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Genome-wide scan of depressive symptomatology in two representative cohorts in the United States and the United Kingdom

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ABSTRACT

Unlike the diagnosed Major Depressive Disorder, depressive symptomatology in the general population has received less attention in genome-wide association scan (GWAS) studies.

Here we report a GWAS study on depressive symptomatology using a discovery-replication design and the following approaches: To improve the robustness of the phenotypic measure, we used longitudinal data and calculated mean scores for at least 3 observations for each individual. To maximize replicability, we used nearly identical genotyping platforms and identically constructed phenotypic measures in both the Discovery and Replication samples.

We report one genome-wide significant hit; rs58682566 in the *EPG5* gene was associated (p = 3.25E-08) with the mean of the depression symptom in the Discovery sample, without confirmation in the Replication sample. We also report 4 hits exceeding the genome-wide suggestive significance level with nominal replications. Rs11774887, rs4147527 and rs1379328, close to the *SAMD12* gene, were associated with the mean depression symptom score (P-values in Discovery sample: 4.58E-06, 7.65E-06 and 7.66E-06; Replication sample: 0.049, 0.029 and 0.030, respectively). Rs13250896, located in an intergenic region, was associated with the mean score of the three somatic items of the depression symptoms score (p = 3.31E-07 and 0.042 for the Discovery and Replication samples). These results were not supported by evidence in the literature.

We conclude that despite the strengths of our approach, using robust phenotypic measures and samples that maximize replicability potential, this study does not provide compelling evidence of a single genetic variant's significant role in depressive symptomatology.

1. Introduction

Major depression is the most common psychiatric disorder with the lifetime prevalence of 16% in the community (Kessler et al., 2003) and also moderately heritable. Studies have estimated the heritability of depression between 16 and 37%, depending on the type of depression and the study design (Gatz et al., 1992; Sullivan et al., 2000). These heritability estimates are now being supplemented with association studies that set out to identify genes with a possible role in susceptibility to depression (Kohli et al., 2011; Wray et al., 2012; Ripke et al., 2013; Hek et al., 2013; CONVERGE Consortium, 2015; Hyde et al., 2016). As for underlying biological mechanisms of depression, recent research suggests that they may differ across the life course. In later life, plausible mechanisms include those that are characteristic to the ageing

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process, such as endocrine changes (for example decreasing testosterone levels) (Blazer and Hybels, 2005), vascular risk factors (hypertension, diabetes and atherosclerosis) and neurodegenerative diseases (Alzheimer disease and dementia) (Weisenbach & Kumar, 2014).

On the other hand, depressive symptoms and trait depression have received less attention as phenotypic measures in GWAS studies (Terracciano et al., 2010), although literature suggests that diagnosable depression exists on a continuum with subthreshold depressive symptoms (Lewinsohn et al., 2000). Moreover, the presence of depressive symptoms is important on its own, as they are affecting the individual's well-being and associated with cognitive (Wilson et al., 2002) and physical decline (Penninx et al., 1998) among other conditions.

Here we report the results of a genome-wide association scan (GWAS) study on depressive symptoms using a discovery-replication design with two independent community representative samples of older adults. The aim was to attempt replication with nearly identical genotyping platforms and carefully constructed identical phenotypic measures in two large independent samples. As a phenotypic measure, we used a self-report scale designed to measure the frequency of depressive symptomatology in the general population, the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977). The CESD scale assesses the level of psychological distress by marking the presence or absence of symptoms of depression. Although the CESD was not designed to measure the prevalence of depression, it performs well against other depression diagnostic inventories. Using 3 as cut-off point for caseness on the short version of CESD, its specificity and sensitivity were over 70% against the World Health Organisation's Composite International Diagnostic Interview's measure, which is commonly used as a substitute for a clinician's diagnosis (HRS Health Working Group, 2000). However, the CES-D questions do not match to the Diagnostic and Statistical Manual (DSM) criteria for depressive disorder in many ways. For example, they do not address duration and intensity, which are important components for a diagnosis of disorder. They also ignore the possibility of other psychological disorders that have other symptoms similar to depression, such as anxiety disorders (HRS Health Working Group, 2000). We used the shorter, eight items version of the CESD scale as a continuum from low to high psychological distress, rather than dichotimising the scores into depressed and not depressed.

We used longitudinal data to construct phenotypic measures that did not represent a single time point, rather was constructed to represent a more stable pattern of symptomatology over the observed period. This approach allowed us to reduce variability due to both temporary effects and random error, and critically, to obtain a more robust phenotypic measure that reflects a trait rather than a state for elevated or reduced symptomatology. This approach minimizes problems with prior GWAS studies that use single assessments in which the phenotype reflects transitory depression, and fluctuations likely reflect environmental influences. Our approach of using a more stable phenotype, that draws from repeat measures data, is preferable and more robust for genetic association studies.

We also conducted confirmatory factor analysis to ensure measurement equivalence in the two samples. We used relatively large sample sizes with over 10,000 individuals in the Discovery sample and over 5000 individuals in the Replication sample. The genotyping platform was nearly identical between the two samples using 2.5 million single nucleotide polymorphisms (SNPs). Using population representative cohorts of older adults, we anticipated that the depressive symptomatology-associated genes will be relevant to emotional health in later life.

2. Materials and methods

2.1. Sample

We used the discovery and replication sample approach. The Discovery sample was drawn from the Health and Retirement Study (HRS), a nationally representative sample of households of older Americans in the United States (http://hrsonline.isr.umich.edu/). We included all participants who were interviewed in wave 2 (1994) through 10 (2010) and were at least 50 years old at any wave of data collection. All participants were provided with written consent forms, and ethical approval was granted by the University of Michigan Institutional Review Board.

The Replication sample was the English Longitudinal Study of Ageing in the United Kingdom (ELSA, http://www.elsa-project.ac.uk/), a nationally representative cohort of individuals living in England aged 50 and older (Steptoe et al., 2013). In this study, we included individuals who were interviewed in wave 1 (2002) through 5 (2010) and were 50 years old or older at first observation. All participants provided signed consent and ethical approval was granted by the London Multi-Centre Research Ethics Committee.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Both samples contain only individuals with at least 3 observations for any phenotypic measure, even if the observed waves were not consecutive.

2.2. Genetic data

The genetic data was obtained by using Illumina's Human Omni2.5-Quad BeadChip methodology (Illumina, San Diego, CA, USA). Genotyping was performed by the NIH Center for Inherited Disease Research (Johns Hopkins University, Baltimore, MD, USA) using HumanOmni2.5-4v1 platform for the Discovery sample. The University College London Genomics (London, UK) performed the genotyping on HumanOmni2.5-8v1 for the Replication sample. Quality control on the genetic data was performed by the data holder.

In brief from the 2,443,179 SNPs in the Discovery sample, 241,808 were excluded based on Hardy-Weinberg equilibrium p-value in European samples < 0.0001 or missingness $\geq 2\%$ or minor allele frequency $= 0\%$ or other QC discrepancies (Health and Retirement Study, Quality Control Report for Genotyping Data, 2012. http://hrsonline.isr.umich.edu/sitedocs/genetics/HRS_QC_REPORT_MAR2012.pdf). During the analysis, SNPs with minor allele frequency below 5% were also excluded.

For the Replication sample similar quality filters were applied by the University College London, Genetics Institute, apart from SNP missingness, which was $> 5\%$. As a result of quality control, the number of SNPs analysed were 1,223,220 and 1,490,612 for the Discovery and Replication samples, respectively.

In the Discovery sample, participants were excluded based on relatedness ($n = 88$) and chromosome anomalies ($n = 79$), yielding 12,341 individuals with genotype data. In the Replication sample 41 individuals were excluded for non-white ethnicity and sex discrepancies.

To minimize population stratification and maximize genetic similarity between the samples, we only analysed self-reported white individuals. As a result, the number of individuals in the analysis was 10,123, (including 773 Hispanic whites) in the Discovery sample and 5251 in the Replication sample.

2.3. Phenotypic measures: 8-item, 6-item measures and separate mood and somatic measures

Eight-item measure. We used a shortened, eight-item version scale of the CESD. The 8 items were selected for their psychometric properties in assessing the continuum of depressive symptoms compared to the full scale (Kohout et al., 1993), and demonstrate very similar construct and external validity to the original inventory (HRS Health Working Group, 2000; Turvey et al., 1999). These 8 questions ask whether the following was true for the respondent much of the time during the past week, that (s)he:

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