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ARTICLE

Genome-wide association study of panic disorder reveals genetic overlap with neuroticism and depression

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Abstract

Panic disorder (PD) has a lifetime prevalence of 2–4% and heritability estimates of 40%. The contributory genetic variants remain largely unknown, with few and inconsistent loci having been reported. The present report describes the largest genome-wide association study (GWAS) of PD to date comprising genome-wide genotype data of 2248 clinically well-characterized PD patients and 7992 ethnically matched controls. The samples originated from four European countries (Denmark, Estonia, Germany, and Sweden). Standard GWAS quality control procedures were conducted on each individual dataset, and imputation was performed using the 1000 Genomes Project reference panel. A meta-analysis was then performed using the Ricopili pipeline. No genome-wide significant locus was identified. Leave-one-out analyses generated highly significant polygenic risk scores (PRS) (explained variance of up to 2.6%). Linkage disequilibrium (LD) score regression analysis of the GWAS data showed that the estimated heritability for PD was 28.0–34.2%. After correction for multiple testing, a significant genetic correlation was found between PD and major depressive disorder, depressive symptoms, and neuroticism. A total of 255 single-nucleotide polymorphisms (SNPs) with $p < 1 \times 10^{-4}$ were followed up in an independent sample of 2408 PD patients and 228,470 controls from Denmark, Iceland and the Netherlands. In the combined analysis, SNP rs144783209 showed the strongest association with PD (pcomb $= 3.10 \times 10^{-7}$). Sign tests revealed a significant enrichment of SNPs with a discovery p-value of <0.0001 in the combined follow up cohort ($p = 0.048$). The present integrative analysis represents a major step towards the elucidation of the genetic susceptibility to PD.

Introduction

Panic disorder (PD) is one of the most severe anxiety disorders with a lifetime prevalence of around 2–4% and a lifetime morbid risk of 6% [1]. PD is characterized by sudden and repeated attacks of fear that last for several minutes or longer. These are called panic attacks accompanied by a range of additional physiological or cognitive symptoms. Pathological worry about panic attacks, and the

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effort spent trying to avoid attacks, cause typically significant problems in various areas of the person's life, including the development of agoraphobia and long-term disability [2]. Family and twin studies indicate that the majority of cases with PD have a complex genetic basis [3], and have generated heritability estimates for PD of around 40% [4]. However, on the molecular level little is known about the genetic contribution to PD, with only few and inconsistent findings reported to date.

A genome-wide association study (GWAS) and follow up investigation by Erhardt et al. found evidence for an association between PD and two single-nucleotide polymorphisms (SNPs) in the gene *TMEM132D* on chromosome 12q24 [5, 6]. A GWAS by Otowa et al. [7] identified several suggestive PD loci that failed to reach genome-wide significance [7]. A recent GWAS meta-analysis of anxiety phenotypes—including PD—and quantitative phenotypic factor scores identified two genome-wide significant loci. These comprised an SNP in an uncharacterized noncoding RNA locus on chromosome 3q12, and an SNP within the gene *CAMKMT* on chromosome 2p21 [8]. While both SNPs are implicated in a shared anxiety disorder susceptibility, no study to date has investigated their contribution to specific clinical diagnoses, e.g., PD.

The aim of the present study was to improve the characterization of PD on the molecular genetic level through the performance of a GWAS case-control meta-analysis of data from more than 10,000 individuals.

In addition to the identification of single-marker associations, analyses were performed to determine: (1) the degree of heritability attributable to common genetic variation; and (2) genetic relationships between PD and anxiety-related phenotypes, other psychiatric disorders, education phenotypes and personality traits.

Materials and methods

Sample description

The GWAS discovery meta-analysis comprised 2248 PD patients and 7992 controls of European ancestry. The study was approved by the respective local ethics committees, and all participants provided written informed consent prior to inclusion. Six GWAS case-control cohorts were investigated. These originated from four European countries: Denmark, Estonia, Sweden, and Germany. The latter comprised three distinct cohorts: Germany I, Germany II, and Germany III. Patients were recruited at the following sites: Aarhus ($n = 99$: Denmark); Copenhagen ($n = 155$: Denmark); Tartu ($n = 346$: Estonia); Gothenburg ($n = 192$: Sweden); Stockholm ($n = 423$: Sweden); Munich ($n = 6$: Germany I, $n = 251$: Germany II); Würzburg ($n = 426$: Germany I, $n = 290$: Germany III); and Bonn ($n = 60$: Germany I). All patients had a lifetime diagnosis of PD according to DSM-III-R, DSM-IV, or ICD-10 criteria. Detailed descriptions of the samples are provided in the Supplemental Note.

Controls for the three German cohorts were drawn from: (a) the population-based Heinz Nixdorf Recall (HNR) Study [9] ($n = 1882$: Germany I); and (b) a Munich-based community cohort [10] ($n = 538$: Germany II; $n = 856$: Germany III). The controls for the German II and III cohorts were screened for the presence of anxiety and affective disorders using the Composite International Diagnostic Screener. Only individuals negative for the above mentioned comorbid disorders were included as controls.

Swedish controls ($n = 2617$) [11] had no lifetime diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder. Controls from Denmark ($n = 1034$) and Estonia ($n = 1065$) had no lifetime history of PD or any other mental disorder.

Genotyping

Genomic DNA was prepared from whole blood using standard procedures. DNA samples of PD patients were genome-wide genotyped using the Infinium HumanCoreExome (patients from Denmark, Estonia, Sweden, and Germany I), 317K/610Q (Germany II) and 660W-Quad (Germany III) BeadChips (Illumina, San Diego, CA, USA). Genotyping of the German II patients was conducted at the Max-Planck-Institute of Psychiatry, Munich, Germany. For the remaining PD patients, genotyping was performed at the Department of Genomics, Life & Brain Center, University of Bonn, Germany.

Controls from Germany I were genotyped using the Illumina OmniExpress BeadChip at the Department of Genomics, Life & Brain Center, University of Bonn, Germany. For the remaining controls, genome-wide genotype data were obtained from previous studies (for further details see Supplemental Note). Genotyping in these studies was performed using: OmniExpress (Denmark, Estonia, and Sweden); 317K/610Q (Germany II); and 550K (Germany III).

To facilitate data comparability, patients and controls from a given country were genotyped on arrays with large sets of overlapping markers. The individual cohorts, number of individuals, and genotyping arrays used in the present PD GWAS are summarized in Supplementary Table 1.

Quality control and imputation

All quality control (QC) and imputation procedures are described in detail elsewhere [12, 13]. Briefly, the QC

parameters used for the exclusion of individuals and SNPs were the following: SNP missingness >0.05 (prior to the removal of individual subjects); SNP missingness per individual >0.02; autosomal heterozygosity deviation (|Fhet| > 0.2); SNP missingness >0.02; difference in SNP missingness between patients and controls >0.02; and deviation of an SNP from Hardy-Weinberg equilibrium ($p < 10^{-10}$ in patients, $p < 10^{-6}$ in controls).

Imputation of genotype data in each of the six individual case-control cohorts was carried out using IMPUTE2/SHAPEIT (pre-phasing/imputation stepwise approach; default parameters and a chunk size of 3 megabases (Mb)) [14, 15]; and the 1000 Genomes Project reference panel (release "v3.macGT1") [16].

Across all six case-control cohorts, relatedness testing and population structure analysis was conducted using a subset of 47,513 SNPs. These SNPs fulfilled stringent QC criteria (imputation INFO score > 0.8; SNP missingness < 0.01; minor allele frequency (MAF) > 0.05), and had been subjected to LD pruning ($r^2 > 0.02$). In cryptically related individuals, one member of each pair (π-hat > 0.2) was removed at random, with patients being retained in the preference to controls. Principal components (PCs) were estimated from the genotype data, and phenotype association was tested using logistic regression. Impact of PCs on the genome-wide test statistics was assessed using λ.

The QC led to the exclusion of 333 individuals. Reasons for exclusion comprised: (i) insufficient data quality (low call rate): $n = 54$; (ii) discrepancy between documented and genotyped sex: $n = 122$; (iii) high heterozygosity rate deviation: $n = 6$; (iv) subject relatedness (within and between samples): $n = 78$; or (v) population outlier status: $n = 80$.

After stringent QC, the final meta-analysis included data from 2147 PD patients and 7760 controls (Supplementary Table 1).

Association analysis

Meta-analysis of the six case-control GWAS cohorts was performed using the Ricopili pipeline (https://sites.google.com/a/broadinstitute.org/ricopili/) [17]. Single-marker associations were tested using PCs 1–7, 11, 16, and 18 as covariates, and an additive logistic regression model, as implemented in PLINK [18]. Genome-wide significance was set at a p-value threshold of 5×10^{-8}. Meta-analysis was performed using METAL [19], and by combining genetic effects (odds ratios, ORs) with inverse standard error (SE) weights. Summary statistics of the present PD GWAS meta-analysis are available through the Psychiatric Genomics Consortium (PGC) (https://www.med.unc.edu/pgc/results-and-downloads/).

Polygenic risk score analysis

The impact of polygenic risk on PD in the six individual GWAS cohorts was determined by calculating leave-one-out PRS for each subject of a given cohort, as based on the genetic association data of the five remaining GWAS datasets. PRS calculation is described in detail elsewhere [13, 20]. Briefly, to obtain a highly informative set of SNPs with minimal statistical noise, genetic variants with an MAF of <0.05 or an imputation INFO score of <0.9, as well as all insertions or deletions, were excluded. All remaining SNPs were then clumped, whereby markers within 500 kb of, and in high LD ($r^2 \geq 0.1$) with, another more significant marker were discarded. From the major histocompatibility complex region on chromosome 6, only the variant with the most significant PD association was retained. PRS were calculated using 10 p-value association thresholds (5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, and 1.0). PRS computation also comprised multiplication of the natural logarithm of the OR of each variant by the imputation probability for the risk allele. The resulting values were then totaled in order to generate PD PRS for each subject at each of the ten p-value thresholds.

Association between PRS and PD case-control status was analyzed using standard logistic regression. All PCs used in the association analysis (i.e., PCs 1–7, 11, 16 and 18) were used as covariates. To calculate the proportion of variance explained (Nagelkerke's R^2) in PD case-control status for each p-value threshold, scores generated from a full model (covariates and PRS) and a reduced model (covariates only) were compared.

LD Score regression

SNP-based heritability for PD was calculated using the LD Score regression method [21]. To take into account different prevalence estimates, we determined the SNP-based heritability for a PD lifetime prevalence of 2 and 4%.

In addition, LD Hub analyses (http://ldsc.broadinstitute.org/) [22] were performed in order to investigate a possible genetic overlap between PD and other diseases/phenotypes. LD Hub is a centralized database of GWAS summary statistics for a range of diseases and traits that automates the estimation of genetic correlations [22]. In the present study, a focused analysis was performed of a total of 16 psychiatric, personality, and education phenotypes available in LD Hub. In addition, the LD Score regression method and summary statistics of previous GWAS [8, 23, 24] were used to calculate the possible genetic correlation between PD and anxiety phenotypes; posttraumatic stress disorder (PTSD); obsessive-compulsive disorder. The resulting p-values were Bonferroni corrected for multiple testing, taking into account the number of investigated phenotypes ($n = 19$).

No overlap was present between cases from the present PD GWAS meta-analysis and the other GWAS. The LD Score method is robust with respect to partial control overlap.

Additional analyses were conducted to assess the potential influence of comorbid major depressive disorder (MDD) on the reported genetic correlation between PD and MDD. After excluding PD patients with no information on MDD comorbidity, additional GWAS meta-analyses were performed for: (i) PD cases without comorbid MDD ($n = 781$) versus controls; and (ii) PD cases with comorbid MDD ($n = 372$) versus controls. Using these novel GWAS data and the LD Score regression method, the genetic correlation with MDD was then recalculated.

SumHer/linkage-disequilibrium adjusted kinships (LDAK)

To support the LD Score regression estimates of the SNP-based heritability for PD and the significant genetic correlations between PD and MDD, depressive symptoms, and neuroticism, additional analyses were performed using the SumHer tool [25], which allows the user to specify distinct heritability models. The recommended LDAK model was used to estimate heritability and genetic correlations [25]. In brief, the LDAK model integrates LD information, MAF, and chi-squared (χ^2) statistics.

MAGMA analyses

Calculation of gene-based tests, and the performance of gene-set enrichment and tissue enrichment analyses, was performed using the MAGMA software [26], as implemented in the FUMA platform [27]. A detailed description of the biostatistical analyses implemented in FUMA is provided elsewhere [27].

Briefly, the summary statistics of the present PD GWAS were used as input. Due to the absence of genome-wide significant SNPs, an MAF of ≥ 0.01 and an association p-value threshold of 1×10^{-5} were used to define lead SNPs. An r^2 of ≥0.6 and a genomic window of ± 250 kb were used to determine LD with independent lead SNPs.

Follow-up analysis

A total of 255 PD SNPs with a p-value of $< 1 \times 10^{-4}$, an MAF >0.01 and an imputation INFO score of >0.5 were followed-up in an independent sample comprising 2408 PD patients and 228,470 controls. The respective subjects were drawn from three independent European datasets: iPSYCH (Denmark, $n = 905$ cases, $n = 3620$ controls); deCODE (Iceland, $n = 547$ cases, $n = 220{,}285$ controls); and NESDA/NTR (the Netherlands, $n = 956$ cases, $n = 4565$ controls). The Supplemental Note provides detailed information on each follow up GWAS. As in the discovery step, a meta-analysis was performed using inverse SE weighted OR combination. To analyze the ratio of same-direction effects, sign tests were performed on the entire follow up sample.

Results

Single-marker association analysis

A total of 8,757,275 single markers passed QC and were included in the analyses. Single-marker analysis for PD revealed neither genome-wide significant findings nor substantial inflation of association p-values (Fig. 1, Supplementary Fig. 1). Seven independent chromosomal regions showed a suggestive association p-value of $< 1 \times 10^{-6}$. The

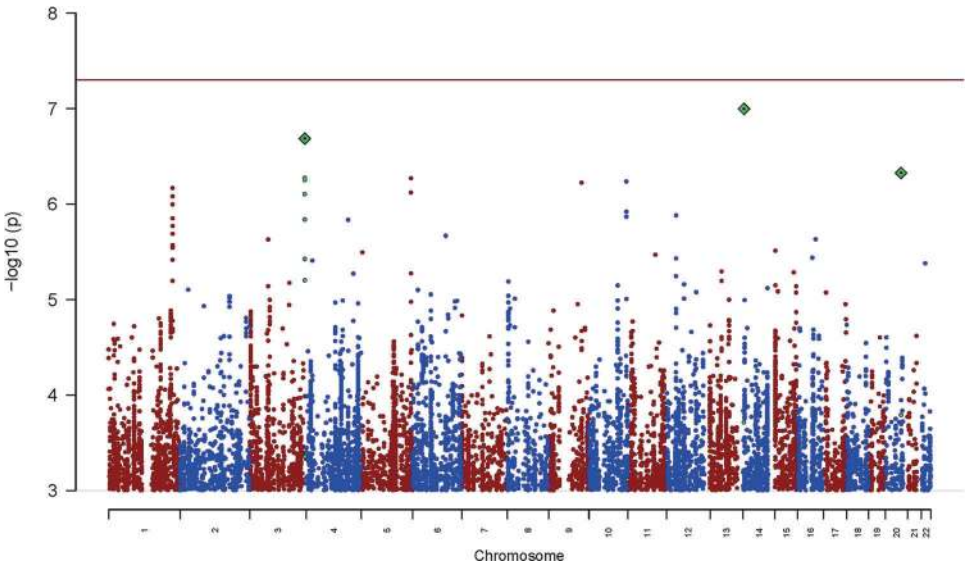

Fig. 1 Manhattan plot for the discovery genome-wide association analysis of data from 2147 panic disorder patients and 7760 controls. −log10 p-values are plotted for all variants across chromosomes 1–22. Green diamonds indicate loci with a lead variant genome-wide association study p-value of $< 5 \times 10^{-7}$. The red line indicates the threshold for genome-wide significance (p-value of 5×10^{-8})

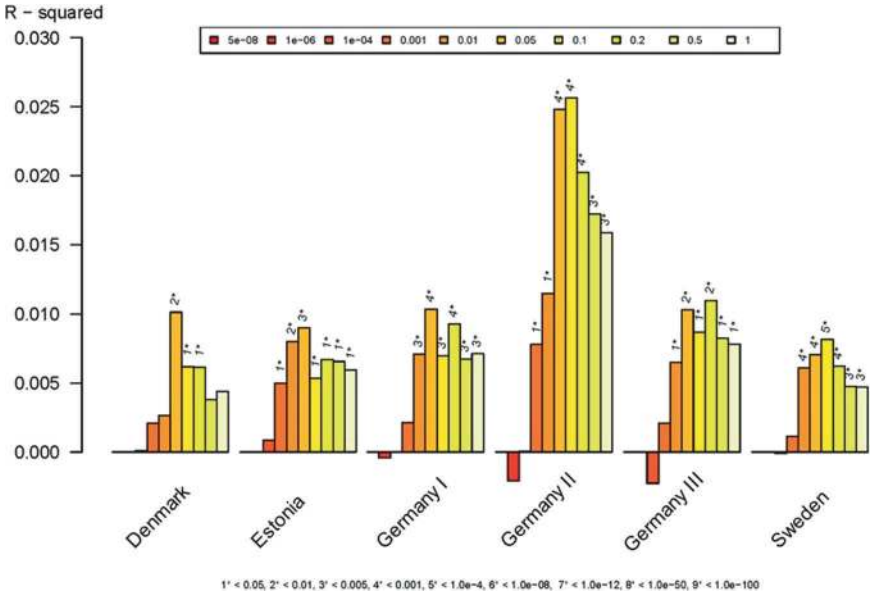

Fig. 2 Leave-one-out polygenic risk score (PRS) analysis. The results of the leave-one-out PRS analysis for the six genome-wide association study (GWAS) cohorts are depicted. Leave-one-out PRS were calculated for each subject of a given cohort using the genetic association data of the remaining five GWAS datasets and ten *p*-value thresholds (denoted by the color of the respective bar). Statistical significance of the variance explained by the PRS (R-squared) is depicted over each corresponding bar

PD variant with the lowest *p*-value was a small deletion in an intergenic region on chromosome 14 ($p = 1.01 \times 10^{-7}$, OR = 1.64, MAF in cases = 0.07, imputation INFO score = 0.59). PD-associated single markers with $p < 1 \times 10^{-5}$ are listed in Supplementary Table 2.

Polygenic risk score analysis

Leave-one-out PRS significantly predicted case-control status in all investigated cohorts (Fig. 2). The analyses demonstrated highly significant PRS, with maximum explained variance ranging from 0.8% (Sweden) to 2.6% (Germany II).

LD Score regression analyses

Using the LD Score regression method, the estimated SNP-based heritability for PD ranged from 28.0% (standard deviation (SD) 5.7%, lifetime prevalence of 2%) to 34.2% (SD 6.9%, lifetime prevalence of 4%).

In the genetic correlation analysis, an experiment-wide significant genetic correlation with PD was found for MDD ($r_g = 0.431$; SE = 0.134; pcorr = 0.025); depressive symptoms ($r_g = 0.322$; SE = 0.093; pcorr = 0.010); and neuroticism ($r_g = 0.316$; SE = 0.082; pcorr = 0.002; Fig. 3).

In addition, nominally significant genetic correlations were found for anxiety disorders; PTSD; the PGC cross-disorder analysis phenotype; schizophrenia; and years of schooling (Fig. 3).

The additional LD Score regression analyses of PD with/without MDD revealed a nominally significant genetic correlation with MDD for PD without MDD ($r_g = 0.415$; SE = 0.209; $p = 0.047$), but not for PD with comorbid

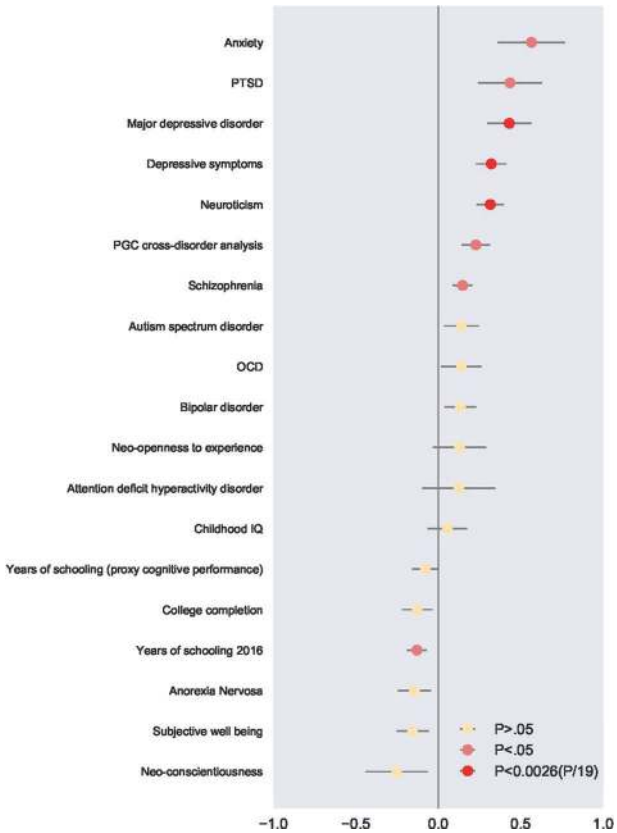

Fig. 3 Genetic correlations between panic disorder and other phenotypes. Genetic correlations between panic disorder and 19 psychiatric, personality, and education phenotypes are shown. For each phenotype, the genetic correlation (dot) and the standard error (line) are shown. The significance level of the genetic correlation is indicated by the color of the respective dot (see legend). Anxiety anxiety disorders, PTSD posttraumatic stress disorder, PGC Psychiatric Genomics Consortium; OCD obsessive-compulsive disorder, IQ intelligence quotient

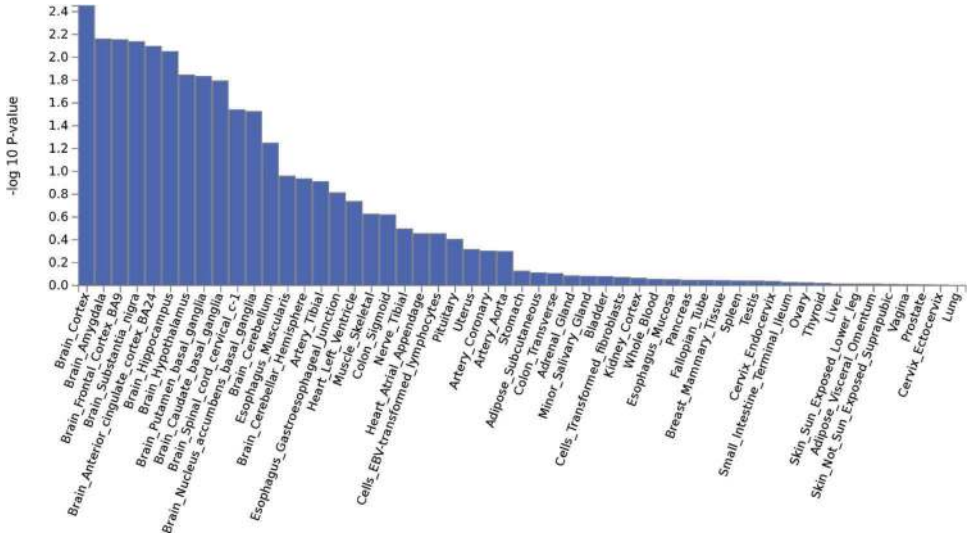

Fig. 4 MAGMA tissue expression analysis. Overview of the results of the MAGMA [26] tissue enrichment analysis, as implemented in FUMA [27], using GTEx data for 53 tissue types [39]. Nominal −log10 *p*-values are shown on the *y*-axis. None of the investigated tissues showed a significant enrichment after correction for multiple testing

MDD ($r_g = 0.662$; SE = 0.422; $p = 0.117$). These results suggest that the observed genetic correlation between PD and MDD is largely independent of MDD comorbidity.

SumHer/LDAK analysis

Using the LDAK model, the SNP-based heritability estimates for PD ranged from 36.3% (SD 4.7%, lifetime prevalence of 2%) to 44.0% (SD 5.7%, lifetime prevalence of 4%). Furthermore, the LDAK method confirmed strong positive genetic correlations between PD and: (i) MDD ($r_g = 0.208$; SD = 0.065); (ii) depressive symptoms ($r_g = 0.275$; SD = 0.092); and (iii) neuroticism ($r_g = 0.260$; SD = 0.077).

MAGMA: gene-based analysis

MAGMA gene-based analyses were performed for a total of 18,335 genes. No gene showed significant association with PD after correction for multiple testing ($P > 0.05/18\,335$ or $P > 2.73 \times 10^{-6}$). Genes with $p < 0.001$ are listed in Supplementary Table 3.

MAGMA: gene-set and tissue expression enrichment analyses

MAGMA gene-set analysis revealed a total of 521 nominally significantly enriched gene-sets or pathways, which showed partial overlap in terms of underlying genes (Supplementary Table 4). However, none of these gene-sets showed significant enrichment in PD after Bonferroni correction for multiple testing ($P > 0.05/10\,891$ or $P > 4.59 \times 10^{-6}$).

MAGMA tissue expression profile analysis revealed that genes identified in the present PD GWAS were enriched for expression in various brain tissues (Fig. 4). The strongest enrichment was observed for genes expressed in the cortex, followed by the amygdala. None of the investigated tissues showed significant enrichment after correction for multiple testing (data not shown).

Follow-up analysis

The combined analysis (including follow up results) revealed no genome-wide significant PD association at $p < 5 \times 10^{-8}$. The lowest *p*-value in relation to PD was found for SNP rs144783209 (pcomb = 3.10×10^{-7}). This variant is located in intron 1 of the gene *SMAD1*. All SNPs from the combined analysis with an association to PD at $p < 1 \times 10^{-5}$ are shown in Table 1.

Sign tests for SNPs with a discovery significance of $p < 0.0001$ ($n = 243$) revealed a significant enrichment of nominally significant associated SNPs with the same effect direction ($n = 135$) in the combined follow up cohort ($p = 0.048$).

Discussion

Although, to our knowledge, the present collaborative study represents the largest GWAS meta-analysis of PD to date, the size of the meta-analysis was insufficient in terms of the identification of genome-wide significant loci. Despite this limitation, the present study provides new insights into the molecular genetic architecture of PD. Leave-one-out PRS significantly predicted case-control status in all investigated sub-cohorts. This demonstrates the consistency of PD association between sub-cohorts on the polygenic level, and suggests that uniform diagnostic criteria were applied. Although the phenotypic variance explained by the use of

Table 1 List of variants with $p < 1 \times 10^{-5}$ in the combined analysis

Variant	Chr	Position (bp)	A1/A2	P	OR	Follow_up_dir	P_follow_up	OR_follow_up	P_comb	OR_comb	Nearby gene/s
rs144783209	4	146403529	T/G	1.47E−06	1.70	+	0.0123	1.30	3.10E−07	1.47	*SMAD1*
rs79919349	20	55282846	A/G	4.71E−07	2.26	+	0.1491	1.30	2.28E−06	1.77	–
rs41280169	9	114982937	T/C	6.00E−07	1.66	+	0.0881	1.18	2.51E−06	1.40	*SUSD1*, *PTBP3*
rs2554444	15	25257585	A/T	5.01E−05	0.79	+	0.0088	0.87	2.84E−06	0.83	*SNRPN*, *SNURF*
rs112586150	15	25246958	A/G	3.10E−06	1.58	+	0.0720	1.20	4.43E−06	1.38	*SNRPN*, *SNURF*
rs6914428	6	63230740	A/G	4.02E−05	0.81	+	0.0161	0.89	4.68E−06	0.85	–

Variants with a *p*-value $< 1 \times 10^{-5}$ in the combined analysis are listed

Chr chromosome, *bp* base pair (hg19), *A1/A2* allele 1/2, *P* p-value in the discovery GWAS, *OR* odds ratio in the discovery GWAS, follow_up_dir effect direction in the combined follow-up sample, *P_follow_up* p-value in the follow up sample, *OR_follow_up* odds ratio in the follow up sample, *P_comb* p-value in the combined analysis, *OR_comb* odds ratio in the combined analysis

the current sample size was relatively small (ranging from $R^2 = 0.8\%$ to 2.6%), it is comparable to that found for other complex genetic phenotypes at comparable sample sizes, e.g., schizophrenia [12, 20].

The present LD Score regression analysis was based on genome-wide genotype data from around 10,000 individuals, and provides the first SNP-based heritability estimate for PD. Estimated heritability ranged between 28% and 34%, suggesting that common genetic variation explains ≥70% of the total heritability estimated by twin studies. This result was confirmed by the SumHer/LDAK analysis, and implies that a large proportion of PD susceptibility is influenced by common genetic variants with small effect sizes. The present analyses identified a significant positive genetic correlation between PD and MDD, depressive symptoms, and neuroticism. The genetic correlation between PD and MDD/depressive symptoms is consistent with their frequently observed comorbidity in clinical practice [28]. In addition, the results are consistent with previous findings of overlapping genetic risk profiles for depression and anxiety scores [29]. Information concerning the presence or absence of a lifetime history of comorbid MDD was available for 1153 of the present PD patients. Of these, 372 individuals had a lifetime history of MDD. To assess the potential influence of MDD comorbidity on the reported genetic correlations, additional analyses of PD with/without MDD were performed. Interestingly, these analyses generated evidence that PD with MDD shows a stronger genetic correlation with MDD than PD without MDD. Notably, however, the positive genetic correlation for PD without MDD was still nominally significant. These findings suggest that while the observed comorbidity might have inflated the extent of the calculated genetic correlation between PD and MDD, the reported genetic correlation is largely independent of MDD comorbidity. For PD patients in the present study, data on other comorbidities or subphenotypes (e.g., neuroticism) were either unavailable or very limited. Therefore, the analyses did not exclude the possibility that: (i) comorbidity inflated the calculated genetic correlations; or (ii) rather than representing specific PD variants, the associated SNPs have pleiotropic effects.

The most significant genetic correlation with PD was found for neuroticism—a trait measure that is highly correlated with all internalizing mental disorders. This is in line with previous findings of a possible correlation between PD and neuroticism [30]. Studies of neuroticism have also identified positive correlations with other anxiety disorders and MDD [31–33]. Previous authors have therefore hypothesized that the trait dimension "neuroticism" may represent an intermediate phenotype [34], which is more directly influenced by the underlying risk genes than the psychiatric phenotype per se. This may suggest that rather than being psychiatric disease states, anxiety

disorders and MDD may represent the (quantitative) extremes of dimensions that underlie normal personality. In terms of PD, a plausible hypothesis is that individuals with high scores for neuroticism are more likely to experience feelings such as anxiety and fear, which might lead to a higher sensitivity to interoceptive signals and symptom perception, and thus to the manifestation of, or vulnerability to, panic attacks.

The present analyses also identified a nominally significant positive genetic correlation between PD and anxiety disorders (including PD); PTSD; the PGC cross-disorder phenotype; schizophrenia; and negative correlation with years of schooling. Future studies are warranted to replicate these findings in larger cohorts.

MAGMA gene-based-, gene-set-, and tissue expression profile analyses revealed no significantly associated genes or enriched gene-sets/tissues after correction for multiple testing. Interestingly, the results might suggest that genes implicated in the present PD GWAS are enriched for expression in various brain tissues, thus providing further evidence that the biological origin of PD lies in the brain. Notably, the strongest enrichment was observed for genes expressed in the cortex and the amygdala, i.e., brain regions that play a central role in the neural network of anxiety and fear [35, 36]. Interestingly, alterations within these brain regions have been reported in neuroimaging studies of patients with PD [35, 37].

As expected for both a GWAS of a complex psychiatric disorder and the size of the respective meta-analysis, no genome-wide significant association was found for PD in the present sample. However, in the combined analysis of all available GWAS data, six SNPs showed a *p*-value of $<1 \times 10^{-5}$ (Table 1). Future studies are warranted to replicate these findings in genetic data from larger cohorts. This could be achieved by combining the GWAS data of individual studies within large international consortia, e.g., the PGC [38].

The present study had several limitations. First, although the total sample size exceeded those used in previous genetic studies of PD, it remained relatively underpowered in terms of the detection of common variants with small effects for the complex PD phenotype [38]. Based on the significant results obtained in the sign test, the present authors anticipate that genetic associations with PD will become increasingly robust with increasing sample sizes, and that a proportion of these currently suggestive findings will achieve genome-wide significance in future studies.

Second, the results were obtained using data from individuals of European ancestry, and may not be generalizable to individuals from other cultural or genetic backgrounds [8].

Third, anxiety disorders are heterogeneous clinical phenotypes, and the extent to which clinical nosology reflects the underlying etiological mechanisms remains unclear. In addition, to varying extents, genetic and environmental risk factors show non-specific effects across the various anxiety disorder categories [8]. Future cross-disorder studies, as well larger meta-analyses of PD and other individual anxiety disorders, are therefore warranted to elucidate the respective genetic architecture.

Conclusion

Although the limited sample size precluded the identification of genome-wide significant loci, the present analyses generated the first SNP-based heritability estimate for PD, and revealed a significant genetic overlap with depression and neuroticism. The results suggest that rather than being a discrete entity, PD has an etiological overlap with personality traits and other psychiatric disorders. Further investigation of shared and nonshared clinical and genetic characteristics is therefore warranted. This will facilitate the development of new and personalized PD treatment approaches.

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Compliance with ethical standards

Conflict of interest TET, SS, HS and KS are employed by deCODE Genetics/Amgen. TW has acted as advisor and lecturer to H. Lundbeck A/S. The other authors declare that they have no conflict of interests.

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