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An Analysis of Two Genome-Wide Association Meta-Analyses Identifies a New Locus for Broad Depression Phenotype

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Abstract

Background—The genetics of depression has been explored in genome-wide association studies that focused on major depressive disorder or depressive symptoms with mostly negative findings. A broad depression phenotype including both phenotypes has not been tested previously using a genome-wide association approach. We aimed to identify genetic polymorphisms significantly associated with a broad phenotype from depressive symptoms to major depressive disorder.

Methods—We analysed two prior studies of 70,017 participants of European ancestry from general and clinical populations in the discovery stage. We performed a replication meta-analysis of 28,328 participants. SNP-based heritability and genetic correlations were calculated using LD score regression. Discovery and replication analyses were performed using a *P*-value based meta-analysis. Lifetime major depressive disorder and depressive symptom scores were used as the outcome measures.

Results—The SNP-based heritability of major depressive disorder was 0.21 (SE=0.02), the SNP-based heritability of depressive symptoms was 0.04 (SE=0.01), and their genetic correlation was 1.001 (SE=0.2). We found one genome-wide significant locus related to the broad depression phenotype (rs9825823, chromosome 3: 61,082,153, $P=8.2\times10^{-9}$) located in an intron of the *FHIT* gene. We replicated this SNP in independent samples ($P= 0.02$) and the overall meta analysis of the discovery and replication cohorts (1.0×10^{-9}).

Conclusions—This large study identified a new locus for depression. Our results support a continuum between depressive symptoms and major depressive disorder. A phenotypically more inclusive approach may help achieve the large sample sizes needed to detect susceptibility loci for depression.

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Keywords

Depressive symptoms; major depressive disorder; CHARGE consortium; Psychiatric Genomics Consortium; genome-wide association study; *FHIT* gene

Introduction

The etiology of depression – a worldwide leading cause of disability (1) – is not well understood. As indicated by family, twin and adoption studies, genetic factors mediate part of vulnerability to major depressive disorder (MDD) with a modest heritability of around 40% (2). However, we understand little of the specific genetic architecture of MDD. Multiple genome-wide association studies (GWAS) for MDD have been published (3–10). The largest MDD GWAS was the mega-analysis by the MDD Working Group of the Psychiatric Genomics Consortium (PGC). In that study, over 9,000 MDD cases and 9,500 controls were analyzed but no association with MDD reached genome wide significance (7). Recently, CONVERGE (China, Oxford and VCU Experimental Research on Genetic Epidemiology) consortium identified two genome-wide significant associations in 5,303 Chinese women with severe and recurrent MDD (near the *SIRT1* gene, $P=2.53\times10^{-10}$ and in an intron of the *LHPP* gene, $P=6.45\times10^{-12}$) (11). A GWAS of depressive symptoms (heritability 23%–29%) (12, 13) in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium in approximately 50,000 people from the general population found no genome-wide significant associations (14). Due to the relatively small sample sizes, the previous GWAS of depressive disorders and depressive symptoms were arguably underpowered to detect small genetic effects (15, 16).

Depression can be conceptualized along a continuum of severity from subthreshold or minor depression to MDD of varying severity (e.g., mild, moderate, and severe) (17). Using a continuum approach may augment statistical power as sample size can be increased substantially and patients who fall into the ‘grey area’ can be assessed. Several lines of evidence support a depression continuum. In longitudinal studies, there is an increased risk of MDD in patients with minor depression and subthreshold depression (18, 19). Statistical studies of disorder classification (taxometric) suggested that severity of depression is continuously distributed and there is no discontinuity in the latent structure of depression (19, 20). Family studies report that relatives of probands with milder forms of depression have greater risk of MDD compared to relatives of probands without any mood disorders (21–24). A higher number of depressive symptoms is related to greater disability, worse quality of life, and a higher mortality risk (18, 25–29). MDD and continuous measures of depression are highly correlated and severity of depressive symptoms along the continuum is linear (30, 31).

The goal of the current study was to combine the results of the largest GWAS using categorical lifetime MDD and continuous measures of depression to identify genetic variants underlying the entire depression continuum.

Methods and Materials

Study Design and Samples

This study was a collaboration between investigators on the PGC MDD and CHARGE genome-wide association meta-analyses (GWAMA). In the discovery phase, we aggregated two GWAMA published in 2013 (7, 14). Basic descriptive features and phenotype definitions of the contributing samples are provided in Table S1. The mega-analysis of MDD consisted of nine studies of 9,240 cases meeting international criteria for lifetime MDD and 9,519 healthy controls. The CHARGE meta-analysis of depressive symptoms included 22 cohorts and comprised 51,258 persons. Each cohort contributing to the GWAMA of the PGC and CHARGE were distinct. In the replication analyses, 16 case-control studies with DSM-IV MDD (6,718 cases and 13,453 controls) were included along with 8,157 subjects from the general population with assessment of depressive symptoms. All subjects were of European ancestry. Institutional review boards approved all studies and all participants provided written informed consent.

Phenotype Characteristics

In the PGC GWAMA, MDD was established with structured clinical interviews (e.g., Clinical Interview Schedule-Revised, Diagnostic Interview for Genetic Studies, and the Structured Clinical Interview for DSM-IV). All clinical evaluations were made by experienced clinicians/interviewers. Most cases were ascertained from clinical sources. Controls were screened in most of the studies to require the absence of MDD and recruited from the general population. Full details about the PGC samples can be found in the previous publication (7). In the CHARGE GWAMA, depressive symptoms were assessed with validated questionnaires. Measures include the Center for Epidemiological Studies-Depression (CES-D) scale, Geriatric Depression Scale (GDS), Patient Health Questionnaire-9, and the Beck Depression Inventory-II (BDI-II) mostly assessing depressive symptoms in previous weeks rather than lifetime MDD (14). Persons with schizophrenia, bipolar disorder, and dementia were excluded. Persons aged 40 and older and with genotype data and depressive symptom score were included.

The 16 MDD case-control replication samples were part of an expanded but unpublished PGC MDD analysis. MDD was diagnosed with interviews. In the depressive symptom replication cohort, the Health and Retirement Study, the 8-item CESD was applied. Respondents were excluded if they were less than 40 years of age or evidence of cognitive impairment.

Genotyping and Imputation

In the PGC samples, (Table S1), individual genotypes were assembled, processed through a central quality control pipeline and imputed using the CEU and TSI HapMap3 reference panels. Quality control procedures were extensive (7). In the CHARGE cohorts, genotype quality control and imputation were conducted in each study separately. The imputation reference was the HapMap2 Central EUrope (CEU) panel (14). In the MDD replication cohorts (Table S3), imputation was performed using IMPUTE2 / SHAPEIT (chunk size of 3 Mb and default parameters). The imputation reference set consisted of 2,186 phased

haplotypes from the 1000 Genomes Project. In the Health and Retirement Study, imputation was performed using the HapMap2 CEU reference panel.

Statistical Analyses

LD score regression was used to compute the SNP-based heritability and the genetic correlation using the 1000 Genomes CEU reference panel (32).

In the PGC GWAMA, a logistic regression analysis was used to test the association between MDD and imputed SNP dosages under an additive model and adjusting for study indicators and five principal components (7). In the CHARGE GWAMA, a linear regression analysis was applied to test the association of depressive symptom score on imputed SNP dosages in the contributing studies adjusting for age and sex. Analyses were adjusted for principal components for most but not all cohorts in the CHARGE GWAMA. A *P* value based meta-analysis was applied in the CHARGE GWAMA (14). Effect size estimates were based on a dichotomous outcome in the PGC and on a continuous outcome in the CHARGE GWAMA. To combine these effect estimates, a *P* value based meta-analysis weighted by sample size with METAL was used. This method allows different weights for each study and takes into account the direction of effect at each SNP (33). To specify the direction of the effect, the PGC used the logistic regression coefficient beta and the CHARGE used *z*-scores. Weights were based on the number of the MDD cases in the PGC study (n=9,240) and the number of individuals in the CHARGE with clinically significant depressive symptoms (n=5,976) using population specific cutoff scores of the questionnaires were considered for weighting. To test whether the results are affected by different sample size weightings, equal weights per study, or no weight as suggested by Stouffer (34), we carried out a series of sensitivity analyses.

We selected the genome wide significant SNPs in two loci from the discovery stage for replication. After analyzing these data, we performed a P value based meta-analysis combining all replication samples. Further, we analyzed the results of the discovery and all replication samples weighting for number of cases.

Results

In the discovery stage, we performed a GWAMA in 70,017 participants of European ancestry by combining the PGC MDD (7) and CHARGE GWAMA (14). We applied an LD score regression to the summary statistics from each study to compute the SNP-based heritabilities and the genetic correlation. As reported previously (35), the SNP-based liability scale heritability of MDD was 0.2 (standard error 0.02) for 20% of prevalence. The lambda was 1.1 and the regression intercept was 1.0 (standard error 0.01). The SNP-based heritability of depressive symptoms was 0.04 (standard error 0.01). The lambda was 1.1 and the regression intercept was 1.0 (standard error 0.01). The SNP-based heritability of the broad depression phenotype was 0.3 (standard error 0.04). MDD and depressive symptoms showed significant co-heritability (1.001, standard error 0.2, Z-score= 4.6, $P=4.6\times10^{-6}$). This result supports the contention of a continuum between depressive symptoms and MDD. However, the genetic correlation should be interpreted carefully as LD regression is quite sensitive to environmental confounding and like twin studies often lacks precision. Also,

different evaluation methods of the depression phenotypes might cause different genetic correlation estimates that cannot easily be compared.

We conducted a meta-analysis of the PGC MDD and the CHARGE depressive symptoms GWAMA using a weighted, *P*-value based meta-analysis. The results are summarized in Figure 1 and Figures S1–S3. The combined meta-analysis was conducted for 918,921 SNPs. Two loci were genome-wide significant: a SNP in an intron of *FHIT* (rs9825823, chr3: 61,082,153, $P=8.2\times10^{-9}$) and a SNP in an intron of *PLEK2* (rs9323497, chr14: 67,873,128, $P=3.3\times10^{-8}$) (Table 1). All SNPs with a *P* value of association $<5\times10^{-5}$ are presented in Table S2. Using different weights or Stouffer's unweighted method had only slight effects on the results (data not shown). Figures S4 and S5 shows forest plots for two SNPs shown in Table 1.

Table 2 presents the replication analyses and the meta-analysis of discovery and replication results. One of the genome-wide significant variants within the *FHIT* gene (rs9825823) was associated with depression continuum in the replication cohorts (*z*-score=2.4, $P=0.02$). The result of the final metaanalysis of discovery and replication samples also indicated a positive replication as indexed by a lower p-value (*z*-score=6.1, $P=1.0\times10^{-9}$). This SNP had a positive association with depressive symptoms in the CHARGE study ($P=5.5\times10^{-4}$) and a similar pattern was observed in the PGC study ($P=4.1\times10^{-6}$). The SNP in an intron of *PLEK2* (rs9323497) was not related to depression continuum significantly (*z*-score=0.2, $P=0.9$).

We performed an additional replication analysis of our two genome-wide significant SNPs using the publicly available data of the recently published GWAMA of depressive disorders in a sample of Chinese women (the CONVERGE study) (11). In CONVERGE, rs9825823 (odds ratio=1.01, P=0.12) and rs9323497 (odds ratio=0.97, P=0.0002, with a different direction of association than in our discovery sample) were not related to depression at the genome-wide significance level although the latter reached nominal significance. However, in the joint meta-analysis of the HRS, PGC MDD and the CONVERGE studies, we found that the association between the rs9825823 and the depression continuum (z-score=2.85, P=0.004) was slightly stronger than our initial replication analysis. When these replication and discovery samples were combined, the association with our top hit also became stronger (analyses without the CONVERGE data: z-score= 6.1, $P = 1\times10^{-9}$; with the CONVERGE data z-score= 6.2, $P = 6.8\times10^{-10}$). Results of additional replication analyses are given in the Table S4.

Discussion

We report the results of a combined GWAMA of depression continuum including MDD (18,759 cases and controls) and depressive symptoms (51,258 participants). In the discovery stage, we found genome-wide significant associations in the *FHIT* and *PLEK2* genes. One SNP in the intron of the *FHIT* gene showed a significant association in the combined analysis of discovery and replication samples of MDD and depressive symptoms samples, and exceeded a genome-wide significance threshold.

The significant locus (rs9825823, chr3: 61,082,153) maps to the intronic region of the fragile histidine triad (*FHIT*) gene, a tumor suppressor protein implicated in several cancers (36). *FHIT* is expressed in multiple brain regions (amygdala, anterior cingulate cortex, caudate nucleus, prefrontal cortex, hippocampus, and hypothalamus, http://www.gtexportal.org/home/gene/FHIT, accessed 10.07.2016). It plays an important role in oxidative stress and level of DNA damage (37), biological processes implicated in MDD (38, 39). *FHIT* is a circadian clock modifier gene (40) and has been related to daytime sleepiness (41), which may be salient to the etiology of depression.

In a GWAS of recurrent, early-onset MDD, three SNPs located in the *FHIT* gene were among the strongest associations in the overall and sex-stratified analyses (8) although none was genome-wide significant. Genetic variants located in *FHIT* have been reported in genetic studies of anxiety,(42) autism (43), mental stress (44), comorbid depressive syndromes and alcohol dependence (45), citalopram-induced side effects (46) and in a latent class analysis of MDD symptoms (7), but none met genome-wide significance.

Several methodological aspects should be discussed. First, we evaluated depression continuum by combining cases from clinical populations diagnosed with MDD and participants from the general population who had been assessed for depressive symptoms. Such an inclusive approach may increase heterogeneity of the phenotype especially because lifetime MDD was evaluated whereas depressive symptoms indicate past weeks only. If anything, such approach would cause an underestimation of the effects as less information on depressive symptoms were obtained. However, the advantages of a large sample can outweigh the disadvantages of a less precisely defined phenotype. This has been observed in the GWAS of educational attainment which was successfully used as a proxy for intelligence (47). Our additional replication analysis showed that increasing the sample size yielded a stronger association of the top hit with depression continuum. It is complex to calculate statistical power of the current analysis as quantitative and qualitative measures were combined. In the current study, a genetic association with the depression continuum may reflect an effect on broad depressive phenotypes but could also be accounted for by an association with low levels of general well-being (12–18% heritability) that co-occur with depressive symptoms (48). Second, we used a *P*-value based meta-analysis, as effect estimates could not be directly evaluated in a straightforward manner. Third, the heterogeneity of the imputation methods used in the PGC and CHARGE discovery samples might reduce the statistical power. However, different imputation references did not change the results in the published PGC MDD study (7).

In conclusion, in this large GWAMA of a broad depression phenotype, we detected a locus associated with depression in clinical and general population samples. Our results suggest the importance a broader depression phenotype to identify genetic variants underlying depression. Large samples with different depression phenotypes may also help disentangle the genetic background of different forms of depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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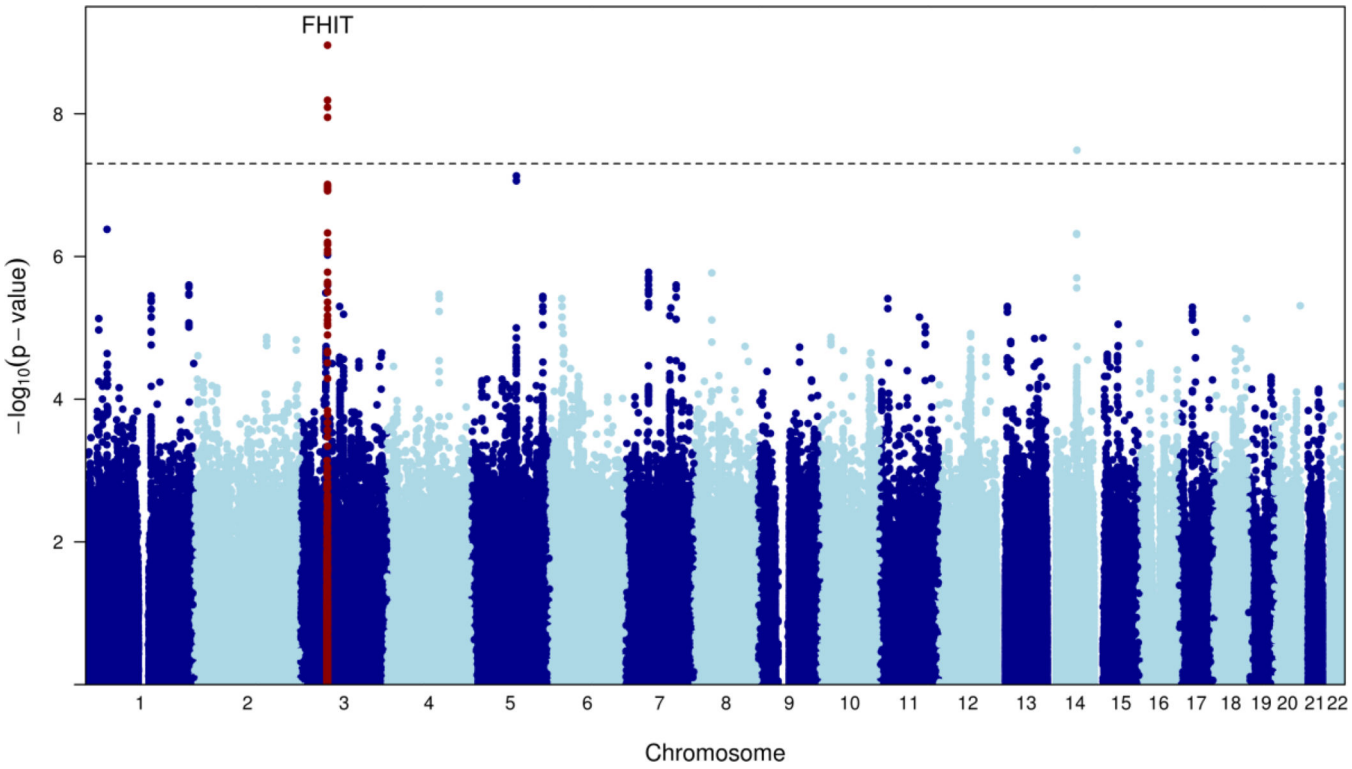

Figure 1. Manhattan Plot

X-axis represents the chromosomal position for each SNP, and y-axis the −log10 *P* value for association with depression.

Table 1

Meta-analysis results of the PGC MDD GWAMA and the CHARGE depressive symptoms GWAMA(discovery)

							Combined meta-analysis* (N_{total}=70,017)		
SNP	**Chr**	**BP**	**Closest Gene**	**Location**	**Allele**	**MAF**	**Direction**	***z*-score**	***P***
rs9825823	3	61,082,153	*FHIT*	intron	T/C	0.46	++	5.8	8.2×10^{-9}
rs9323497	14	67,873,128	*PLEK2*	intron	T/C	0.05	++	5.5	3.3×10^{-8}

Chr: chromosome, BP: base pair, MAF: minor allele frequency (GRCh37/hg19). Allele: Minor/Major on the + strand. Direction of effect: CHARGE (N=51,258; continuous outcome analysis), PGC (N=18,759; of which 9,240 were MDD cases).

*This analysis was weighted for number of participants with clinically significant depressive symptoms in the CHARGE study (n=5,976) and number of cases in the PGC study (n=9,240).

Table 2

Replication analyses and final meta-analysis of discovery and replication stages

			PGC replication (N=20,171)		HRS replication (N= 8,157)		Overall replication (N=28,328)		Meta-analysis of discovery & two replication samples (N= 98,345)			
SNP	**Chr:BP**	**Allele**	**Direct.**[a]	***P***	**Direct.**	***P***	**Direct.**[b]	***P***	**MAF**	**Direct.**[c]	***z*-score**	***P***
rs9825823	3:61,082,153	T/C	+++−−++−+−++−−++	0.04	+	0.2	++	0.02	0.46	+++	6.10	1.0×10−9
rs9323497	14:67,873,128	T/C	+−+−−−−++++−−−++	0.8	−	0.8	+−	0.9	0.05	−++	4.61	4.0×10−6

Chr: Chromosome, BP: base pair, MAF: minor allele frequency (GRCh37/hg19), Direct=Direction. Allele: Minor/Major on the + strand.

[a]Order of the studies: The Cognitive Function and Mood Study (CoFaMS), The PsyCoLaus Study, MDD2000-Edinburgh, GENPOD/NewMeds, Depression Genes Networks, GenRED2, Harvard i2b2, Janssen, The Marx Planck Institute of Psychiatry (MPIP) Munich Antidepressant Response Signature (MARS) Study OMNIex, QIMR COEX, Radiant Irish, Radiant US Cases, Radiant Denmark Cases, Roche, SHIP Trend, TwinGene.

[b]Order of the studies: PGC- replication Health and Retirement Study.

[c]Order of the studies: PGC-replication, Health and Retirement Study, combined meta-analysis of discovery samples.