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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 either 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 analyzed 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. Single nucleotide polymorphism (SNP)-based heritability and genetic correlations were calculated using linkage disequilibrium 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, $p = 8.2 \times 10^{-9}$) located in an intron of the *FHIT* gene. We replicated this SNP in independent samples ($p = .02$) 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 to achieve the large sample sizes needed to detect susceptibility loci for depression.

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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 (GWASs) 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, more than 9000 MDD cases and 9500 control subjects were analyzed, but no association with MDD reached genome-wide significance (7). Recently, the CONVERGE (China, Oxford, and VCU Experimental Research on Genetic Epidemiology) consortium identified two genome-wide significant associations in 5303 Chinese women with severe and recurrent MDD (near the *SIRT1* gene, $p = 2.53 \times 10^{-10}$, and in an intron of the *LHPP* gene, $p = 6.45 \times 10^{-12}$) (11). A GWAS of depressive symptoms (23%–29% heritability) (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). Owing to the relatively small sample sizes, the previous GWASs 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, severe) (17). Using a continuum approach may augment statistical power because sample size can be increased substantially and patients who fall into the gray 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 that 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 with 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 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 GWAMAs published in 2013 (7,14). Basic descriptive features and phenotype definitions of the contributing samples are provided in Supplemental Table S1. The mega-analysis of MDD consisted of nine studies of 9240 cases meeting international criteria for lifetime MDD and 9519 healthy control subjects. 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 was distinct. In the replication analyses, 16 case-control studies with DSM-IV MDD (6718 cases and 13,453 control subjects) were included along with 8157 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 Structured Clinical Interview for DSM-IV). All clinical evaluations were made by experienced clinicians or interviewers. Most cases were ascertained from clinical sources. Control subjects were screened in most of the studies to require the absence of MDD and were 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 scale, Geriatric Depression Scale, Patient Health Questionnaire-9, and Beck Depression Inventory-II, mostly assessing depressive symptoms during previous weeks rather than lifetime MDD (14). Persons with schizophrenia, bipolar disorder, or dementia were excluded. Persons aged 40 years or older with genotype data and depressive symptom scores 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 Center for Epidemiological Studies–Depression scale was applied. Respondents were excluded if they were under 40 years of age or displayed evidence of cognitive impairment.