features are present (Morey, 1988, 1991; Trull, 1995, 2001). Kurtz and Morey (2001), for example, showed that PAI-BOR scores correlated 0.78 with a structured interview-based assessment of BPD. The PAI-BOR was scored according to Morey’s test manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score (Morey, 1991, 2003).

**Statistical analysis**

To evaluate the accuracy of the PAI-BOR to identify individuals with BPD, ROC analyses were conducted among participants in the BPD patient group and the MDD/DYS psychiatric control group. ROC analyses plot the proportion of individuals correctly classified as BPD (true positive rate; sensitivity) by the proportion of individuals falsely classified as BPD (false positive rate; 1 – specificity) at different PAI-BOR score cutoff points. This plot is used to examine the ability of the PAI-BOR to discriminate between individuals with and without BPD. The area under the curve indicates how well the PAI-BOR performs. A value of 0.50 indicates no discrimination (chance level) and a value of 1.0 indicates perfect discrimination between BPD patients and non-BPD patients (Swets, 1996; Mcfall and Treat, 1999). The positive predictive value was calculated by dividing the number of true positives by the sum of the number of true positives and false positives; the negative predictive value was calculated by dividing the number of true negatives by the sum of the number of true negatives and false negatives. ROC analyses were carried out in SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Earlier genetic analysis of the PAI-BOR scores of 5496 male and female twins from The Netherlands, Belgium and Australia showed a heritability of 42% (Distel et al., 2008). There was no evidence that different genes influence BPD features in men and women, as same-sex and opposite-sex twin and sibling correlations were the same. The results of the genetic analyses were the same across three different countries. As women and younger participants tend to have higher scores on the PAI-BOR, scores were adjusted for sex and age before linkage analysis, using linear regression in the entire sample.

DNA from the siblings and their parents was extracted from either whole blood or buccal swabs following
Linkage analysis was performed with full families; however, most information for linkage is obtained from sibling pairs. If a pair of siblings has received the same combination of alleles from a parent at a certain marker locus of the genome, the pair is said to share the parent’s alleles at the locus identical by descent (IBD; Haseman, Elston, 1972). As offspring receive the alleles from two parents, the pair can share 0, 1, or 2 alleles IBD at a locus. If the marker locus is close to a causal gene, then IBD status at the marker locus reflects IBD status at the causal locus (Haseman, Elston, 1972). IBD status will then be associated with trait resemblance in sibling pairs. When the parents are homozygous at the marker locus or when the parents are not genotyped, IBD status cannot be determined exactly. In this case, the probabilities of the pair being 0, 1, or 2 IBD are estimated, making use of the population allele frequencies. IBD estimation for all family pairs and linkage analysis were done with Merlin regress (Abecasis et al., 2002). Allele frequencies were calculated from the data in the whole genotyped sample \((N = 1593)\). Regression analysis implemented in Merlin regress is based on a modified method initially proposed by Haseman and Elston (1972). The multipoint IBD sharing is regressed on trait-squared sums and squared differences, for all pairs of relatives (Sham et al., 2002). The trait-squared sums and differences indicate the resemblance and difference between relatives. The method takes into account incomplete IBD information, but requires the population mean, variance and heritability to be specified. The heritability of BPD features was specified at 42%, based on Merlin calculations after correction of age and sex. The same estimate was found in earlier genetic analyses of the PAI-BOR scores (Distel et al., 2008). Linkage was made on the residual BPD scores corrected for sex and age and had values of 0.0 for the mean BPD score and 68.1 for the variance. Logarithm of odds (LOD) scores were calculated with a grid of 1 cM on the genome.

Empirical \(P\) values for the LOD scores were estimated with 2500 replicates that were simulated under the null hypothesis of no linkage using the simulate option in Merlin. These replicates were analyzed under the same analysis conditions as the original data set. Pointwise empirical \(P\) values were calculated for each location that showed evidence of linkage to determine the probability of the observed LOD score at a given position. Genome-wide empirical \(P\) values were calculated to determine the probability of a certain LOD score given all LOD scores of 2500 replicates genome-wide.

### Results

Mean age and mean BPD score on the PAI-BOR for the genotyped sample \((N = 1032)\) and for the total sample \((N = 5234)\) are shown in Table 1. The participants in the genotyped sample were slightly older (38.1 vs. 36.1 years) and had slightly lower BPD scores (15.1 vs. 16.0), but the differences were small. Corrected for age, the difference in mean BPD score between the genotyped and total sample was even smaller; 1.12 and 0.28 for men and women, respectively, on a scale ranging from 0 to 72.

ROC analysis showed an area under the curve of 0.78 (95% confidence interval: 0.70–0.87) indicating that the PAI-BOR discriminates between BPD patients and MDD/DYS patients reasonably well. At the best cutoff

### Table 1  Mean age and mean BPD score on the PAI-BOR for the genotyped sample and for the total sample

<table>
<thead>
<tr>
<th></th>
<th>Genotyped sample</th>
<th>Total sample</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n) Mean age (SD) Mean BPD score (SD)</td>
<td>(n) Mean age (SD) Mean BPD score (SD)</td>
</tr>
<tr>
<td>Male</td>
<td>369 38.6 (12.7) 13.2 (7.4)</td>
<td>1663 36.4 (12.8) 14.5 (7.8)</td>
</tr>
<tr>
<td>Female</td>
<td>663 37.8 (11.2) 16.2 (8.7)</td>
<td>2686 35.9 (11.3) 16.6 (8.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1032 38.1 (11.8) 15.1 (8.4)</td>
<td>5234 36.1 (11.8) 16.0 (8.3)</td>
</tr>
</tbody>
</table>

BPD, borderline personality disorder; PAI-BOR, Personality Assessment Inventory-Borderline Features scale.
point of 42, the sensitivity was 71% and the specificity 69%. The positive predictive value and negative predictive value were 76 and 64%, respectively.

The results of the genome-wide linkage scan for BPD features are shown in Fig. 1. The strongest evidence of linkage was found on chromosome 9 at 15.7 Kosambi cM with a LOD score of 3.548 (empirical $P = 0.0004$, genome-wide $P = 0.0001$) (Fig. 2). Suggestive linkage peaks were found on chromosomes 1, 4, and 18 with LOD scores of 1.602, 1.491, and 1.441, respectively. Table 2 provides an overview of the chromosome regions that may harbor genes influencing the development of BPD.

**Discussion**

BPD is a common psychiatric disorder associated with many negative outcomes. This is the first study aiming to detect the location of quantitative trait loci for BPD features as measured by the PAI-BOR. ROC analysis showed that the PAI-BOR performs reasonably well in discriminating BPD patients and non-BPD depressed psychiatric patients, supporting the validity of PAI-BOR scores. For this linkage analysis genotype and phenotype data from 1032 offspring, and genotype data from 561 parents were used. Significant linkage was found on chromosome 9 near marker D9S286, with a LOD score of 3.548 and a genome-wide empirical $P$ value of 0.0001.

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**Fig. 1**

Results of the genome-wide linkage analysis of borderline personality disorder.

**Fig. 2**

Results of the genome-wide linkage analysis for chromosome 9 with the position of the markers in cM (Kosambi) on the $x$-axis.
In addition, suggestive linkage signals were found on chromosomes 1q31 ($P = 0.0054$), 4p16 ($P = 0.0069$) and 18q23 ($P = 0.0077$).

There were six families in the sample that included individuals with very high PAI-BOR scores. These families had a relatively large contribution to the LOD score on chromosome 9 in the Merlin regression analysis. We examined the PAI-BOR scores and additional information of these individuals more closely and found some to being diagnosed with BPD and some using antidepressive medication.

To evaluate if our linkage results are also associated with other psychiatric disorders we consulted the search engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine designed by P. Sullivan: Sullivan Lab Evidence Engine. Our most pronounced linkage result, the region on chromosome 9p24, has been associated with other psychiatric disorders before in linkage studies. A genome-wide linkage scan for bipolar disorder obtained a linkage signal on chromosome 9p24 (D9S286), but it did not reach significant evidence for linkage [non-parametric linkage (NPL) 1.55, $P = 0.063$] (Fallin et al., 2004). Although BPD and bipolar disorder are distinct disorders, the symptoms (especially relating to affective instability) do show considerable overlap (Deltito et al., 2001). A genome-wide linkage scan for schizophrenia also showed suggestive evidence for linkage on 9p24, but at another marker close by (D9S288; NPL 1.70, $P = 0.05$) (Faraone et al., 1998).

We found some evidence of a relationship of BPD with the region surrounding D1S238/D1S518 (1q31.1), which was also reported by Garver et al. (2001) (D1S518; NPL 1.56, $P = 0.029$) for schizophrenia. In the surrounding area of our linkage signal on chromosome 4p15-16, a signal for schizophrenia was detected by Lerer et al. (2003) (D4S394; NPL 2.18, $P = 0.02$). The 18q23 region is also mentioned by two other studies for bipolar disorder. The NIMH Genetics Initiative Bipolar Group reported that the D18S70 marker showed allele sharing with nominal $P < 0.05$ in a genome survey of 97 families with multiple cases of bipolar illness (Nurnberger et al., 1997). McInnis et al. (2003) found a NPL peak at D18S878 (18q22) of 2.9 ($P = 0.004$) for bipolar disorder.

To determine the importance of chromosomes 1, 4, 9, and 18 in the development of BPD it is essential that the results of this study are replicated by others. If the results are replicated in other samples, candidate genes under the peaks can be considered for association analysis. Localizing and identifying the genes that influence the development of BPD will not only be important for scientific purposes, but will also have clinical implications. A better insight into the etiology of BPD may have great implications for the development of both pharmacologic and psychosocial treatment programs in the future.

### Acknowledgements

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### Conflict of interest: none declared.

### References


Distel MA, Ligthart L, Willemsen G, Nyholt DR, Trull TJ, Boomsma DI (2007b). Personality, health and lifestyle in a questionnaire family study: a comparison

### Table 2 Markers and positions of possible QTLs

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Marker</th>
<th>Position cM Kosambi</th>
<th>LOD score</th>
<th>Point-wise $P$ value</th>
<th>Genome-wide $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q31.1</td>
<td>D1S518</td>
<td>198</td>
<td>1.602</td>
<td>0.0048</td>
<td>0.0054</td>
</tr>
<tr>
<td>4p16.1</td>
<td>D4S2935–D4S403</td>
<td>19.6</td>
<td>1.491</td>
<td>0.0060</td>
<td>0.0069</td>
</tr>
<tr>
<td>9p24.1</td>
<td>D9S2169–D9S286</td>
<td>15.7</td>
<td>3.548</td>
<td>0.0004</td>
<td>0.0001</td>
</tr>
<tr>
<td>18q23</td>
<td>D18S462</td>
<td>117.6</td>
<td>1.441</td>
<td>0.0116</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

LOD, logarithm of odds; QTL, quantitative trait loci.


