HHS Public Access

Author manuscript

Psychiatr Ann. Author manuscript; available in PMC 2022 March 14.

Published in final edited form as:

Psychiatr Ann. 2021 April ; 51(4): 165–169. doi:10.3928/00485713-20210315-01.

The Genetics of Major Depression: Perspectives on the State of Research and Opportunities for Precision Medicine

Roseann E. Peterson, PhD [Assistant Professor]

Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University.

Abstract

Major depression (MD) is a leading cause of disability worldwide; it arises from the action and interaction between genetic and environmental factors, and is often comorbid with other psychiatric and medical conditions. To date, upwards of 100 genetic loci have been associated with MD, giving clues to biological underpinnings. Although recent progress has yielded modest insight into the genetic architecture of MD, most studies have been in populations with European ancestry, seriously limiting precision medicine efforts. Broadening diversity of study populations will empower genomic research by expanding discovery and enhancing our understanding of the role of genomic variation in disease etiology. To fully realize the potential of pharmacogenetics and precision medicine, we will need to address the major gaps in our knowledge of the genetic and environmental risk architecture of MD across ancestries, including sex differences, to improve etiologic understanding, diagnosis, prevention, and treatment for all.

Major depression (MD) is a multifactorial disorder with a wide range of biological, psychological, and social risk factors.[1] It is a common psychiatric disorder and a leading cause of disability worldwide.[2] MD is characterized by persistent feelings of sadness and loss of interest or pleasure (anhedonia) for at least 2 weeks and is accompanied by additional symptoms such as changes in appetite, weight, sleep, and energy, reduced concentration, feelings of worthlessness, and suicidal thoughts. MD is often comorbid with other psychiatric disorders such as anxiety and substance use disorders[4] as well as other medical conditions including obesity, cardiovascular disease, and type 2 diabetes.[5] Twin studies estimate the heritability of MD as approximately 37%,[6] supporting a complex etiology with both genetic and environmental etiologic factors.

THE CURRENT STATE OF MD GENETICS

Genome-wide association studies (GWASs) have identified numerous common genetic risk variants for many complex traits.[7] Whereas initial genetic studies of MD met difficulties in identifying individual-associated variants, recent studies have been more successful (Table 1). The first replicated genome-wide significant associations for MD were detected by the China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic

Address correspondence to Roseann E. Peterson, PhD, PO Box 980003, Richmond, VA 23298; roseann.peterson@vcuhealth.org.

Disclosure: The author has no relevant financial relationships to disclose.

Epidemiology (CONVERGE) study of severe, recurrent MD in Han Chinese women, and identified two genetic loci—SIRT1 and LHPP.[8] After this, GWASs achieved increased sample sizes by using a broader depression phenotype and were largely limited to people of European descent. For example, the direct-to-consumer DNA testing company, 23andMe, reported 15 genetic loci associated with self-report of clinical depression (75,607 cases),[9] an analysis in the United Kingdom Biobank (N = 113,769 cases) identified 14 independent loci associated with broad depression phenotypes,[10] and the Psychiatric Genomics Consortium major depressive disorder working group (135,458 cases) reported 44 independent loci.[11] Subsequently, Howard et al.[12] combined the three studies in a meta-analysis (246,363 cases) and identified 102 independent variants of which 87 replicated in an independent sample including variants in and near DRD2, CELF4, and FTO. A number of these larger cohorts used shallow phenotyping including single-item self-report measures of clinical depression and depressive symptom scales. Evidence suggests that such approaches are not without problems and may produce genetic signals that are less specific as they likely confound the loci that predispose to clinical depression with those that impact on risk for mild dysphoria.[13] Nonetheless, replicated genetic loci for depressive phenotypes account for less than 5% of the variance in liability (and even less in non-European populations), underscoring the importance of further research on the genetic architecture of MD, particularly in diverse ancestries.[14,15]

UNDERREPRESENTATION OF DIVERSE POPULATIONS SERIOUSLY LIMITS UNDERSTANDING OF MD ETIOLOGY

A disproportionate majority (>78%) of participants in published GWASs are of European descent, and studies of major psychiatric disorders are no exception.[15] Broadening diversity of studied populations will improve the effectiveness of genomic medicine by expanding the scope of known genomic risk and resilience factors and advancing our understanding of disease etiology. Consensus in the field points to many benefits of increased representation of more diverse populations for locus discovery, fine-mapping of causal variants, polygenic risk scoring, and addressing existing health disparities. To date, the participants in large-scale genetic studies of MD are overwhelmingly of European descent (97.8%)[15] with only two large studies in non-European populations. The first was the aforementioned CONVERGE study.[8] The second, a study of 12,310 people from the Hispanic Community Health Study/Study of Latinos, investigated the genetics of depressive symptoms using the Center for Epidemiological Studies of Depression Scale.[16] There were no replicated genome-wide significant findings but there was some support for sex differences among the top variants. There is significant room for improvement with respect to polygenic risk-based predictions for MD. Initial findings specific to MD support modest transferability of findings across European, East Asian, and Latinx studies.[11,16,17] However, larger sample sizes are critically needed to clarify issues of statistical power, phenotyping, etiological heterogeneity, or true population differences. Nonetheless, increasing diversity among study participants will advance our understanding of genetic architecture in all populations and ensure that genetic research is broadly applicable and generalizable.

SEX DIFFERENCES ARE UNDERSTUDIED IN MOLECULAR GENETIC STUDIES OF MD

Women have a consistently higher risk of MD than men, with prevalence ratios ranging from 1.6 to 3.1 worldwide.[18,19] The largest twin studies of MD to date found that (1) the heritability of MD was greater among women compared to men and (2) genetic risk factors for MD were not identical between the sexes.[20,21] Despite evidence of sex differences in prevalence and presentation, the underlying basis of these differences is not well understood. One example of sex-limited gene-expression in depressive disorders is postpartum depression, which has been shown to be familial beyond the background risk for MD.[22] Additionally, results from the X chromosome are rarely reported on in GWAS. Research suggests that sex differences in common complex traits are likely to include a genetic component beyond that contributed by sex chromosomes.[23] Understanding the biological basis of sex differences in MD is imperative for developing sex-informed diagnostics, treatments, and ultimately precision medicine.

INCLUSION OF ENVIRONMENTAL FACTORS IN LARGE-SCALE GWASs OF MD IS SPARSE DESPITE KNOWN EFFECTS

Evidence from twin and adoption studies suggests that genetic risk factors for MD not only alter average risk but also influence sensitivity to the depressogenic potential of environmental adversities, particularly childhood maltreatment and stressful life events (SLE) during adulthood.[24] Despite known large effects of environmental exposures on complex disease risk, there have been limited efforts to incorporate these factors into large-scale molecular genetic studies. Most gene-by-environment interaction (GxE) studies for MD have been underpowered, focused on candidate genes, and were conducted using samples of primarily European descent.[25,26] There have been two genome-wide GxE studies of depression reported in the literature in non-European populations. The first, a study of depression symptoms in African American women (N = 7,179) and Hispanic/Latina (N = 3,138) women examined GxE with SLE and social support. Among the African American women, a genetic variant near CEP350 showed significant interaction with SLE but was not observed in a smaller replication cohort (N = 1,231).[27] Second, the CONVERGE consortium reported three significant GxE loci (in and near LPGAT1, C1ORF95, SLC25A37) with exposure to severe adversity.[28] These results underscore the need for expanded GxE investigations in larger, diverse populations with carefully measured and harmonized environmental exposures. Greater representation of diverse people is critically needed to increase our understanding of whether the interrelated contributions of genes and environment vary across social and cultural groups and, if so, what differences are seen.

PHARMACOGENETICS IS BEGINNING TO PROVIDE GUIDANCE ON MD TREATMENT CHOICE

In patients with MD, nonresponse to treatment, incomplete treatment symptom remission, and medication side effects are common (+30%).[29–31] Pharmacogenetics has the potential

to improve these outcomes by using genetic information to provide guidance on treatment choice and potential drug tolerance and side effects. Functional variants in two cytochrome P450 enzyme genes, *CYP2D6* and *CYP2C19*, can be used to predict antidepressant drug (tricyclics, selective serotonin reuptake inhibitors) metabolizing status of a person (eg, poor metabolizer, ultra-rapid metabolizer).[32] The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group report[13] antidepressant drugs with pharmacogenomic biomarkers in *CYP2D6* and *CYP2C19*. However, standardized guidelines are needed to determine for whom pharmacogenetic testing should be recommended and when. Implementation of pharmacogenetic testing into psychiatric clinics is underway but is not yet standard protocol.[33]

TOWARDS PRECISION MEDICINE FOR MD

The integration of genomics into health care has the potential to improve disease prediction and optimize treatments. However, a lack of diversity among study participants will limit the utility of pharmacogenetics and precision medicine efforts. For example, some therapeutics may be more effective or safer in certain populations because of differences in allele frequency, effect size, and penetrance of variants associated with drug metabolism.[29,30] To fully realize the potential of pharmacogenetics and precision medicine, we will need to address the major gaps in our knowledge of the genetic and environmental risk architecture of MD across ancestries, including sex differences, to improve etiologic understanding, diagnosis, prevention, and treatment for all.

Acknowledgment:

The author thanks Drs. Bradley T. Webb and Kenneth S. Kendler (Virginia Commonwealth University) for their insightful feedback on the state of the research regarding cross-population genetic studies and sex differences in major depression.

Grants:

R.E.P. is supported by a grant (K01MH113848) from the National Institute of Mental Health and a National Alliance for Research on Schizophrenia & Depression grant (28632) from The Brain & Behavior Research Foundation.

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Table 1.

Progression of Depression GWAS Findings

Study	Cases	Loci	Year
PGC-MDD1[34]	9,240	0	2013
CONVERGE[8]	5,303	2	2015
Hyde 23andMe[9]	75,607	15	2016
Howard UKB[10]	113,769	14	2018
PGC-MDD2[11]	130,664	44	2018
PGC-Howard-Hyde[12]	246,363	102	2019

Abbreviations: CONVERGE, China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic Epidemiology; GWAS, genome-wide association study; MDD, major depressive disorder; PGC, Psychiatric Genomics Consortium; UKB, United Kingdom Biobank.