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Genetic determinants of depression: Recent findings and future directions

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Abstract

Depression is one of the most prevalent, disabling, and costly mental health conditions in the United States. One promising avenue for preventing depression and informing its clinical treatment lies in uncovering both the genetic and environmental determinants of the disorder as well as their interaction (i.e. gene-environment intervention; GxE). The overarching goal of this review paper is to translate recent findings from studies of genetic association and GxE related to depression, particularly for readers without in-depth knowledge of genetics or genetic methods. This review is organized into three major sections. In the first section, we summarize what is currently known about the genetic determinants of depression, focusing on findings from genome-wide association studies (GWAS). In the second section, we review findings from studies of GxE, which seek to simultaneously examine the role of genes and exposure to specific environments or experiences in the etiology of depression. In the third section, we describe the challenges to genetic discovery in depression and promising strategies for making progress.

Keywords

depression; genetics; gene-environment interaction; genome-wide environment interaction study; genome-wide association study; rare variants; copy number variant

Introduction

Depression is one of the most prevalent, disabling, and costly mental health conditions in the United States, with lifetime prevalence estimates of 11.7% among adolescents¹ and 16.6% among adults.² It is projected to be *the* leading cause of disease burden worldwide by 2030.³ Although the impact of depression can be minimized or prevented through early detection, treatment, and ongoing care, numerous individual and structural barriers, including stigma, lack of health insurance, and other barriers to accessing mental health services, prevent many from seeking help. Indeed, only slightly more than half of all people who experience depression seek treatment and those who do tend to dropout prematurely or receive poor quality care.^{4,5} Existing treatments for depression are also modestly effective; only about one-fifth of adults receiving cognitive behavioral therapy or psychodynamic therapy alone⁶ and one-third of adults receiving antidepressant medication alone^{7,8} will experience remission after an initial course of treatment. In children and adolescents, the efficacy of existing treatments is also limited.⁹⁻¹¹ Moreover, nearly three-quarters of people with depression will experience a relapse at some point in their life.¹² These findings underscore the urgent need to prioritize prevention, alongside treatment.

A deeper understanding of the etiology of depression, including both its genetic and environmental determinants, as well as their interplay (e.g., gene-environment interaction; GxE) will have implications for preventing depression and informing its clinical treatment. There are now numerous established environmental risk factors for depression, including poverty,^{13,14} negative family relationships and parental divorce,^{15,16} child maltreatment,^{17,18} and other stressful life events more generally.^{19,20} While the risk of depression is elevated in the immediate aftermath of experiencing these environmental adversities, the effects of adversity can persist over the lifecourse.^{21,22}

There is also now a robust literature implicating genetic factors in the etiology of depression and other psychiatric disorders. Depression is known to run in families; people with major depressive disorder are three times more likely than those without the disorder to have a first degree relative who also has depression.²³ Twin studies, which allow for simultaneous quantification of genetic and environmental influences, suggest that depression is moderately heritable. Specifically, twin studies have estimated that approximately 40% of the variation in the population risk of depression is attributable to genetic variation.²⁴

In recent years, the combination of advances in our understanding of human genomic variation (e.g., Human Genome Project; HapMap Project; 1,000 Genomes Project) and cost-effective genotyping techniques have led to extraordinary growth in molecular genetic studies of depression and other “complex” psychiatric phenotypes. These studies typically examine whether specific alleles (e.g., alternative forms of DNA sequence at a specific locus) or genotypes (e.g., the combination of alleles at a given locus) are associated with the phenotype of interest. Until recently, genetic studies of depression focused largely on candidate genes, or genes hypothesized to be implicated in the neurobiology of depression. Some of the most commonly studied candidate genes have been those regulating serotonin (5-HT) and dopamine (DA) neurotransmission, given the suspected involvement of these neurotransmitters in the pathophysiology of depression and the fact that these are targets of

antidepressant drugs.²⁵⁻²⁷ Unfortunately, most candidate gene studies have been underpowered and replication of findings has been rare. More recently, the availability of DNA microarrays have enabled genomewide association studies (GWAS) that do not rely on prior hypotheses. The GWAS approach allows for the analysis of a million or more variants across the entire genome. The ultimate goal of these genetic association studies is to improve diagnosis, prevention, and treatment through a nuanced understanding of the genetic underpinnings of the disease.

In this paper, we review recent findings from studies of genetic association and GxE related to depression and outline areas for future research. Several excellent reviews of this literature aimed at the genetic research community have already been published (see for example ^{28,29-33}). We aimed to provide a review for a broad audience of readers who may be unfamiliar with genetic concepts and methods. We organized this review into three major sections. In the first section, we describe recent findings based on GWAS of depression. We begin with GWAS, rather than older methods (i.e., linkage and candidate gene association studies), as the latter have already been extensively covered by prior reviews. We also do not review studies on genetic markers of antidepressant treatment response, or pharmacogenomics,³⁴ as our focus was on the genetic determinants of illness risk. In the second section, we review findings from GxE studies, which aim to simultaneously examine the role of genetic variants and environmental exposures in the etiology of depression. As described below, GxE studies have the potential to help identify genetic variants associated with risk or resilience against depression that are only revealed in specific subgroups of the population who have experienced a given environment. In the third section, we address the challenges that face genetic studies of depression and describe emerging strategies that may be useful for overcoming these challenges. We encourage readers who may be unfamiliar with basic genetic concepts to refer to the following resources^{35,36} as well as the resources listed in Table 1.

Findings from Genome-Wide Association Studies (GWAS)

GWAS have been one of the most widely used methods for identifying risk loci in the past decade.³⁷⁻⁴⁰ In a typical GWAS, one million or more common variants known as single nucleotide polymorphisms (SNPs) are examined for their association to disease. “Common variants” are generally defined as those alleles that are carried by at least 5% of the population. GWAS are typically conducted using a case-control design in which allele frequencies are compared between cases with a disease to controls without the disease. Compared to candidate gene studies, GWAS provide a hypothesis free or “unbiased” approach to detecting susceptibility loci. However, to account for the large number of tests conducted, the threshold for declaring genome-wide significance in a GWAS is a p-value of less than 5×10^{-8} , equivalent to a p-value of 0.05 corrected for a million independent tests ($p < 0.00000005$).⁴¹ Because common variant effects are typically modest, large samples (on the order of 10,000 or more cases and controls) are usually needed to have sufficient power to detect such effects at this statistical threshold.

According to the National Human Genome Research Institute (NHGRI) GWAS catalog, more than 2,000 GWAS have been published to date.⁴² A total of 14 GWAS have been

conducted for either major depressive disorder (MDD) or depressive symptoms. In addition, one GWAS focusing on age at onset of major depressive disorder was conducted. These 15 studies were identified by conducting a systematic search of PubMed for papers published before October 2013. We searched the PubMed database using the following MESH terms: (“Depression”[Mesh] OR “Depressive Disorder”[Mesh] OR “Depressive Disorder, Major”[Mesh] OR “Depressive Disorder, Treatment-Resistant”[Mesh]) AND “Genome-Wide Association Study”[Mesh]. We also searched for articles by examining the references pages of review articles, meta-analyses, and other empirical articles published since 2005. As shown in Table 2, all of these studies were based on samples of European ancestry and represent a combination of population-and clinic-based samples.

The first GWAS of depression was published in 2009 and included 1,738 cases and 1,802 controls. Although no SNPs reached genome-wide significance, 11 of the top 200 SNPs were found in a 167 kilobase (kb) region overlapping the gene *PCLO* (piccolo presynaptic cytomatrix protein), which is involved in establishing active synaptic zones and synaptic vesicle tracking.⁴³ In several subsequent studies,^{44,49,58} investigators found mixed evidence regarding the association of *PCLO* SNPs and MDD. In the first study to report a genome-wide significant association for depression, Kohli and colleagues⁵⁰ found support for a recessive effect of a SNP (rs1545843) in the gene *SLC6A15* (solute carrier family 6, neutral amino acid transporter, member 15) that is involved in transporting neutral amino acids. They provided additional evidence in support of this association by demonstrating that risk alleles were correlated with reduced *SLC6A15* expression in hippocampal tissue (taken from individuals undergoing surgery for epilepsy) and reduced hippocampal volume and neuronal integrity using neuroimaging. Mice susceptible to chronic stress were also found to have reduced hippocampal *SLC6A15* expression. Of note, however, this locus has not emerged as a prominent finding in subsequent depression GWAS (described below).

One of the major lessons from these early GWAS of depression, as with other complex traits,^{59,60} was that the effect of most SNPs was small in magnitude (allelic odd ratios of around 1.3 or less) and therefore considerably larger samples would be needed to identify genetic loci associated with depression. To enhance the power of psychiatric GWAS studies, the Psychiatric Genomics Consortium (PGC) was established in 2007 as an international collaborative effort to define the spectrum of risk variants across psychiatric disorders (<http://www.med.unc.edu/pgc>). One of the major goals of the PGC was to conduct mega-analyses for MDD in addition to schizophrenia, bipolar disorder, autism, and attention deficit hyperactivity disorder.⁶¹⁻⁶³ A mega-analysis pools individual-level phenotype and genotype data from across many studies; this approach differs from a meta-analysis, where the summary statistics produced by each study are analyzed. In 2012, the PGC published the results of a GWAS mega-analysis of MDD comprising 9,240 cases and 9,519 controls across 9 primary samples, all of European ancestry.⁶⁴ Although this was the largest sample to date, no SNP reached genome-wide significance. The most significant SNPs in the discovery sample were rs11579964 ($p=1.0 \times 10^{-7}$), a variant closest to several genes (*CNIH4*, *NVL*, *WDR26*) and rs7647854 ($p=6.5 \times 10^{-7}$) a variant closest to *C3orf70* and *EHHADH*. However, these findings were not supported in a large independent replication sample.

GWAS of depressive symptoms have also been largely unrevealing. The first GWAS of depressive symptoms did not find any SNPs reaching genome-wide significance.⁵⁵ One modestly associated ($p=1.59\times 10^{-6}$) SNP (rs7582472) did show evidence of replication in two independent cohorts. However, this SNP was more than 300kb away from two genes and neither gene showed significant association to depression in a gene-based analysis. A second study of depressed mood also did not find any genome-wide significant SNP, but did find an intronic SNP (rs12912233) in *RORA* (retinoid related orphan receptor alpha gene) was modestly associated in the meta-analysis ($p=6.3\times 10^{-7}$). While interesting, because another *RORA* SNP has been linked through GWAS to post-traumatic stress disorder,⁶⁵ this result awaits replication. In the largest study, which was a meta-analysis comprising 17 population-based studies ($n=34,549$ individuals) as the discovery sample, no SNP reached genome-wide significance.⁵⁶ The strongest association was for rs8020095 ($p=1.05\times 10^{-7}$), located in the gene *GPHN*. When the discovery and replication samples were combined into one meta-analysis of 22 studies with 51,258 respondents, one region (indexed by the SNP rs40465) was associated with depressive symptoms at genome-wide levels of significance.⁵⁶ This variant is in a “gene desert,” an area of the genome where there are long regions without protein-coding sequences and unknown biological function.

Another major lesson from depression GWAS has been that popular candidate genes have generally not shown evidence of association. Prior to the GWAS era, meta-analyses of candidate gene studies concluded there was nominally significant evidence (at $p<0.05$) for six candidate genes in depression: *APOE*, *DRD4*, *GNB3*, *MTHFR*, *SLC6A3*, and *SLC6A4*.^{66,67} However, none of these genes nor any of the more than 100 frequently examined candidate genes have shown evidence of significant association in the published GWAS of depression to date. Replication of candidate genes in GWAS is challenging, however, as several widely studied candidate gene markers, including the serotonin transporter 5-HTTLPR variable tandem number repeat (VNTR), are not directly captured by typical GWAS platform. Some groups have developed techniques to impute or derive best-guess estimates of these genetic markers using available SNP data,^{68,69} though these efforts have not yet been widely adopted. However, the overwhelming evidence for many candidate genes has not been compelling.

Another interesting observation from GWAS has been the lack of consideration of the role of environment. As we describe below, we think GWAS may be limited by not examining how genetic influences on depression may vary among individuals with certain environmental exposures. One exception is a study by Powers and colleagues,⁵⁷ who used propensity score matching to conduct a GWAS among case-control pairs matched on exposure to recent stressful life events. Use of propensity score matching enabled them to reduce sample heterogeneity and compare cases to controls with a similar level of exposure, though they did not formally test for GxE. In their analysis, no SNPs however, were genome-wide significant or even suggestive ($p<5\times 10^{-6}$), though this was likely due to the very small sample size ($n=805$).

Findings from Gene-Environment Interaction (GxE) Studies

The longstanding recognition that both genes (“nature”) and environments (“nurture”) contribute to the etiology of depression has motivated a great deal of interest in studying GxE. GxE studies examine the degree to which genetic variants modify the association between environmental factors and depression (or similarly, the extent to which environmental factors modify the association between genes and depression).⁷⁰⁻⁷² Typically, GxE studies have assumed a “diathesis-stress” model, where a genetic liability, also referred to as a diathesis, interacts with a stressful life event to give rise to depression. In this model, genes either exacerbate or buffer the effects of stress.⁷³ More recently, however, the concept of GxE has been expanded to incorporate more positive aspects of the environment, such as social support, psychosocial interventions, and other protective factors that reduce risk for disease.^{74,75} Here, emerging work has focused on differential susceptibility to the environment,^{76,77} or the extent to which genetic variation makes individuals more likely to respond adversely to negative environments, but more positively to salutary environments.

Research on GxE in depression was essentially launched with a publication in *Science* in 2003. In this study, Caspi and colleagues⁷⁸ used data from a 26-year longitudinal study in New Zealand to test whether a functional length polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) interacted with stressful life events to increase risk for depression. Results of the Caspi study suggested that individuals with at least one short (s) allele (i.e. who had the “s/s” or “s/l” genotype of the biallelic coded version) had more depression whether measured in terms of level of depressive symptoms, a depression diagnosis, or incident depression, as well as suicidality, in response to the number of stressful life events when compared to subjects who were not s allele carriers. They also found that s allele carriers had a greater probability of experiencing depression relative to those without an s allele as a result of exposure to probable or severe childhood maltreatment. The Caspi paper has become one of the most influential studies in the field, having been cited more than 5,000 times.

Since the publication of Caspi et al.'s seminal research, numerous replication attempts have been made. Most of these have also focused on 5-HTTLPR, though other genetic variants have also been studied, including variants in *BDNF* (brain derived neurotropic factor), *MAOA* (monoamine oxidase A), *FKBP5* (FK506 binding protein 51), *CRHR1* (corticotropin releasing hormone receptor 1), *COMT* (catechol-O-methyltransferase), and *CREB1* (also known as CAMP or responsive element binding protein 1). Many replication attempts have focused on recent or childhood stressful life events, as well as child maltreatment, namely physical abuse, sexual abuse, or neglect. All of these are appropriate “candidate” environments to study in GxE research. Child maltreatment, for example, is one of the most potent environmental stressors in the etiology and course of depression and other types of psychopathology. Extant studies suggest that childhood maltreatment at least doubles the risk for internalizing problems, including depression.^{18,20,21,79,80}

The large number of empirical studies trying to replicate Caspi's GxE findings for depression have been summarized in several reviews focusing on GxE with 5-HTTLPR (see for example ^{72,81,82-88}). These reviews ultimately fueled a heated debate regarding the

plausibility of the Caspi findings. Including somewhat identical individual studies, review papers have drawn opposing conclusions about the support for GxE effects, with some studies finding consistent GxE effects and others failing to detect them.^{84,85} Meta-analyses have provided a quantitative summary of these studies, but have also reached opposing conclusions. Specifically, the results of two meta-analyses,^{82,86} which found evidence against a consistent GxE effect, differed from a third meta-analysis,⁸³ which concluded there was strong evidence to support the 5-HTTLPR GxE. These conflicting results may be explained by differences in the selection of studies for inclusion in the meta-analyses.^{89,90} For example, the meta-analyses that used the most stringent inclusion criteria^{82,86} failed to support the GxE association.⁹¹ Some have also noted there is an inverse relationship between the power of the replication studies and support for the 5-HTTLPR association, precisely the opposite of what one would expect if the association is valid.⁹¹ Moreover, the most direct replication attempt of the Caspi findings, which was not included in any prior meta-analysis, found no evidence in support of the GxE effect on depression. This was a longitudinal birth cohort study following a similar population (New Zealand residents), for a similar length of time (30 years), and using comparable phenotypic measures.⁹² The authors observed no interaction between stressful life events and 5HTTLPR genotype, even after conducting 104 different regression models.⁹²

On the other hand, some have argued that support for the 5HTTLPR GxE has been more consistent when childhood maltreatment is the exposure variable⁸³⁻⁸⁵ or when direct-interview assessments (as opposed to self-report questionnaires) have been used.^{84,85} This finding is important, as there has been substantial variability in the characteristics of study populations, measurements of depression and environmental exposures, and analytic methods used across empirical studies to test for GxE in depression.⁷² Some have also tried to place these individual GxE studies in the context of the broader literature examining genetic variability and stress sensitivity on depression. Here, some have appealed to the more consistent findings from animal studies showing that loss of function mutations in the serotonin gene have been associated with depressive-like behavior in rodents and that genetic variation in the serotonin transporter gene has been linked to depression among non-human primates.⁹³ Proponents have also noted that the results are more convincing when considered alongside experimental imaging studies showing 5-HTTLPR variation in amygdala activity, and treatment response studies showing 5-HTTLPR variation in antidepressant treatment response.^{93,94} Overall, the validity of the influential 5-HTTLPR GxE finding remains unclear.

GxE studies focusing on other candidate genes, however, have found more consistent results. For example, studies examining *FKBP5* and *CHRH1* have shown that variants in these genes moderate the effect of exposure to child maltreatment, childhood adversities, or negative life events on adult depression.⁹⁵⁻⁹⁸ These genes are interesting candidates because they regulate the stress response via the hypothalamic-pituitary-adrenal (HPA) axis.⁹⁹ Additional replications of these candidates would be helpful to further evaluate their role in shaping risk for depression. Evidence for other candidates, such as *BDNF*, has been more mixed. For instance, a recent review found stronger evidence to support interactions with the *BDNF* Val66Met polymorphism and stressful life events compared to childhood

adversity.¹⁰⁰ As we later discuss, genome-wide approaches to GxE remain an important, but relatively unexplored area.

Current and Future Directions for Research

The limited success of GWAS for depression is in contrast with other psychiatric disorders, where established risk variants are accumulating through GWAS. For example, at the time of this writing, there are now more than 100 loci that have been associated with schizophrenia and bipolar disorder at stringent levels of statistical significance.¹⁰¹⁻¹⁰⁶ Despite the fact that individual risk loci have not been identified for depression, we know that such variants will be found given adequate sample sizes. For example, it is now possible to use genome-wide complex trait analysis (GCTA) to estimate the common variant contribution to depression using genome-wide SNP data (these estimates are sometimes referred to as SNP-heritability).¹⁰⁷ Through these methods, estimates of the common variant contribution to depression have ranged from a high of 32%¹⁰⁸ to a low of 21%.¹⁰⁹ It should be noted that these are lower bound estimates because SNP-chip heritability only reflects the effect of common variation that is captured on genotyping arrays.

Thus, the field faces two major questions: what explains the lack success of GWAS and GxE studies for depression and how can we best move forward? As described below (and summarized in Table 3), there are several likely explanations for the limited progress to date and several strategies that may help overcome these challenges.

Genetic Architecture and the Need for Larger Studies

The genetic architecture of depression is likely to be highly complex. Genetic architecture refers to the number of genetic loci associated with a phenotype, the effect size of each locus, and the manner in which these loci behave (e.g., whether they have additive or multiplicative effects). While all psychiatric disorders are thought to be polygenic, or influenced by multiple genes, the genetic basis of depression may reflect an even larger number of loci of individually small effect. Results from studies that have calculated polygenic risk scores (capturing aggregate effects of loci across the genome) support such a hypothesis.^{64,110} Therefore, it is likely that much larger samples than those examined to date will be needed to detect these individually small effects. Simulations suggest that, to have comparable power to GWAS of schizophrenia or bipolar disorder, studies of depression will need to have sample sizes as much as five times larger.⁵² Experience with GWAS for other disorders has established that, once a critical sample size threshold is crossed, larger and larger sample size yields more and more loci.

If depression is driven by many thousands of loci of weak effect, another strategy may be to combine genetic signals across many SNPs into functionally-defined gene sets or pathways. Pathway approaches can be considerably more powerful than single variant analyses, as the aggregation of weak signals from multiple causal variants may yield statistically significant evidence in support of a given gene or pathway.^{111,112} Thus far, investigators have primarily examined pathways related to specific biological functions (e.g., axon guidance, cell functioning) as defined by human-curated bioinformatics resources, such as the Kyoto Encyclopedia of Genes and Genomes (KEGG)¹¹³ or Gene Ontology.¹¹⁴ Recent studies of

candidate gene pathways have found evidence that genes involved in glutamatergic synaptic neurotransmission,¹¹⁵ among others,¹¹⁶ were significantly associated with depression. Evidence in support of gene sets or pathways also comes from several GWAS described previously and shown in Table 2, which found significant support for some pathways.^{46,56} One of the major drawbacks of gene-set analyses is that they require predefined sets of genes. Gene sets defined by current annotation databases, such as KEGG or GO, vary in their completeness; some pathways are more complete than others. Moreover, databases also vary in how they define gene sets. Thus, a given gene may belong to one pathway in one database and a second pathway in another. Although these challenges are not unsubstantial, we think greater use of pathway-type analyses is needed.

Understudied Components of the Genetic Architecture of Depression

A related consideration is that GWAS are designed to capture common but not rare genetic variation. Rare variants can include genetic single nucleotide variations (“SNVs” present in <1% of the population) and rare copy number variations (“CNVs,” that is, structural variations in DNA sequence that involve the duplication or deletion of thousands or more than a million base pairs). Such variants have now been shown to play a role in autism^{117,118} and schizophrenia^{119,120} and bipolar disorder,¹²¹ but to date these components of the genetic architecture of depression have been largely unexplored.

Fortunately, advances in sequencing technology now provide an opportunity to address the role of rare SNVs. In recent years, the cost of direct DNA sequencing has dropped dramatically and technologic advances have facilitated the development of “high-throughput” sequencing.^{122,123} To date, these “next generation sequencing technologies” have been largely applied to study variants in exons, which are the protein-coding regions of the genome collectively known as the “exome.” Exons comprise about 30 megabases of DNA or 1% of the total genome. Although no exome-sequencing studies of depression have been reported at the time of this writing, such studies are underway. Next generation sequencing technologies can also be applied to the entire genome (“whole genome sequencing”), enabling researchers to explore a full range of genetic variants in both coding as well as non-coding regions of the genome.

The major strength of sequencing is that it captures variants that have been previously uncharacterized by candidate gene and GWAS methods and thus may provide new insights into the genetic underpinnings of depression. Like all techniques, however, sequencing approaches face a number of challenges. For example, despite enormous reductions in the cost of sequencing, well-powered studies are still very expensive. Whole genome sequencing costs at least \$1,000 US per genome, whereas exome sequencing costs several hundreds of dollars. Exome sequencing also assesses polymorphisms that by definition are rare and thus occur with much less frequently than common variants. To have sufficient statistical power to identify an association between these rare variants and depression, very large sample sizes, on the order of 10,000 or more cases, are needed. In addition, rare variant association methods are still largely under development.

Structural variation, including CNVs, are also a potential source of depression risk loci. CNVs can be inherited or spontaneous, also referred to as *de novo*. *De novo* CNVs—those

that are present in offspring but not in either parent, have been shown to be important risk factors for several neuropsychiatric disorders, namely autism,^{117,118} schizophrenia^{119,120} and bipolar disorder.¹²¹ After conducting a systematic literature search of PubMed for papers published by December 2013 using the MESH terms for depression described previously and the phrase “Copy Number Var*,” we identified four studies, which provide preliminary evidence implicating CNVs in depression.¹²⁴⁻¹²⁷ In the largest of these studies, Glessner and colleagues found 12 CNV regions that were exclusive to cases with MDD. The region with the highest frequency in cases was a locus on chromosome 5 (5q35.1) that overlapped the genes *SLIT3*, *CCDC99*, and *DOCK2*. The finding of a CNV overlapping the gene *SLIT3* is interesting, as *SLIT3* is known to play a role in axon development and neurodevelopmental disorders.

One of the major strengths of studying CNVs is that the methods for association testing are similar, by and large, to examining common variants. Simultaneous examination of SNPs and CNVs in large samples may identify whether CNVs play a significant role in depression and what their importance is relative to common variants. One of the major drawbacks of association testing with CNVs is that catalogs of these variants do not exist with the same level of number or specificity as they do for SNPs. For example, the location, size, and boundary of CNVs in these publicly available resources have been relatively imprecise. As a result, opportunities for misclassification of variants is much higher for CNVs than for SNPs.¹²⁸ Efforts are now underway to provide a more comprehensive catalog of CNVs (see for example: <http://www.sanger.ac.uk/research/areas/humangenetics/cnv/>). Moreover, until recently there has also not been a commercially-available genotyping array that could detect both SNPs and CNVs. With the advent of the “PsychChip,” a customized genotyping chip for psychiatric phenotypes, investigators will soon be able to simultaneously examine multiple genetic variants, including SNPs, CNVs, and rare variants. The importance of rare variants to depression risk remains to be seen, but large-scale studies will be needed to clarify their contribution.

Accounting for the Role of Gene-Environment Interaction

As noted previously, existing studies have not systematically addressed the possibility that a substantial proportion of the risk of depression is attributable to non-additive effects, including GxE. Moreover, GxE studies to date have focused on a limited set of candidate genes and have typically been underpowered, creating a risk of both false positive and false negative results. It is well established that environmental factors, including exposure to stressful life events and child maltreatment, are important risk factors for depression, but we still know little about whether these environmental effects are moderated by genetic variation and, if so, which genetic variants are relevant.

One approach to filling this gap may come from genome-environment wide interaction studies (GEWIS), pronounced “G-Whiz.”^{129,130} In a GEWIS, investigators test for statistical interaction or GxE, with the “G” defined as the genetic loci (e.g., SNPs) included in a GWAS and the “E” defined as a known environmental exposure. Unlike candidate gene GxE, GEWIS offers the opportunity to conduct a genetically unbiased search—that is, one in which prior genetic or biologic hypotheses are not required. In one type of GEWIS,

investigators could focus on loci for which a main effect of a genetic variant has been established by GWAS. In this scenario, loci identified by GWAS become candidates for GxE analysis, but with the advantage over traditional candidate gene studies that the locus is already known to influence the phenotype of interest.

To our knowledge, no GEWIS of depression has been published to date. Though research on GEWIS of depression and other psychiatric phenotypes is lacking, a small but emerging body of research on other complex phenotypes suggests GEWIS can yield important new gains. For example, studies have identified significant genome-wide GxE interactions in cancer,^{131,132} diabetes¹³³ and insulin resistance,¹³⁴ Parkinson's disease¹³⁵, pulmonary function¹³⁶, and nonsyndromic cleft palate.¹³⁷ While interest in GEWIS is growing, there are several challenges to conducting this type of study.¹²⁹ The first is identifying the best methods to test for genome-wide GxE. Several methodological approaches have been developed (see for example reviews by^{138,139}); however there is no consensus on what methods are most ideal. Selection of a specific analytic method depends largely on whether the goal is to leverage GxE to discover novel loci or characterize the joint effect of genetic variants and environmental factors.¹⁴⁰

Second, the “environment” is to some extent unbounded in a way the genome is not. Both children and adults are exposed to a range of experiences across the multiple social and physical contexts in which they are embedded (e.g., families, school, neighborhoods, workplaces); all of these experiences and exposures can contribute to health.¹⁴¹ Focusing on well-defined measures of environment where there has been robust and consistent evidence to support a relationship between the exposure and depression is one way to start. Such a list of measures could include in utero exposures (e.g., viruses, toxins, alcohol and drugs), social deprivation (e.g., poverty, child maltreatment), and enrichment (e.g., psychosocial interventions and treatments). However, even if we select the same environment, such as child maltreatment, there are still multiple different types of maltreatment, multiple ages to consider when the maltreatment occurred, and multiple ways to measure maltreatment (e.g., self report, administrative records, clinical interview).

Finally, and perhaps the biggest challenge, is the need to balance the trade-off between the need for large samples and identifying precise measures of environmental exposure. Large samples are needed to detect GxE (larger even than those needed in standard GWAS). However, large samples often lack the depth and breadth necessary to capture data on environmental or phenotype measures. Although smaller samples frequently have rich and repeated measures, they are underpowered to establish robust associations. Smaller samples can be combined to increase statistical power. However, challenges will arise in trying to harmonize measures of environment across these datasets. In other words, efforts to ensure adequate sample size for each unique combination of risk factors and GxE strata can lead to a “watered-down” environmental measure that lacks any meaningful variability; a classic example would be an instance where respondents are simply classified as “exposed” or “non-exposed.” Longitudinal birth cohort studies, which can include prospective measures of environmental exposures along with detailed phenotype data and genome-wide data, may be one promising avenue for conducting GEWIS in the future. Moreover, the growing interest in the concept of the “exposome,” environment-wide association studies (EWAS)

and ways to systematically identify relevant environmental factors (see for example^{142,143}) could yield new insights to guide GEWIS in the future.

The Phenotypic Complexity of Depression

Another obstacle to progress in identifying susceptibility loci is the fact that depression is a heterogeneous phenotype. Indeed, it is possible to meet DSM-IV or DSM-5 diagnostic criteria for a major depressive episode through at least 227 different symptom combinations.¹⁴⁴ As currently described by DSM-5, MDD can manifest with or without: (1) anxious distress; (2) mixed features; (3) melancholic features; (4) atypical features; (5) mood-congruent psychotic features; (6) mood-incongruent psychotic features; (7) catatonia; (8) peripartum onset; and (9) a seasonal pattern.¹⁴⁵ These subtypes of major depressive disorder could reflect different genetic contributions. Consistent with such a hypothesis, studies suggest that depression with a history of child maltreatment has a different onset, course, and response to treatment when compared a depression that arises among individuals without a history of abuse.^{146,147} Recent twin studies have also suggested that genetic liability to MDD reflects not *one*, but *three* distinct symptom dimensions (psychomotor/cognitive, mood, and neurovegetative symptoms).¹⁴⁸ Thus, GWAS that simply examine “depressed” cases versus controls may decrease the ratio of “signal to noise” by combining multiple disorder subtypes that vary in their genetic etiology. In light of evidence suggesting that there is no truly categorical threshold for depression caseness,¹⁴⁹ and that different lifetime prevalence estimates of depression are found when comparing cross-sectional retrospective reports to cumulative evaluations based on multiple interviews,¹⁵⁰ it is reasonable to posit that misclassification of individuals as cases or controls may be undermining the power of typical case-control GWAS.

We think there are several strategies to reduce the heterogeneity in depression. First, examination of the full range of variation in depression (e.g., depressive symptoms), rather than dichotomizing the phenotype (cases and controls), could be a statistically more powerful approach to identify variants associated with depression.¹⁵¹ This would be consistent with evidence that the diagnostic threshold for MDD has been artificially imposed on a continuity of depression risk.¹⁴⁹ Second, more data-driven approaches to examine shared features or subtypes of depression through use of latent class analysis¹⁵² may also prove helpful. Prior studies applying such methods in both adolescents and adults have found distinct subtypes that differ based on severity, symptoms, and episode length.^{153,154} Examination of these subtypes in a genetic association study may help to identify variants that are common across or unique to specific subtypes. Third, another strategy would be to continue efforts to examine phenotypes thought to be more proximal to a genetic substrate than are clinically-defined categories.¹⁵⁵ Putative “intermediate” or “endophenotypes” related to depression include emotion-based attention biases,^{156,157} impaired reward function,¹⁵⁸ and deficits in domains of executive functioning, such as learning and memory.¹⁵⁹ Investigation of endophenotypes is consistent with the National Institute on Mental Health (NIMH) Research Domain Criteria Initiative (RDoC);¹⁶⁰⁻¹⁶³ which aims to provide a bottom-up characterization of psychopathology incorporating genetics, neural circuitry, and behavioral phenotypes. Endophenotypes have not yet been the subject of large-scale studies that might fully evaluate their power relative. One exception is the

ENIGMA consortium, through which GWAS meta-analyses of structural MRI phenotypes yielded a genome-wide significant association with hippocampal volume,¹⁶⁴ one of the best-established biomarkers of depression risk. However, this result still required sample sizes in the thousands, challenging the view that endophenotype-based studies will be more powerful than studies of major depressive disorder itself.

Conclusions

Research on the genetic underpinnings of depression is at an exciting, yet challenging crossroad. On the one hand, genotyping technologies have allowed for the characterization of individual and population-based genetic variation and have provided analytic tools to examine the individual and joint effects of genetic and environmental determinants. On the other hand, GWAS of depression have yet to see the same success achieved with other psychiatric or medical disorders. Moreover, studies of GxE have thus far not led to great clarity but have fueled plenty of debate. Some argue that positive findings reflect chance results among small, underpowered studies,⁸⁶ while others see consistencies when focusing on studies that are methodologically comparable.⁸³⁻⁸⁵

We have also reviewed some of the potential explanations for the lack of success to date for GWAS and GxE studies of depression. Given the established heritability of depression, there is every reason to expect that increasingly well-powered studies will indeed identify risk loci. However, the genetic and phenotypic complexity of depression may mean that such successes will require samples on the order of tens of thousands of participants. Efforts to parse the heterogeneity of depression and validate phenotypic subtypes may also be essential to facilitate gene identification. Further, as we have noted, potentially important areas of the genetic basis of depression--specifically, rare variation and GxE--remain relatively unexplored on a large-scale. It remains to be seen how much of the "missing heritability" of depression will be revealed through studies of these components.

Although the path forward to detect genetic risk loci for depression remains challenging, what is certain is that a deeper understanding of the etiology of depression is needed. Existing treatments for depression are based on decades-old biology and genetic discoveries have already begun to identify promising targets for novel therapies in other disorders. Given the enormous burden of depression, identifying its genetic underpinnings may be essential to preventing the onset of this disorder and improving the lives of those who already suffer.

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Table 1
Resources to learn more about concepts and findings from genetics and genomics

<ul style="list-style-type: none">• National Human Genome Research Institute: www.genome.gov/Glossary. A detailed glossary of genetic terms and concepts.• National Coalition for Health Professional Education in Genetics: www.nchpeg.org. Provides health professionals with online training and continuing education series on topics related to human genetics for health professionals.• NIH Pharmacogenetics Research Network: www.pgrn.org. A network of scientists focused on research identifying genetic influences on medication response.
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Table 2

Published genome-wide association studies (GWAS) of major depressive disorder (MDD), depressive symptoms, or age at onset of MDD

Author	Discovery Sample	Definition of Depression	GWAS Discovery Results	Replication Sample	GWAS Replication Results	Other Genetic Findings
Sullivan et al (2009) ⁴³	1,738 cases (mainly drawn from primary care screening and outpatient mental health clinics) 1,802 controls (drawn from twin registry; selected to be at low liability for depression) European ancestry	Lifetime diagnosis of DSM-IV MDD based on CIDI	No SNP reached GWS Of the top 200 SNPs, 11 were within a 167kb region overlapping the gene <i>PCLO</i> Top loci: rs2715148 ($p=7.7 \times 10^{-7}$); rs2522833 ($p=1.2 \times 10^{-6}$) Secondary analyses revealed findings were largely driven by women and participants with recurrent early onset MDD.	5 independent samples 6,979 cases 5,893 controls	No SNP reached significance after correction. The replication sample most similar to the discovery had a nominal effect: rs2522833 6.4×10^{-8}	Examined 75 candidate genes and found significant effect for <i>NOS1</i> ($p=0.0006$)
Rietschel et al (2010) ⁴⁴	597 cases (hospital-based) 1,295 controls (population-based) European ancestry	Lifetime MDD based on SCI, medical records, or family history method.	No SNP reached GWS Top three hits were: rs2765501 ($p=1.66 \times 10^{-7}$) located in <i>CD5L</i> rs7713917 ($p=5.87 \times 10^{-5}$) located 20kb upstream of <i>HOMER1</i> rs9943849 ($p=6.22 \times 10^{-5}$) located 14kb upstream of <i>CPM</i> Did not replicate previous findings for <i>PCLO</i>	409 cases 541 controls	The two top hits showed a trend towards significance in replication sample: rs7713917 ($p=7.61 \times 10^{-3}$) rs9943849 ($p=1.59 \times 10^{-2}$) Meta-analysis with discovery and replication samples: rs9943849 ($p=3.24 \times 10^{-6}$) located upstream of <i>CPM</i> rs7713917 ($p=1.48 \times 10^{-6}$) located in <i>HOMER1</i>	Examined genes that contained SNPs with p -values < 0.001 and found the most significant pathway related to cell signaling (included <i>GRM5</i> and <i>HOMER1</i>). After correcting for gene size, found 6 of 22 genes that had a probability $> 10\%$ of being selected by chance (<i>ACTN2</i> , <i>CYP17A1</i> , <i>DLCL1</i> , <i>GRM5</i> , <i>MAP2K4</i> , <i>MAP2K4</i> , <i>RSU1</i>). Conducted fMRI follow-up analyses with top variants to examine several intermediate phenotypes and found some differences by genotype group in working memory.
Terracciano et al (2010) ⁴⁵	3,972 participants European ancestry	Depression inventory from the revised NEO-PI	No SNP reached GWS Top hit: rs349475 ($p=2.4 \times 10^{-7}$) in <i>CDH18</i>	839 community dwelling respondents from the Baltimore Longitudinal Study of Aging European ancestry	No SNP reached GWS Top hit: rs4885589 ($p=2.4 \times 10^{-4}$)	Conducted meta-analysis in combined sample ($n=4811$) Top hit in meta-analysis: rs12912233 ($p=6.3 \times 10^{-7}$) an intronic SNP in <i>RORA</i> Described rs17864092 ($p=5.5 \times 10^{-6}$) in <i>GRM8</i> as most biologically plausible top hit
Muglia et al (2010) ⁴⁶	926 recurrent MDD cases (clinical sample) 866 controls (age and gender matched from community sample) European ancestry	Recurrent MDD (at least 2 separate episodes of severe intensity) as assessed by the SCAN instrument Cases allowed to have comorbid anxiety (no OCD or PTSD); 26% did	No SNP reached GWS	492 recurrent cases (clinical sample) 1,052 controls (from community survey) European ancestry	No SNP reached GWS in replication sample. Little agreement between discovery and replication sample with respect to the most significant SNP associations identified. Conducted meta-analysis. No SNP reached GWS. Most significant SNP was for	Gene-based analysis found the most significant results were similar to the SNP-level analysis. Strongest adjusted gene-based association ($p=0.009$) was for <i>SMG7</i> . Examined whether top 104 genes ($p < 10^{-4}$) from meta-analysis were found in a previous study to associate with mood disorders or

Author	Discovery Sample	Definition of Depression	GWAS Discovery Results	Replication Sample	GWAS Replication Results	Other Genetic Findings
Lewis et al (2010) ⁴⁷	1,636 cases (from 3 clinic-based groups) 1,594 controls (primary care screening; screened negative for depression or anxiety) European ancestry	recurrent depression of at least moderate severity defined by SCAN	No SNPs reached GWS Four genotyped SNPs showed suggestive evidence: 2 SNPs in <i>BICC1</i> : rs9416742 ($p=1.3 \times 10^{-7}$) and rs999845 ($p=3.1 \times 10^{-7}$), rs2698195 located closest to <i>KIAA1841</i> ($p=3.54 \times 10^{-9}$), and rs8050326 located closest to (over 100 kb from) <i>IRF8</i> ($p=4.07 \times 10^{-6}$) After imputing SNPs in the <i>BICC1</i> region, found GWS for 6 SNPs in strong LD. Strongest evidence at rs7903712 ($p=5.7 \times 10^{-9}$).	Conducted meta-analysis 1,418 cases (recurrent depression from clinical sample) 1,918 controls (from population-based study)	No SNP attained GWS in meta-analysis. Top hit: rs606149 ($p=2.57 \times 10^{-6}$) near <i>LOC647167</i> No replication for <i>BICC1</i> .	Analyzed haplotypes in discovery at two SNPs in <i>BICC1</i> (rs7903712 and rs9416742) and found association ($p=9.04 \times 10^{-8}$). Conducted sex-specific analyses for top 20 SNPs in discovery and found GWS association for women with rs9416742 in <i>BICC1</i> ($p=1.8 \times 10^{-8}$). In women, 4 additional SNPs had suggestive evidence (rs8067196, rs2930553; rs13079811; rs987390). In men, rs6989226 (near <i>TUSC3</i>) had suggestive evidence ($p=1.81 \times 10^{-6}$). Analyzed 84 candidate genes and found strongest evidence for rs13050655 in <i>PDE9A</i> ($p=3.58 \times 10^{-5}$)
Shi et al (2011) ⁴⁸	1,020 cases (with recurrently early onset MDD; clinical sample) 1,636 controls (no lifetime MDD; population-based) European ancestry	MDD based on DIGS and consensus by two independent reviewers	No SNP reached GWS Top hit: rs17077540 ($p=1.83 \times 10^{-7}$)	Compared results to other meta-analyses described in Shyn.	No SNPs reached GWS. Strongest support for rs17144465 ($p=8.38 \times 10^{-7}$)	Examined 41 candidate genes using single SNP tests and found the lowest p-value ($p=6.7 \times 10^{-5}$) for <i>CACNA1C</i> Also conducted an aggregate test (of whether p-values in gene were more significant than expected by chance) and found no significant findings.

Author	Discovery Sample	Definition of Depression	GWAS Discovery Results	Replication Sample	GWAS Replication Results	Other Genetic Findings
Aragam et al (2011) ⁴⁹	1,726 cases and 1,630 controls, both population-based European ancestry	MDD diagnosis based on CIDI	No SNP reached GWS Top hit: rs1558477 ($p=2.63 \times 10^{-7}$) in <i>ADCYAP1R1</i> 4 SNPs in <i>PCLLO</i> had marginal effects rs2715148 ($p=1.38 \times 10^{-6}$) rs 2522833 ($p=2.46 \times 10^{-6}$) rs2522840 ($p=4.38 \times 10^{-6}$) rs2107828 ($p=1.48 \times 10^{-5}$)	None	Nominally significant association in four of the five initial replication samples with recessive model GWS replication for rs1545843 ($p=4.37 \times 10^{-8}$) in meta-analysis, after adjustment for multiple testing Further replicated findings for rs154843 in second replication sample ($p=0.008$)	Also conducted sub-group analyses stratified by sex. Best SNP for males: rs9352774 ($p=2.26 \times 10^{-6}$) in <i>LGSN</i> Best SNP for females rs2715148 ($p=5.64 \times 10^{-7}$) in <i>PCLLO</i> Also tested for interactions by gender and found best SNP in rs12692709 ($p=5.75 \times 10^{-6}$)
Kohli et al (2011) ⁵⁰	353 cases (inpatients in tertiary clinic) 366 matched controls (no lifetime MDD; community sample) European ancestry	Met DSM-IV criteria for first depressive episode or recurrent depressive disorder and had HAM-D score 14	One SNP reached GWS: rs1545843 ($p=5.53 \times 10^{-8}$)	Six independent samples of different racial/ethnic background	Examined 41 candidate genes in discovery, but none were supported. Best finding was for rs3788477, a SNP intronic to <i>SYN3</i> ($p=1.64 \times 10^{-4}$). No other SNP achieved $p < 10^{-3}$. Also examined in meta-analysis. Aggregate analysis did not suggest an excess of low p -values among these candidates.	Further validated findings in analyses of: (1) associations to pre-mortem human hippocampus and lymphoblastoid cell line expression profiles; (2) imaging; and (3) hippocampal expression in mouse model of chronic social stress.
Shyn et al (2011) ⁵¹	1,221 cases (from STAR*D; outpatient clinics) 1,636 controls (population-based; no lifetime history or MDD) European ancestry	Diagnosis of MDD by clinician rating and score of 14 on HAM-D by independent raters	No SNP reached GWS in analyses of genotyped SNPs Top hit: rs12462886 ($p=1.73 \times 10^{-6}$) located in gene desert.	Meta-analysis with two additional datasets (GenRED and GAIN) ($n=3,957$ cases and $n=4,328$ controls). Examined broad (all cases) and narrow phenotype (recurrent depression with onset before age 31).	No SNP (imputed or genotyped) reached GWS Strongest evidence in broad meta-analysis was for intronic SNPs in <i>ATP6V1B2</i> (rs1106634; $p=6.78 \times 10^{-7}$), <i>SP4</i> (rs17144465; $p=7.68 \times 10^{-7}$), and <i>GRM7</i> (rs9870680; $p=1.11 \times 10^{-6}$). Best SNP in narrow analysis was in stratified analysis of males only (rs11710109; $p=5.64 \times 10^{-8}$).	Examined 41 candidate genes in discovery, but none were supported. Best finding was for rs3788477, a SNP intronic to <i>SYN3</i> ($p=1.64 \times 10^{-4}$). No other SNP achieved $p < 10^{-3}$. Also examined in meta-analysis. Aggregate analysis did not suggest an excess of low p -values among these candidates.
Wray et al (2012) ⁵²	2,431 cases 3,673 controls (population-based and family members without disease; drawn from five different sites) European ancestry	Lifetime diagnosis of MDD through CIDI or other interview instrument	No SNP reached GWS Top loci in total sample: rs3732293 ($p=1.5 \times 10^{-6}$) rs17226852 ($p=1.5 \times 10^{-6}$)	Compared results to other published studies and meta-analyses.	No SNPs reached GWS.	Tested 183 candidate genes and found none reached significance after correction in the discovery sample, other published studies, or in meta-analysis.
Psychiatric GWAS Consortium (2012) ⁵³	9,240 cases and 9,519 controls (mostly population-based; no lifetime history of depression). Came from 9 primary samples. European ancestry	Lifetime MDD established using structured diagnostic instruments from direct interviews or clinician-administered checklists	No SNP reached GWS in mega analysis. Top hits: rs11579964 ($p=1.0 \times 10^{-7}$) and rs7647854 ($p=6.5 \times 10^{-7}$) Top 201 SNPs and 1655 in LD with those did not overlap with literature from the NHGRI GWAS catalog, transcripts	6,783 cases and 50,695 controls (7 independent samples from discovery European ancestry)	Tried to replicate 554 SNPs with $p < 0.001$. Did not find SNPs that replicated in the same direction as discovery analysis more frequently than chance. No SNP achieved GWS for a joint analysis of the discovery and replication samples. Top hit	Conducted a cross-disorder meta-analysis and a set of secondary analyses (by sex, recurrent early age at onset, and subtype). Direction of effects was generally consistent between discovery and replication for analyses restricted to women

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Author	Discovery Sample	Definition of Depression	GWAS Discovery Results	Replication Sample	GWAS Replication Results	Other Genetic Findings
Power et al (2013) ⁵⁷	805 case-control pairs matched first on ancestry and second on exposure to stressful life events from the RADIANT study (see ⁴⁷) European ancestry	Recurrent depression of at least moderate severity defined by SCAN	No SNPs achieved GWS or suggestive evidence ($p < 5 \times 10^{-6}$).	None		

BDI = Beck Depression Inventory; CESD = Center for Epidemiological Studies of Depression Scale; CIDI = Composite International Diagnostic Interview; DIGS = Diagnostic Interview for Genetic Studies; fMRI = functional magnetic resonance imaging; GAIN = Genetic Association Information Network; GCTA = genome-wide complex trait analysis; GenRED = Genetics of Recurrent Early-Onset Depression; GWS = genome wide significant; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; LD = linkage disequilibrium; POMS = Profile of Mood States; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCI = Structured Clinical Interview; SNPs = single nucleotide polymorphism; STAR*D = Sequenced Treatments to Relieve Depression

Table 3
Possible explanations for the lack of success of genome-wide association studies (GWAS) and gene-environment interaction (GxE) studies for depression and strategies to increase gene-finding

<u>Explanations</u>	<u>Strategies to Address</u>
Depression has a different genetic architecture	<ul style="list-style-type: none"> • Increase sample size to improve power to detect associations of individually small effect loci • Aggregate genetic signals into gene-sets or pathways • Examine rare variants and other types of structural variants (e.g., copy number variants) in addition to common variants
Previous GWAS did not consider the role of environment	<ul style="list-style-type: none"> • Conduct genome-environment wide interaction studies (GEWIS) • Test for GxE using candidate genes from GWAS
Depression is highly heterogeneous	<ul style="list-style-type: none"> • Examine depressive symptoms (quantitative phenotype) rather than only diagnoses of depression • Use novel analytic methods (e.g., factor analysis; latent class analysis) to identify and refine distinct sub-types • Focus on intermediate or endophenotypes, consistent with the National Institute of Mental Health Research Domain Criteria Initiative (RDoC)

Genome-Wide Association Studies = GWAS; Genome-Environment Wide Interaction Studies = GEWIS; National Institute of Mental Health Research Domain Criteria Initiative (RDoC)