

ORIGINAL ARTICLE

Genome-wide analyses of borderline personality features

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The heritability of borderline personality (BP) features has been established in multiple twin and family studies. Using data from the borderline subscale of the Personality Assessment Inventory Borderline Features Scale (PAI-BOR) collected in two Dutch cohorts ($N = 7125$), the Netherlands Twin Register and The Netherlands Study of Depression and Anxiety, we show that heritability of the PAI-BOR total score using genome-wide single-nucleotide polymorphism (SNPs) is estimated at 23%, and that the genetic variance is substantially higher in affect instability items compared with the other three subscales of the PAI-BOR (42.7% vs non-significant estimates for self-harm, negative relations and identity problems). We present results from a first genome-wide association study of BP features, which shows a promising signal on chromosome 5 corresponding to *SERINC5*, a protein involved in myelination. Reduced myelination has been suggested as possibly having a role in the development of psychiatric disorders characterized by lack of social interaction. The signal was confirmed in a third independent Dutch cohort drawn from the Erasmus Rucphen Family study ($N = 1301$). Our analyses were complemented by investigating the heterogeneity that was implied by the differences in genetic variance components in the four subscales of the PAI-BOR. These analyses show that the association of SNPs tagging *SERINC5* differs substantially across the 24 items of the PAI-BOR. Further, using reverse regression we showed that the effects were present only in subjects with higher scores on the PAI-BOR. Taken together, these results suggest that future genome-wide analyses can benefit substantially by taking into account the phenotypic and genetic heterogeneity of BP features.

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INTRODUCTION

Borderline personality (BP) disorder is a severe psychiatric disorder that is characterized by a pervasive dysregulation of emotion as well as behavior, including suicidal behaviors, instability of relations and self image and impulse control. The disorder is highly comorbid with mood and anxiety disorders, substance use and other personality disorders.^{1–3} Heritability estimates of BP in twin and family studies vary between 30 and 70% depending on age group, the type of measurement (diagnosis vs dimensional) and the statistical approach (latent trait vs observed measurements).^{4–7}

This study is a first genome-wide association analysis focusing on BP features. The study uses data from three cohorts, a Dutch population based-sample that originated from the Netherlands Twin Register (NTR, $N = 5802$), a subsample of the Netherlands Study of Depression and Anxiety study with available borderline phenotypes (NESDA, $N = 1332$) and a Dutch sample from the Erasmus Rucphen Family study (ERF, $N = 1301$).^{8–10}

In all participants, the phenotype was assessed with the same 24 items of the borderline subscale of the Personality Assessment Inventory-Borderline Features (PAI-BOR).¹¹ By design the PAI-BOR scale is divided into four subscales each consisting of six items. The four subscales target affect instability (AI), identity problems (IP), negative relations (NR) and self-harm (SH), respectively. Initial factor analytical studies supported the designed four-factor structure, whereas more recent studies indicate that six factors, or an alternative four-factor solution might provide a better fit to the data.^{11–13} The factors in these studies have moderate to high

intercorrelations, underlining the fact the 24 PAI-BOR features have substantial common variability. This is in line with evidence of high clinical validity of the PAI-BOR total score in discriminating diagnosed vs non-diagnosed subjects (73–80% correct assignment).^{14–16} The PAI-BOR expands on the nine Diagnostic and Statistical Manual of Mental Disorders-IV borderline criteria. The Diagnostic and Statistical Manual of Mental Disorders-IV criteria support a single factor, although a similarly well-fitting three-factor structure has been advocated as providing more detailed information concerning the different aspects of BP (that is, disturbed relatedness, behavioral dysregulation and affective dysregulation).^{17–19}

BP has been described as phenotypically heterogeneous, and different biological pathways may be associated with the different aspects of BP.^{20,21} In the context of this paper, we define phenotypic heterogeneity as differences in the phenotype profiles across subgroups in the population. Examples are gender and age differences especially of the impulsivity and AI symptoms, and gender differences in comorbidity patterns.^{22,23} We define genetic heterogeneity as differential genetic effects across subgroups. Phenotypic heterogeneity can indicate but does not imply genetic heterogeneity. In addition to phenotypic and genotypic heterogeneity, it is possible that genetic effects differ for different aspects of BP.²⁴ Our main analyses focus on the common core of the 24 features assessed with the PAI-BOR using an aggregate score; however, these analyses are complemented by a set of analyses that address phenotypic and genetic heterogeneity as well as differential genetic effects across PAI-BOR subscales and items.

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The total sample size in the current study is relatively small for a genome-wide analysis of a psychiatric disorder ($N = 8426$ for the three cohorts); however, the study benefits from the fact that the phenotype is measured with exactly the same instrument in all participants. Using different measures of a disorder across samples can prioritize different aspects of the disorders in the different samples, which dilutes power in the meta-analysis. Furthermore, the borderline phenotype in our association study is quantitative, which can provide considerably increased power compared with case/control phenotypes.²⁵

We present analyses consisting of the following: (1) a phenotype comparison between the NTR and NESDA samples; (2) an estimation of single-nucleotide polymorphism (SNP) heritability using the software package genome-wide complex trait analysis (GCTA) v1.11 in the NTR and combined NTR/NESDA samples;²⁶ (3) a genome-wide association study (GWAS) with NTR/NESDA as discovery sample and ERF as replication sample; (4) an inverse variance meta-analysis of all three samples; and (5) a set of analyses addressing heterogeneity. For the GCTA and association analyses (that is, (2), (3) and (4)), we aggregated the 24 PAI-BOR items to obtain a dimensional measure of BP features. Previous research has suggested that a dimensional conceptualization of borderline personality disorder is preferable compared with a case/control approach because a dimensional approach does not necessitate a cutoff, and is more robust against fluctuations over time between sub-threshold and above threshold levels of the disorder.²⁷ The GCTA analyses (2) were also done on the subscale level, and for parts (1) and (5), we assessed item level data.

MATERIALS AND METHODS

Participants

NTR sample. The sample used in the analyses described below consisted of $N = 5802$ participants of the NTR.⁸ NTR participants are ascertained because of the presence of twins or triplets in the family and consist of multiples, their parents, siblings and spouses. Twins are born in all strata of society and NTR represents a general sample from the Dutch population. For all analysis, we excluded one monozygotic twin per pair. Additional corrections for family resemblance are analysis specific, and described where appropriate. Age ranged between 13 and 90 (median 38), and 62.7% was female.

NESDA sample. We included $N = 1323$ participants from NESDA with available phenotype data that passed quality control. NESDA is a longitudinal study focusing on the course and consequences of depression and anxiety disorders.⁹ Subjects for NESDA were recruited from three sources, namely the general population, mental health organizations and general practices. The vast majority of NESDA subjects is selected for depression and anxiety, but the sample also includes healthy controls without lifetime psychiatric disorders.⁹ Age ranged between 18 and 65 in NESDA (median 43), and the proportion of females was 66.1%.

ERF sample. ERF is embedded in the Genetic Research in Isolated Population (GRIP) program. The ERF study selected 22 related (first/second degree, non-consanguineous) couples living in Rucphen, the Netherlands, between 1850 and 1900, and having at least six children. All living descendants of those couples were invited to participate in the ERF.¹⁰ About 4000 relatives included in the study form a very complex pedigree, which consists of more than 23 000 members. A total of 1466 individuals from this population were phenotyped for BP features, and 1301 that passed quality control were included in the current analyses. ERF has an age range of 18–80 with a mean of 47.9, and 56% females.

Phenotype

BP features were measured with the borderline subscale of the PAI-BOR.¹¹ The PAI-BOR consists of 24 items that are grouped in parcels of six items focusing on AI (for example, 'mood shifts', 'little control over anger'), IP (for example, 'can't handle separation', 'feel empty'), NR (for example, 'mistakes in picking friends', 'stormy relations') and self-harm (for example, 'when

upset hurt self', 'too impulsive'). Item level data were available for analyses in the NTR and NESDA samples. We excluded subjects with response rates per subscale $< 67\%$, resulting in a median missing proportion across items of 0.0027. The same aggregate scores were computed in the ERF sample and were used for the replication of association results and meta-analysis.

Genotype

Genotyping in the NTR and NESDA samples was done on multiple platforms for partly overlapping subsets of the total sample (Affymetrix, Santa Clara, CA, USA; Perlegen 5.0, Mountain View, CA, USA; Illumina 370, San Diego, CA, USA; Illumina 660, Illumina Omni Express 1M and Affymetrix 6.0). Quality control was done within as well as between platforms. Imputation was done in IMPUTE v2.1 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.1.0.html) using the 1000 Genomes panel as a reference set. SNP removal criteria included mismatching alleles, allele frequencies differing > 0.20 with the reference set, minor allele frequency $< 1\%$, Hardy-Weinberg equilibrium P -value < 0.00001 and call rate $< 95\%$. Samples were excluded in case of sex mismatch, genotype missing rate $> 10\%$ or Plink F inbreeding value was either > 0.10 or < -0.10 (heterozygosity). On the merged data, the Hardy-Weinberg equilibrium and minor allele frequency SNP filters were reapplied, as well as the reference allele frequency difference < 0.20 check, and an imputation quality cutoff $R^2 < 0.30$. Finally, all SNPs were removed that were by then known to show problems in the reference sequence data of the phase I Interim set.

Genotyping in the ERF sample was also performed on different platforms including Illumina 318K, Illumina 370K, Illumina 610K and Affymetrix 250K. Quality control was comparable to the protocol described above. Pre-imputations quality control included SNP call rate $> 95\%$, individual call rate $> 90\%$, Hardy-Weinberg equilibrium P -value $= 10^{-06}$, high autosomal heterozygosity (FDR $< 1\%$), high identity-by-state (≥ 0.95), minor allele frequency > 0.01 , ethnic outliers and sex mismatch. Post imputation quality control included removal of monomorphic variants. Genetic imputations were performed using minimac 2012.8.15 (<http://genome.sph.umich.edu/wiki/Minimac>) and the 1000 Genomes phase1 v3 as the reference set.

Software

SNP heritability was calculated using the package GCTA (Genome-wide Complex Trait Analysis; GCTA v1.11; <http://www.complextaitgenomics.com/software/gcta/>).²⁶ Plink was used for the association analyses.²⁸ All other analyses were carried out in R.²⁹

RESULTS

Phenotype analysis in the NTR and NESDA samples

Most means of the individual items were elevated in the NESDA sample, which is expected based on the comorbidity of BP features and mood and anxiety disorders, and the fact that the majority of NESDA subjects were selected for elevated levels of depression and anxiety disorders. Not surprisingly, the most pronounced difference concerned AI item 'happy person'. However, the elevated pattern was not observed for all items. NR item 'let people know they've hurt me', IP item 'can't handle separation' and SH item 'too impulsive' had significantly higher means in NTR subjects, and SH items 'do things impulsively' and 'when upset hurt self' did not differ significantly across the two samples. Correcting for the level of depression using the 28-item Inventory of Depressive Symptomatology score did not change the dissimilarity of the pattern of mean differences between the two samples.³⁰ As expected, depression levels explained a large proportion of variance of the aggregate score of NESDA subjects ($r^2 = 46\%$), but the influence varied considerable across the individual items (0.4–45.5%) and subscales (9.6–46.1%).

Owing to the item mean differences between the NTR and NESDA samples, all subsequent analyses were done for NTR and NESDA samples separately as well as jointly. For all joint analyses, we used an NTR/NESDA indicator as covariate to adjust for the overall elevated scores in the NESDA sample.

The PAI-BOR is designed to measure four interrelated aspects of the borderline phenotype (for example, AI, self-harm, SH, negative relationships, NR and IP). We explored the relations between the 24 PAI-BOR items in our sample using multidimensional scaling, which confirmed the common content of five of the six AI items, but also showed a less clear grouping of the items of the other three scales.³¹ A projection of the 24 items onto two dimensions is shown in Figure 1. Using three dimensions did not increase the clarity of the grouping of the items.

For the association study, we aggregated item level data by averaging the items. This aggregate score represents the common content of the PAI-BOR items and has been shown to have good validity in discriminating between cases and controls.¹⁴ Averaging cancels out item-specific content; item-specific analyses are presented in part 5 of our analyses.

On the basis of previous studies, we assessed the effect of age, gender and their interaction on the total aggregate score as well as the four subscale scores. In the NRT sample, the interaction between age and gender significantly predicted total and subscale scores with younger males having relatively more elevated scores compared with older females, although females had generally higher scores. The interaction was most pronounced in the IP subscale ($P = 1.15e-09$) explaining 4.7% of the variance. Interestingly, we found no significant age or gender effects in the NESDA sample. The age/gender effects were included as covariates in the association and SNP-heritability analyses.

Heritability estimated from SNP data

We used the software package GCTA v1.11 to estimate the heritability of the aggregate measure of BP features in the NTR and combined NTR/NESDA samples that is due to all SNPs.²⁶ We also estimated the variance in the four subscales AI, NR, ID and SH that is due to SNPs. We used likelihood ratio tests (LRTs) to establish significance. In all analyses, we used a cutoff of 0.025 to limit genetic relatedness. Results presented in Table 1 show that in the combined NTR/NESDA sample, the SNP heritability of the total score is significant (23.1%, $P_{LRT} = 0.003$). The estimate in the NTR sample was somewhat lower, 20.7%, and had larger standard errors (SE's) due to the smaller sample size. The proportion of phenotypic variance due to SNPs was still significant with $P_{LRT} = 0.03$. Note that AI had a substantially higher genetic component (42.7% in the combined sample) compared with NR (11.5%, not significant) and IP and self-harm, which had essentially zero estimates. This result is consistent with the multidimensional

scaling results (see Figure 1), which showed that AI items are closely grouped, reflecting their common content. The items of the SH, IP and NR subscales are more spread out, indicating comparatively more item-specific content. The higher within subscale diversity of the SH, IP and NR subscales explains at least to some extent the lower genetic variance estimates for these subscales as item-specific variance cancels out when aggregating items in a subscale. The results are also consistent with a twin study showing larger subscale-specific genetic variance components for those subscales compared with AI.²⁴ Differential genetic effects across the 24 individual BP features are further explored in part 5 of our analyses.

GWAS

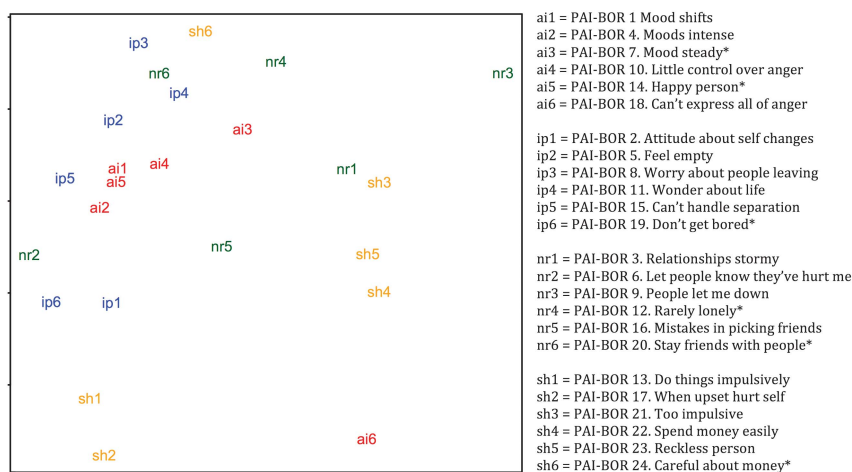
After quality control, a total of 6 670 475 SNPs and $N = 7125$ and $N = 5802$ were included in the association studies for NTR/NESDA and NTR, respectively. The association study was carried out using the average PAI-BOR score described above as an outcome in a linear additive genetic model implemented in Plink, with

Table 1. Estimating SNP heritability with GCTA v1.11

	Total score	AI	NR	IP	SH
<i>NTR/NESDA, N = 3951</i>					
V(G)/Vp	0.231	0.427	0.115	0.083	0.0599
SE	0.088	0.087	0.088	0.087	0.0868
LRT	7.437	26.575	1.765	0.941	0.484
P-value	0.003	1e-07	0.09	0.2	0.2
<i>NTR, N = 3300</i>					
V(G)/Vp	0.207	0.257	0.174	0.119	0.089
SE	0.106	0.105	0.106	0.105	0.104
LRT	3.773	6.349	2.738	1.291	0.757
P-value	0.03	0.006	0.05	0.1	0.2

Abbreviations: AI, affect instability; GCTA, genome-wide complex trait analysis; IP, identity problems; LRT, likelihood ratio test; SE, standard error; SH, self-harm; NR, negative relations; NTR, The Netherlands Twin Register; NESDA, the Netherlands Study of Depression and Anxiety; SNP, single-nucleotide polymorphism.

Note: We used a cutoff of 0.025 of genetic resemblance resulting approximately in one member per family in all analyses. In the analyses of the combined NTR/NESDA sample, an NTR/NESDA indicator was used as a covariate. Other covariates were age, gender, their interaction and a PC controlling for stratification within the Dutch population.



Note: Multidimensional scaling of the 24 PAI-BOR items. Items indexed with * are reverse scored.

Figure 1. Phenotype analysis of the 24 Personality Assessment Inventory-Borderline Features (PAI-BOR) items.

covariates sex, age, interaction between sex and age, a study indicator (NTR vs NESDA), and a principal component to correct for population stratification within the Dutch population. To minimize computation time, we carried out the association analysis first using all subjects but excluding one monozygotic twin per pair. This step provided a crude ranking of all SNPs although *P*-values and summary statistics are biased due to remaining family relatedness (for example, DZ twins). Next, we selected the top 100 000 SNPs, and carried out an analysis of variance to control for differential associations across platforms, and eliminated eight SNPs that had platform effects at a conservative level $P < 5e-5$. Seven SNPs that emerged as promising association signals (defined as $P < 5e-6$ in the analysis of variance) were tested using generalized estimating equations to control for non-independence of observations owing to family relatedness.³²

The seven SNPs were all located in a small region on chromosome 5. Detailed results concerning these SNPs are shown in Table 2. The *P*-values of these SNPs from fitting generalized estimating equations were between $3.28e-6$ and $8.22e-7$ in the NTR sample, and between $4.89e-5$ and $3.02e-6$ in the

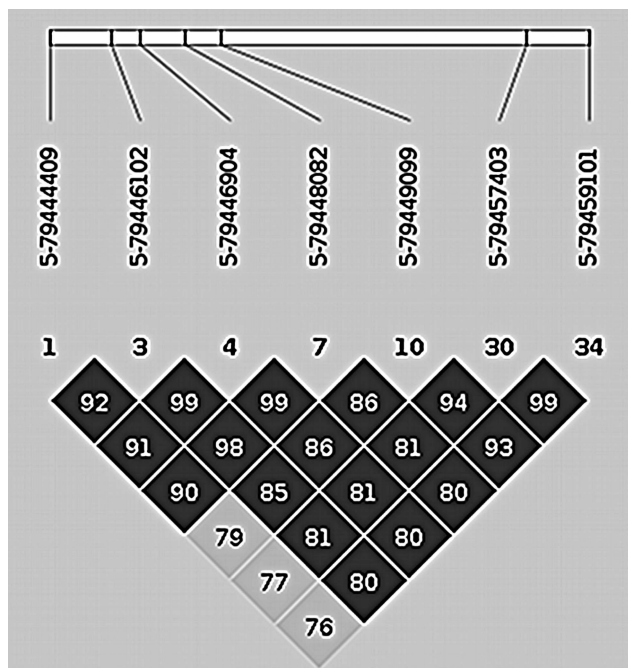


Figure 2. Heat map of the seven single-nucleotide polymorphism (SNPs) on chromosome 5.

combined NTR/NESDA sample. Linkage disequilibrium of the top seven SNPs is shown in Figure 2.

Replication of the seven SNPs was carried out in the ERF sample. Correction for family structure in the ERF sample was done using the Grammar-Gamma method in GenABEL v1.7-4 (<http://www.genabel.org>).³³ To correct for multiple testing of correlated SNPs, we used the program matSpD to obtain a conservative significance level, which for the seven SNPs was 0.027.³⁴ Using this significance level, two of the seven SNPs were significantly associated with the total aggregate phenotype in the ERF sample,

Table 3. Replication in the ERF sample and meta-analysis NTR/NESDA/ERF

<i>rs id</i>	ERF replication, N = 1301			Meta-analysis NTR/NESDA/ERF
	Coefficient	SE	<i>P</i> -value	<i>P</i> -value
rs6882423	-1.60132	0.87256	0.06648	9.36e-07
rs6866910	-1.59989	0.88724	0.07135	5.03e-07
rs73772260	-1.72634	0.91117	0.05814	3.61e-07
rs6888413	-1.74865	0.90877	0.05433	4.10e-07
rs6894288	-1.43317	0.76133	0.05977	7.41e-07
rs73125991	-1.64513	0.61909	0.00788	1.27e-06
rs11951568	-1.67161	0.61933	0.00695	2.85e-06

Abbreviations: ERF, Erasmus Rucphen Family; NTR, The Netherlands Twin Register; NESDA, The Netherlands Study of Depression and Anxiety; SE, standard error.

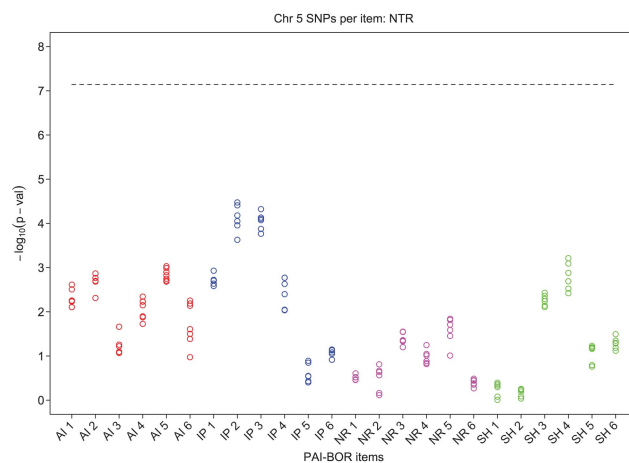


Figure 3. Associations of 24 Personality Assessment Inventory-Borderline Features (PAI-BOR) items with seven SNPs on chromosome 5.

Table 2. Promising SNPs on chromosome five tested using GEE in the NTR sample $N = 5802$

<i>rs id</i>	Location	Alleles	MAF	Coefficient	SE	<i>P</i> -value
rs6882423	79444409	G/t	0.1987	-0.0378	0.00800	2.29e-06
rs6866910	79446102	A/G	0.1963	-0.0389	0.00803	1.28e-06
rs73772260	79446904	A/G	0.1955	-0.0397	0.00806	8.55e-07
rs6888413	79448082	T/G	0.1953	-0.0392	0.00808	1.24e-06
rs6894288	79449099	T/G	0.2166	-0.0377	0.00764	8.22e-07
rs73125991	79457403	A/T	0.2203	-0.0366	0.00759	1.40e-06
rs11951568	79459101	T/C	0.2200	-0.0352	0.00757	3.28e-06

Abbreviations: GEE, generalized estimating equations; MAF, minor allele frequency; NTR, The Netherlands Twin Register; SE, standard error; SNP, single-nucleotide polymorphism. Note: in the GEE analyses, the covariates were age, gender, their interaction and a PC controlling for stratification within the Dutch population.

Table 4. Reverse regression of SNPs on total score in high vs low scoring subjects derived by median split of the NTR sample

	<i>rs6882423</i>	<i>rs6866910</i>	<i>rs73772260</i>	<i>rs6888413</i>	<i>rs6894288</i>	<i>rs73125991</i>	<i>rs11951568</i>
High	0.00108	0.00058	0.00093	0.00090	0.00033	0.00059	0.00092
Low	0.49323	0.78759	0.85842	0.89423	0.49091	0.45804	0.56495

Abbreviations: NTR, The Netherlands Twin Register; SNP, single-nucleotide polymorphism.

Note: for this analysis we selected 1 subject per family, total $N = 3142$, high $N = 1605$, low $N = 1537$.

and hence replicated the results in the discovery sample. Interestingly, when testing the association using the subscales as phenotype in the ERF sample, only the AI subscale was significantly related to some of these SNPs. All other subscales had insignificant associations. The results of the replication are presented in Table 3.

Meta-analysis

We combined the NTR, NESDA and ERF samples as three cohorts in an inverse variance meta-analysis to assess the SNPs on chromosome 5.³⁵ Results presented in Table 3 show that P -values of the seven SNPs range between $2.85e-6$ and $3.61e-7$.

The genomic location of these SNPs is 5:79444409-79459289, which corresponds to serine incorporator 5 (*SERINC5*, synonyms: *TPO1*, *C5orf12*). The *C5orf12* protein belongs to a protein family that facilitates the biosynthesis of lipids, an important component of the nervous system. More specifically, the protein incorporates serine into newly forming membrane lipids.³⁶ Myelin in the brain is enriched with *SERINC5*. A recent mouse study established a relation between social isolation and decreased myelination in the brain, leading the authors to hypothesize a relation between myelination and psychiatric disorders in humans characterized by lack of social interaction.³⁷ A different study showed that N-acetylaspartate, which supplies acetyl groups for myelin lipid synthesis, is decreased in the prefrontal region in borderline patients.^{38,39} *SERINC5* has not been reported in any GWAS; however, SNPs tagging *SERINC5* were included in a genotype score that was developed to predict the chance of success of smoking cessation.⁴⁰

Heterogeneity

Given the evidence concerning the differential heritability of the four BP subscales that emerged from the heritability analyses carried out in Part 1, we conducted *post-hoc* tests of the top seven SNPs for each of the 24 PAI-BOR items separately. Figure 3 shows lower P -values especially for items of the AI and IP subscales, whereas items of the NR and self-harm subscales (with one exception) seem to have much weaker or no associations. Note that the reliability of the BP aggregate score is higher than that of individual items because when summing items, error in individual items cancels out. This explains the larger P -values of the individual items. The items with the smallest P -values were IP items 'feel empty' and 'worry about people leaving' and AI item 'happy person'.

Next we analyzed whether the relation between the top SNP and the quantitative BP phenotype was the same for all subjects, or whether the effect was more pronounced depending on the level of BP, in other words, whether the basic assumption in GWAS that SNPs have a fixed effect is correct. This question was addressed by dividing the aggregate BP phenotype into high and low groups using a median split, and carrying out a reverse regression. Importantly, the variance of the BP aggregate score was very similar in the higher and lower scoring groups, showing that the variability in BP features is comparable across the two groups, and that only the means differ. We then estimated the regression coefficients when regressing the SNPs on the phenotype in each of the two groups. In the low group, none of

the seven SNPs were related to BP features (all P -values > 0.05), whereas in the higher scoring group P -values ranged between 0.00033 and 0.00108. Detailed results are shown in Table 4. The results show that for these SNPs, the assumption of a fixed effect is not correct, and suggest genetic heterogeneity.

DISCUSSION

This first genome-wide analysis of BP features as measured by the PAI-BOR in three Dutch cohorts (NTR, NESDA and ERF) showed a number of interesting results. First, SNP heritability of the total aggregate score of all 24 items estimated using the package GCTA v1.1 was 23.1% in the NTR/NESDA sample, which, taking into account imperfect linkage disequilibrium of imputed SNP with causal variants, is consistent with estimates in twin and family studies.^{6,24} Interestingly, this result is driven almost entirely by the AI subscale with an estimated 42.7% of variance due to SNPs, whereas none of the other subscales had significant variance components in our sample. This result suggests that differentiating between aspects of a disorder can substantially increase the statistical power to detect genetic effects.

The GWAS showed a promising signal in a small region on chromosome 5. Seven SNPs in this region had P -values between $3.28e-6$ and $8.22e-7$, and effects of two of these SNPs were successfully replicated in an independent sample (ERF). An inverse variance meta-analysis combining the three cohorts also confirmed the associations. The SNPs tag the *SERINC5* gene (synonyms *TPO1*, *C5orf1*). SNPs in this region have previously been included in genotype score in a smoking cessation.⁴⁰ Furthermore, complementary DNA *TPO1* recognizes mRNA that is highly expressed in the human brain tissue during myelination.³⁶ A recent study using a mouse model showed that social isolation is related to decreased myelination in the brain, which might provide a basis to generalize to a role of myelination in psychiatric disorders that are characterized by lack of social interaction.³⁷ A study focusing on borderline patients showed that N-acetylaspartate, which supplies acetyl groups for myelin lipid synthesis in the brain, is decreased in the prefrontal region in borderline patients.^{38,39} Further research is clearly needed to confirm the potential association of *SERINC5* with BP features.

Our study provided suggestive evidence concerning phenotypic and genetic heterogeneity, as well as evidence for differential effect sizes across the different borderline features. In addition to the differences in the proportion of genetic variance in the different subscales, we showed that especially identity and affect dysregulation items seemed to be more strongly related to the SNPs tagging *SERINC5*. Moreover, there was a distinct difference in effect size for high and low scoring subjects concerning SNPs tagging *SERINC5*. These results indicate that increasing sample size is not necessarily the only option to improve statistical power in gene finding studies. Addressing phenotypic heterogeneity using multivariate outcomes can substantially increase effect sizes and therefore statistical power.⁴¹ Similarly, studies that reveal differences in biological correlates between individuals belonging to different subtypes of a disorder can provide the basis to take into account potential genetic heterogeneity.⁴² Heterogeneity across subgroups requires statistical methods focusing on

clustering, and further research concerning suitable methods seems advantageous especially for investigations of the genetic basis of phenotypes such as BP features. Taken together, the results of this study suggest that phenotypic and genetic heterogeneity have an important role in the heritability of BP features.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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