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The genetics of major depression: Moving beyond the monoamine hypothesis

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SYNOPSIS

Efforts to unlock the biology of major depressive disorder (MDD) are proceeding on multiple fronts. In this article, we review our current understanding of epidemiologic evidence for a heritable component to MDD risk, as well as recent advances in linkage, candidate gene, and genome-wide association analyses of MDD and related disease subtypes and endophenotypes. While monoamine signaling has preoccupied the bulk of scientific investigation to date, non-traditional gene candidates such as *PCLO* and *GRM7* are now emerging and beginning to change the landscape for future human and animal research on depression.

Keywords

genetics; major depression; genome-wide association

INTRODUCTION

Over the course of a lifetime, major depressive disorder (MDD) afflicts one in six individuals in the general U.S. population[1], women twice as often as men2, and is the leading cause of disability among adults younger than 45 years of age3. MDD is characterized by dysphoria and/or anhedonia plus several additional symptoms for diagnosis which may include: changes in sleep/appetite, excessive feelings of guilt or worthlessness, anergia, psychomotor slowing, impaired ability to think, and, in more severe cases, suicidality. The DSM-IV further defines MDD as the presence of at least one two-week depressive episode and excludes cases in which bipolar disorder, substances, or a general medical condition is etiologic4.

The pathophysiology of MDD remains a mystery almost half a century since Joseph Schildkraut first proposed the monoamine hypothesis of depression 5, which followed the twin serendipitous discoveries of the therapeutic benefits of iproniazid (an antimycobacterial with inhibitory effects on monoamine oxidase)[6] and imipramine (a failed antipsychotic which came

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to represent a new class of drugs known as tricyclic antidepressants)7. Despite the compelling nature of this disease model, to date, no DNA variants in monoamine synthesis or signaling genes have been consistently linked to the etiology of affective disorders8. This review explores current efforts in gene discovery and alternative hypothesis generation for unipolar depression.

EPIDEMIOLOGY AND MDD SUBTYPES

Family studies demonstrate that first-degree relatives of MDD probands have a relative risk for MDD of 2.8 over the general population risk9. This number is further increased to between 3.0 and 8.0 for recurrent early-onset depression (MDD-REO)10. Recurrence of depressive episodes and earlier age-of-onset have been the two clinical features that have shown the most consistent ability to predict greater familial aggregation, though it has been observed that the relative risk estimates quoted for MDD-REO are derived from family studies and not large population-based analyses11. The most optimal age at which to define a cut-off for 'early-onset' is also unclear, but, in the GenRED (Genetics of Recurrent Early-onset Depression) project, the largest MDD-REO genetic study effort to date, Levinson et al used a cut-off of 30 years. The argument for a genetic contribution to MDD comes from twin studies which estimate an overall heritability of 37–43% despite a lack of biologic markers and our reliance on an imperfect set of syndromal criteria for diagnosis9. While less heritable than schizophrenia and bipolar affective disorder, this estimate is similar to that described for type 2 diabetes mellitus12, a complex trait for which a number of risk loci have been successfully identified13.

There are multiple DSM-defined specifiers elaborating a range of clinical subtypes of MDD. These include: severe MDD with psychotic features, melancholic depression, atypical depression, and depression with postpartum onset. Dysthymic disorder, a frequently more chronic MDD-spectrum disorder, albeit with a lower symptom burden, is also clinically recognized. Finally, there is a growing awareness of "anxious depression" as an MDD variant —but, as yet, no consistent or formalized definition for this clinical construct[14].

The need for such varied specifiers and nosologic exclusions highlights the extraordinary clinical heterogeneity of depression—a heterogeneity which also represents one of the great stumbling blocks in epidemiologic and genetic studies of MDD. Most research efforts have focused on non-psychotic depression. Meanwhile, subtypes, such as melancholic and atypical depression, though generally not excluded from MDD studies, have received less individual attention than the construct of MDD as a whole.

Melancholic depression appears to represent a more severe variant of MDD as patients' loss of pleasure more closely approaches absolute anhedonia and neurovegetative symptoms take on greater intensity. A twin study of melancholic depression concluded that melancholic and non-melancholic depression demonstrated quantitative (e.g., higher concordance rates of MDD in melancholic co-twins compared to non-melancholic co-twins) but not qualitative differences, suggesting shared rather than disparate etiologic mechanisms[15].

Atypical depression is characterized by hypersomnia, hyperphagia, and mood reactivity (e.g., brightening in response to positive events). Atypical criteria also include 'leaden paralysis' in the limbs and long-standing patterns of 'interpersonal rejection sensitivity'—symptoms which are inherently more difficult to standardize or objectively measure. Despite the possible presence of mood reactivity, it is not necessarily the case that atypical depression represents a 'milder' form of MDD: Atypical depression shows greater chronicity, has higher comorbidity with anxiety disorders and Cluster B and C personalities, displays an earlier age of onset, and has a greater propensity to include females[16].

Postpartum depression, or depression occurring in the first four weeks after childbirth, is a specialized case of major depression and may lie on a continuum with postpartum blues (a non-DSM-defined syndrome where full criteria for a major depressive episode are not met) as well as with antepartum depression. There are suggestions of a familial component to both perinatal and postpartum depression (stronger for postpartum depression) in an analysis of the GenRED sample[17] but, with the limited number of perinatal depression cases in that study, it was not possible to determine if this was due to genetic factors distinct from those responsible for major depression in women more generally. The GenRED sample was also not specifically collected for the purpose of examining questions about perinatal depression, and the authors rightly point out that recall bias and cohort effects cannot be ruled out. As we were unable to locate any major genetic studies of postpartum depression, this topic is not further discussed in this review. Postpartum psychosis, believed to be more closely associated with bipolar disorder than MDD18, is also not discussed here.

Dysthymic disorder, or the presence of two years of depressive symptoms which are subthreshold for an episode, has received comparatively less attention than has MDD. By DSM-IV criteria, dysthymic disorder is not mutually exclusive with MDD if a major depressive episode occurs after the first 2 years of dysthymia or remits two months prior to the onset of dysthymia. These idiosyncratic timing requirements, however, complicate the ability of research groups to collect accurate data and properly classify research participants whose recall of the chronology of past episodes may be imprecise.

The issue of anxious depression raises questions about whether it is more useful to utilize syndromal or subsyndromal criteria for anxiety and depression, and whether these clinical components have common etiologic mechanisms or it is more appropriate to treat them as separate entities14. DSM-IV preliminarily outlines a set of research criteria for “mixed anxiety-depressive disorder” (MADD) which effectively hybridizes symptom checklists for MDD and generalized anxiety disorder (GAD)4. There are conflicting reports about the prevalence of MADD, its longitudinal stability, and, therefore, its diagnostic validity19, 20, and further revision to clinical criteria for anxious depression will likely be necessary. There does appear to be a difference in treatment outcomes, however; Fava et al found that 53% of the MDD cases in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study were anxious- depressed, and that remission was less likely and took longer to be achieved in this subset21. Of note, Fava et al did not use DSM-IV-defined research criteria for MADD, but instead defined a cut-off for anxious depression using the anxiety-somatization factor of the Hamilton Rating Scale for Depression. Whether these poorer outcomes stem from quantitative or qualitative differences between anxious and non-anxious depression is not yet known. Currently, there are few published genetic studies on shared genetic risk factors between anxiety and depression. A recent review22 finds that, while the evidence for common genetic etiologies is mixed in family studies, that from twin studies is more consistently supportive. Factor analyses demonstrate a particularly strong correlation between MDD and GAD, and suggest this may be mediated by shared personality traits that may represent more optimal phenotypes for identifying relevant genes. One such personality trait, neuroticism, is discussed further below.

ENDOPHENOTYPES

An endophenotype is a trait that is intermediate between genotype and disease, not necessarily beholden to the diagnostic criteria for a single illness, but a construct whose purpose is to help simplify our understanding of otherwise complex or heterogeneous disorders. As outlined by Gottesman and Gould[23], an endophenotype can be “[neuro]physiologic[al], biochemical, endocrinological, [neuro]anatomical, cognitive, or [neuro]psychological.” They further propose that an endophenotype should: (1) be “associated with illness in a population”; (2) be

heritable; (3) manifest, when inherited, regardless of the presence/absence of the full syndromic condition; (4) co-segregate with illness in families; and (5) be found in affected and unaffected family members or probands "at higher rate[s] than in the general population."

Perhaps one of the best studied endophenotypes related to MDD is neuroticism, a construct first introduced by Eysenck to describe a high-order personality factor associated with "dysphoria, anxiety, tension, and emotional reactivity."24 Approximately 55% of MDD's genetic risk may be shared with neuroticism25, and, indeed, a number of the linkage studies we summarize below utilized neuroticism as the study phenotype. Hasler et al[26] raise some concerns about insufficient reduction of complexity substituting MDD with neuroticism, and, in an elegant outline of alternative MDD endophenotypes, mention other possibilities such as tryptophan depletion, the dexamethasone suppression test, and neuroimaging—though these run into limitations of their own (typically related to ease of high-throughput administration and cost). Many of these alternatives, unfortunately, also have not yet received sufficient epidemiologic examination and validation.

LINKAGE STUDIES

Linkage studies are genetic analyses of pedigrees and are well-suited for studying disorders with a clear pattern of Mendelian inheritance and disorders driven by genes of large effect. While neither of these conditions is likely to operate in depression, the discovery and definition of a rare familial variant would still accelerate the development of greater insight into etiologic mechanisms. There have been few reports of notable pedigrees segregating an identifiably high-penetrance syndrome involving depression27, 28, and even then, these have typically demonstrated additional psychiatric disorders other than MDD in members of the same family. A comprehensive summary of MDD linkage studies was recently published[24] and will not be repeated here. Summarized in this previous review were four linkage studies of three MDD samples which utilized a range of phenotypes from MDD to MDD-REO, with/without anxiety disorders, and including/excluding cases of bipolar I and bipolar II as affected family members. Supportive findings include regions on chromosomes 1, 3, 4, 6, 8, 11, 12, 15, and 18. It has generally been difficult to replicate linkage findings at a level comparable to that reported in any region's initial respective positive report, and power analyses suggest that much larger samples (on the order of approximately 1,000 affected sibling pairs) would be necessary to reliably detect a locus with a risk odds ratio (OR) of 1.25[24].

Since Levinson's review, there have been three additional published linkage studies of MDD. These include two reports from the GenRED group29, 30 and a third paper by Middeldorp et al31. Holmans et al30 present the final genome-wide linkage scan report for GenRED, a collection of 656 families, each with at least two MDD-REO cases. Included in this group were 1,494 informative affected relative pairs and 894 independent affected sibling pairs. The same group had earlier published their first wave of samples (i.e., 297 families) and preliminarily identified a region on chromosome 15q25-26 as genome-wide significant10. This same region again emerged as their most significant linkage peak, though with a reduced logarithm of odds (LOD) score of 2.06 (down from the original score of 3.73). Holmans et al were unable to identify a clinical feature that distinguished their first and second waves of family samples, and, therefore, to explain why their second wave did not further bolster their linkage signal at 15q. The proposed (and most likely) scenario is that upward bias in the first half of their sample overestimated the magnitude of linkage. In a companion paper, a follow-up fine-mapping effort focused on 88 single nucleotide polymorphisms (SNPs) in a 22.5 megabase (Mb) window (from 77.6 – 100.1 Mb) centered on the 15q linkage peak29. Of note, only families of European ancestry (631 of the original 656 families) were retained for this second analysis since there were insufficient numbers in the non-European families for a meaningful linkage study. A maximum LOD score of 4.78 (exact P-value of 1.4×10^{-6}) was detected at 92.6 Mb, and,

somewhat reassuringly, there was nominal significance even for the second wave of the GenRED sample ($p<0.04$). These investigators then tested 781 SNPs in a subset of their pedigrees involving 1,195 individuals in 300 families across a 9 Mb segment of the linkage region. The authors noted nominally significant family-based association results near *NTRK3*, a gene encoding a receptor for neurotrophin 3. Based on a prevailing hypothesis linking depression and neuronal growth factors, the authors re-sequenced the coding regions of *NTRK3* in 176 cases and 176 controls to examine association for novel DNA variants. While they did not discover any plausible functional variants at appreciable allele frequencies (e.g., two predicted non-synonymous SNPs were each seen in single individuals), they found several common variants showing continuing support for association to MDD (including rs4887379, one-tailed $P = 0.008$, allelic odds ratio 1.61, 95% confidence interval 1.11–2.32)[32]. None of these SNP results were considered significant after correcting for multiple tests, but the study does generate interest in *NTRK3* as a potential MDD risk locus.

Middeldorp et al[31] examined 110 Australian and 23 Dutch MDD pedigrees (1,943 subjects genotyped) with at least two affected siblings. Both samples were drawn from twin registries, but the Australian group was pre-selected for either highly discordant or highly concordant normalized scores for neuroticism and the Dutch group was screened with a factor score reflecting genetic predisposition to “anxious depression.” Neither of these traits served as proxies for MDD, however, as blinded interviewers subsequently conducted a telephone-administered Composite International Diagnostic Interview (CIDI) to screen for MDD. Individuals with a history of hypomanic episodes or bipolar disorder were excluded. The ensuing linkage scan identified a maximum LOD score of 2.11 on chromosome 17 (52.6 cM), an interval which includes *SLC6A4*, the serotonin transporter. Notably, however, their follow-up analysis did not identify the promoter length polymorphism in *SLC6A4* to be associated with MDD or any related proxy phenotype, strongly suggesting that another *SLC6A4* polymorphism or a polymorphism in a different gene within this linkage region drove their signal. Middeldorp et al suggested that their most promising finding was on chromosome 8 (2.7 cM), where they obtained a smaller LOD score of 1.87 but which had also been implicated in two previous linkage studies of personality traits—one, at a significant level, examining harm avoidance[33] (another potential endophenotype) and a second, at a suggestive level, examining neuroticism34.

Although linkage efforts in the study of MDD have yet to yield confirmed gene candidates, the studies performed to date represent an important effort that may yet have further use in correlating data from other types of genetic studies (such as those detailed below). A summary of MDD linkage results is provided in Table 1.

CANDIDATE GENE STUDIES

An alternative to linkage studies is the association study, in which the frequencies of specific polymorphic alleles are measured for enrichment in one group versus another. Typically a group of unrelated individuals comprising the case group is compared at one or many loci with a group of similarly unrelated individuals comprising the control group, although family-based designs are also available. Traditionally, a gene was chosen for its location within a linkage peak. Currently, the choice of candidate loci typically constitutes part of an investigator’s best guess or hypothesis about etiologic mechanisms, and is informed by biologic plausibility based on the limited knowledge we have gleaned from sources such as animal models, disease-correlated changes in clinical indices, or existing treatments for a disorder. There have been hundreds of candidate gene studies of MDD (most frequently examining candidates related to monoamine signalling, neurotrophins, neuroendocrinology, or immunology/inflammation) and it would be beyond the scope of this review to completely catalog each of these efforts. We will instead focus on several recently published meta-analyses of candidate gene studies.

Lopez-Leon et al[35] recently published the most comprehensive of these meta-analyses, and, after surveying 183 papers covering 393 polymorphisms in 102 genes, found that only 22 polymorphisms (5.6%) were examined in at least three independent primary studies. The strongest evidence for association (meta-analysis $P \leq 0.001$) was found for a polymorphism in *APOE* (apolipoprotein E), with lower levels of significance ($P \leq 0.01$) for variants in *GNB3* (guanine nucleotide-binding protein, beta 3), *MTHFR* (methylene tetrahydrafolate reductase), and *SLC6A4* (serotonin transporter).

In the case of *APOE*, there were a total of 827 cases and 1,616 controls (over 7 studies), and a pooled per-allele odds ratio (OR) of 0.51 suggesting decreased risk of MDD with the ε2 allele v. the ε3 allele. *APOE*, one may recall, is also the locus that was found to be a major susceptibility factor for late-onset Alzheimer's Disease (AD) when an individual carries one or two copies of a third allele, ε4[36]. A more recent study investigated the *APOE*-MDD question stratifying by AD (since cognitive status is a potential confounder), and found that, although MDD was overrepresented in ε4 carriers ($P < 0.001$), this association did not survive stratification in either the AD(+) or AD(−) groups. The dataset here was underpowered to examine the ε2 allele, but, importantly, did not demonstrate a trend toward an effect on MDD by ε2.[37]

The short/long (s/l) polymorphism in the promoter region of *SLC6A4* has been the subject of the most studies to date (n = 24), for a total count of 3,752 cases and 5,707 controls in the Lopez-Leon et al meta-analysis. The s-allele demonstrated a per-allele OR of 1.11 over the l-allele, suggesting a modest increase in risk for MDD with the s-allele.

For *MTHFR*, Lopez-Leon et al examined the C677T (rs1801133) polymorphism in a pool of 875 cases and 3,859 controls, and obtained a pooled per-allele OR of 1.20 (i.e., greater risk with the minor allele, T). A subsequent meta-analysis by Gaysina et al[38] (1,443 cases and 1,123 controls), however, found no statistically significant association with MDD.

Interestingly, Lopez-Leon et al did not find a robust association with the oft-studied Val66Met (rs6265) polymorphism in *BDNF* (brain-derived neurotrophic factor). A more recent meta-analysis of *BDNF* and MDD employing 3,879 cases also obtained a negative result at rs6265[39].

TPH1 encodes tryptophan hydroxylase-1, which is the rate-limiting enzyme in serotonin (5HT) synthesis. The most extensively studied *TPH1* polymorphism, A218C (rs1800532), was recently examined in a meta-analysis by Chen et al[40]. Across 8 MDD samples (1,812 cases and 2,223 controls), no association was found for any rs1800532 genotype and MDD. Of note, within the same paper, a separate meta-analysis across a different set of study samples did find an association with bipolar disorder. Several years ago, a group studying *TPH2* (a separate tryptophan hydroxylase locus with greater CNS expression) identified what appeared to be a variant overrepresented in MDD cases.[41] This locus, G1463A (rs7305115), initially generated a great deal of enthusiasm because it was found to functionally reduce 5HT synthesis by up to 80%. At least three groups subsequently communicated, however, that the A allele could not be detected in either cases or controls in multiple additional large samples42⁻44.

While candidate gene studies of MDD have allowed investigators to test favored hypotheses about the neurobiological origins of the disorder, they have yielded few solidly replicated findings. Indeed, those candidate genes best supported in meta-analysis have often been those with the least obvious mechanistic connection to depression, such as *APOE*, *GNB3*, and *MTHFR*. Moreover, the available replicated genes confer very small amounts of risk, suggesting that many as-yet unidentified loci may contribute to predisposition to MDD.

GENOME-WIDE ASSOCIATON STUDIES

Linkage studies, as previously discussed, are best suited for detecting genetic variants (including rare variants) of strong effect and with a clear pattern of Mendelian transmission. Association studies, in contrast, are better suited to detecting multiple variants of modest effect, and perform best when the variants being studied are relatively common in the general population. When association studies are focused on particular candidate genes, they are constrained by the limits of investigator imagination and the body of previously accumulated evidence (which may not be sizeable). With the advent of multi-center genomics initiatives such as the International HapMap Project45 and of improved genotyping technologies for higher throughput analysis, a new type of association study, the genome-wide association study (GWAS), exploded onto the scene. GWAS, presaged in an exposition by Risch and Merikangas46, typically interrogate hundreds of thousands to upwards of one million biallelic SNPs located throughout the genome. They represent an advance in human genetics because they are more comprehensive and less biased than candidate studies. Because of the unprecedented amount of hypothesis testing (and the resultant inflation of type I error), the standard in the field has been to set 'genome-wide significance' at $P \leq 5.0 \times 10^{-8}$ (or 0.05 divided by one million, the predicted number of independent common DNA variants in the human genome). This raises interesting theoretical questions about how to evaluate single candidate gene association papers achieving P-values on the order of 10^{-2} or 10^{-3} even if the history of a sample or a given locus does not include the execution of a GWAS.

GWAS have already advanced our understanding of mechanisms underlying general medical illnesses such as diabetes, Crohn's disease, and rheumatoid arthritis—as exemplified by a seminal paper published by the Wellcome Trust[47]. For MDD, there are now four published GWAS.

The first of these, by Sullivan et al[48], was facilitated by the Genetic Association Information Network (GAIN) and utilized a semi-community-based sample of 1,738 cases and 1,802 controls from the Netherlands. The authors examined 435,291 SNPs and found their top signal to be at rs1558477 (trend-test p-value of 1×10^{-6}), 12.4 kb downstream of *ADCYAP1R1*, or adenylate cyclase-activating polypeptide 1 (pituitary) receptor type I. They focused their subsequent efforts, however, on a set of 11 clustered association signals (within their top 200 findings) localized to *PCLO* (or Piccolo), a presynpatic protein which is also known as Aczonin. The authors pursued this finding with an expanded collection of close to 12,000 independent subjects, but were unable to replicate their *PCLO* findings. A retrospective analysis suggested that the *PCLO*-MDD association may only be optimally detected in population-based (as opposed to clinically-obtained) case samples such as the original GAIN MDD sample and only one of their replication samples. Although this hypothesis has not yet been tested, *PCLO* remains an intriguing candidate. Beyond a possible role in facilitating dopamine transporter internalization[49], PCLO appears to more generally negatively regulate synaptic vesicle exocytosis by decreasing transport of vesicles from reserve pools to readily-releasable pools through an action on synapsin [50]. *PCLO* is also expressed outside the CNS at such diverse locations as the neuromuscular junction[51] and in pancreatic beta cells (where it helps regulate insulin release)[52], though these are less likely to have relevance to MDD.

The second published GWAS of MDD, by Muglia et al[53], utilized a German clinic-based sample of 1,022 recurrent depression (MDD-R) cases and 1,000 controls and interrogated 494,678 SNPs. As in the Sullivan et al study, there were no genome-wide significant findings. Muglia et al performed a meta-analysis combining the first sample with a second population-based sample of Swiss origin (494 cases and 1,052 controls), and found their best signal at rs4238010 ($P = 5.8 \times 10^{-6}$), 260 kb from the closest gene (*CCND2*, or cyclin D2). A gene-based analysis obtained results generally similar to those of their original SNP-based analysis.

These authors then carried out a more focused examination of SNPs in the vicinity of a number of previously published MDD and bipolar disorder candidate loci, where they found that their most significant association lay in *GRM7* (metabotropic glutamate receptor 7) at rs162209, though this is not in linkage disequilibrium with rs1485171, the SNP previously identified by the Wellcome Trust as moderately associated with bipolar disorder at a p-value of 9.7×10^{-5}.

Additional GWAS of MDD, one derived from GenRED54 and another from STAR*D55, have followed. For simplification, we will focus on the results of a meta-analysis by Shyn et al[55], which combined results from GenRED, STAR*D, and the GAIN MDD study (i.e., Sullivan et al). The GenRED GWAS consisted of 1,020 MDD-REO cases while the STAR*D GWAS consisted of 1,221 MDD cases. Both were sampled from North American individuals of European ancestry and both shared a common set of 1,636 controls. By including subjects contributed from the publicly available GAIN MDD GWAS, there were a total of 3,956 cases and 3,428 controls in this three-sample meta-analysis. Using imputation (a method that takes known correlations between individual markers to probabilistically 'fill-in' genotypes missing in one, two, or all three studies), a total of 2,339,408 autosomal and 51,795 chromosome X SNPs were analyzed. The model was a broadly inclusive one, and treated as cases all patients with DSM-IV-defined MDD. Additional exploratory analyses, however, were also examined and included a 'narrow' analysis (MDD-REO only) and sex-specific analyses. Disappointingly, there were no genome-wide significant findings in either the primary analysis or any of the secondary analyses. Intronic markers from three genes, however, achieved meta-analysis P-values of better than 10^{-6}: *ATP6V1B2*, *GRM7*, and *SP4*. *ATP6V1B2* encodes a vacuolar protein pump ATPase subunit, and has a potentially related finding in bipolar disorder: Sklar et al[56] obtained a p-value of approximately 10^{-5} in a SNP in *ATP6V1G1*, a gene which contributes a distinct subunit to the same molecular complex. Additionally, it remains possible that the implicated *ATP6V1B2* SNP in the MDD GWAS meta-analysis may affect the adjacent gene *VMAT1* (or vesicular monoamine transporter 1). *GRM7*, which was additionally highlighted in Muglia et al (and also mentioned briefly in Sullivan et al), is perhaps the most promising finding since there is a significant body of literature linking GRM7 to the mechanistic action of mood stabilizers and antidepressants[57–59]. As a cell surface receptor, GRM7 would represent a highly tractable target for novel therapeutic agents, should subsequent studies continue to suggest a prominent role for this receptor in mood regulation. Finally, *SP4* encodes a brain-specific zinc-finger transcription factor. Most notable for *SP4*, so far, are studies demonstrating an association between bipolar disorder and *SP4*[60] and an Sp4-binding site in *GRK3* (G-protein receptor kinase 3) [61], as well as a series of murine studies demonstrating that mice with *SP4* deleted have deficits in hippocampal granule cell density in the dentate gyrus[62] and in hippocampal integrity (with resultant phenotypes in contextual memory) [63]. Adult neurogenesis of hippocampal granule cells has been linked to depression and to antidepressant action64, and so the locus of these *SP4* mutant phenotypes is intriguing. See Table 2 for a summary of published MDD GWAS to date.

Although the results of each individual GWAS and the three-study GAIN/GenRED/STAR*D meta-analysis did not reach the desired level of statistical significance, these studies do support interesting candidate genes and genomic regions for further study. Additionally, pooled analysis of multiple GWAS samples has yielded findings for other complex traits that were not apparent in any single GWAS[13, 65, 66]. With this in mind, a meta-analysis of MDD utilizing over 12,000 cases and nearly 10,000 controls is underway[67].

ENVIRONMENT

One possible explanation for poor replication of psychiatric genetic findings is insufficient consideration of gene-environment (or 'G × E') interactions. An elegant demonstration of a

possible G × E effect was reported by Caspi et al in an examination of the s/l polymorphism in *SLC6A4* (abbreviated 5HTTLPR) in 847 prospectively studied Caucasians from age 3 to 26[68]. Alone, genotypic data for this locus had little predictive value for whether an individual developed adult MDD, but, using multiple regression methodology, Caspi et al found that the number of stressful life events was significantly correlated with probability of developing MDD when one or two copies of the 's' allele were present (at a significance level of approximately $p \sim 10^{-2}$ to 10^{-3}). These findings were also robust to an examination of sequence of events (i.e., stressful life events pre-dating adult diagnosis with MDD).

Subsequent groups have employed similar approaches to the study of MDD or dimensional measures of depressive or anxious symptomatology in adults +/− a history of childhood abuse and *CRHR1* (Corticotropin-releasing hormone receptor 1) SNPs[69]—and in healthy adults +/− early life stress and the *BDNF* SNP, rs6265[70]. 'G × E' interaction studies are still relatively few in number, however, and this is likely due, in part, to difficulties inherent in standardizing or quantifying disparate life experiences as well as the challenges posed by extra instances of multiple-hypothesis testing. Finally, a recent systematic review and meta-analysis suggests that the original Caspi et al finding, when extended to the subsequent '5HTTLPR and stressful life events' literature, has only equivocal support at best[71]. A similar meta-analysis of this literature, comprising >14,000 individuals, with 1,769 having MDD, showed that serotonin transporter genotype was not associated with depression—or depression when measured in interaction with stressful life events[72].

FUTURE DIRECTIONS

Despite its unmatched impact on public health among psychiatric disorders, MDD has received only comparatively recent attention in human genetic studies because of its lower heritability, likely propensity for phenocopies, and significant clinical heterogeneity. In this review, we have summarized possible approaches to deconstructing this heterogeneity and identifying subpopulations within MDD cohorts who are likely to have enriched heritability. Additionally, we have discussed key highlights from linkage analysis, candidate and genome-wide association studies, the use of endophenotypes, and 'G × E' interaction analyses which are beginning to move our understanding of the biology of MDD from beyond the shadow of the monoamine hypothesis of depression. In the near future, efforts will likely be extended to larger collaborations and pooled analyses, to integration of disease genetics with results generated from pharmacogenomics, and, also, to the utilization of newer approaches such as analysis of copy- number variations (CNVs) and other types of genomic rearrangements. As the cost of large- scale sequencing continues to come down, next-generation sequencing approaches will undoubtedly also grow in importance and allow investigators access to rarer sequence variants, perhaps allowing for a more complete accounting of 'missing heritability.' These technologies may additionally allow efficient identification of epigenetic variation, such as cytosine methylation and histone modification, that could impact MDD risk. Finally, growing sophistication not only with 'G × E' interaction analyses, but 'G × G' (or gene x gene) interaction studies must necessarily complement these future steps.

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References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):593–602. [PubMed: 15939837]

2. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU. Sex differences in rates of depression: cross-national perspectives. J Affect Disord 1993;29(2–3):77–84. [PubMed: 8300980]
3. World Health Organization. The global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 ; summary. Published by the Harvard School of Public Health on behalf of the World Health Organization and the World Bank. Harvard University Press; Cambridge, Mass: 1996. p. 43
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disordersl: DSM-IV-TR. 4. American Psychiatric Association; Washington, DC: 2000. text revision edn
5. Schildkraut JJ, Kety SS. Biogenic amines and emotion. Science 1967;156(771):21–37. [PubMed: 5335690]
6. Deverteuil RL, Lehmann HE. Therapeutic trial of iproniazid (marsilid) in depressed and apathetic patients. Can Med Assoc J 1958;78(2):131–133. [PubMed: 13489643]
7. Kuhn R. The treatment of depressive states with G 22355 (imipramine hydrochloride). Am J Psychiatry 1958;115(5):459–464. [PubMed: 13583250]
8. Stahl SM. Blue genes and the monoamine hypothesis of depression. J Clin Psychiatry 2000;61(2):77–78. [PubMed: 10732653]
9. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157(10):1552–1562. [PubMed: 11007705]
10. Holmans P, Zubenko GS, Crowe RR, DePaulo JR Jr, Scheftner WA, Weissman MM, et al. Genomewide significant linkage to recurrent, early-onset major depressive disorder on chromosome 15q. Am J Hum Genet 2004;74(6):1154–1167. [PubMed: 15108123]
11. Levinson DF, Zubenko GS, Crowe RR, DePaulo RJ, Scheftner WS, Weissman MM, et al. Genetics of recurrent early-onset depression (GenRED): design and preliminary clinical characteristics of a repository sample for genetic linkage studies. Am J Med Genet B Neuropsychiatr Genet 2003;119B (1):118–130. [PubMed: 12707949]
12. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008;455(7215):894–902. [PubMed: 18923511]
13. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40(5):638–645. [PubMed: 18372903]
14. McGrath, PJ.; Miller, JM. Anxious Depression: Concepts, Signifiance, and Treatment Implications. In: Simpson, HB.; Neria, Y.; Lewis-Fernandez, R.; Schneier, F., editors. Understanding Anxiety. (in-press)
15. Kendler KS. The diagnostic validity of melancholic major depression in a population-based sample of female twins. Arch Gen Psychiatry 1997;54(4):299–304. [PubMed: 9107145]
16. Thase ME. Recognition and diagnosis of atypical depression. J Clin Psychiatry 2007;68 (Suppl 8): 11–16. [PubMed: 17640153]
17. Murphy-Eberenz K, Zandi PP, March D, Crowe RR, Scheftner WA, Alexander M, et al. Is perinatal depression familial? J Affect Disord 2006;90(1):49–55. [PubMed: 16337009]
18. Jones I, Hamshere M, Nangle JM, Bennett P, Green E, Heron J, et al. Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16. Am J Psychiatry 2007;164(7):1099–1104. [PubMed: 17606662]
19. Zinbarg RE, Barlow DH, Liebowitz M, Street L, Broadhead E, Katon W, et al. The DSM-IV field trial for mixed anxiety-depression. Am J Psychiatry 1994;151(8):1153–1162. [PubMed: 8037250]
20. Weisberg RB, Maki KM, Culpepper L, Keller MB. Is anyone really M.A.D?: the occurrence and course of mixed anxiety-depressive disorder in a sample of primary care patients. J Nerv Ment Dis 2005;193(4):223–230. [PubMed: 15805817]
21. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 2008;165(3):342–351. [PubMed: 18172020]
22. Hettema JM. What is the genetic relationship between anxiety and depression? Am J Med Genet C Semin Med Genet 2008;148C(2):140–146. [PubMed: 18412101]
23. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160(4):636–645. [PubMed: 12668349]

24. Levinson DF. The genetics of depression: a review. Biol Psychiatry 2006;60(2):84–92. [PubMed: 16300747]
25. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A longitudinal twin study of personality and major depression in women. Arch Gen Psychiatry 1993;50(11):853–862. [PubMed: 8215811]
26. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29(10):1765–1781. [PubMed: 15213704]
27. Mercuro G, Carpiniello B, Ruscazio M, Zoncu S, Montisci R, Rudas N, et al. Association between psychiatric disorders and Marfan's syndrome in a large Sardinian family with a high prevalence of cardiac abnormalities. Clin Cardiol 1997;20(3):243–245. [PubMed: 9068910]
28. St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, et al. Association within a family of a balanced autosomal translocation with major mental illness. Lancet 1990;336(8706):13–16. [PubMed: 1973210]
29. Levinson DF, Evgrafov OV, Knowles JA, Potash JB, Weissman MM, Scheftner WA, et al. Genetics of recurrent early-onset major depression (GenRED): significant linkage on chromosome 15q25-q26 after fine mapping with single nucleotide polymorphism markers. Am J Psychiatry 2007;164(2):259–264. [PubMed: 17267788]
30. Holmans P, Weissman MM, Zubenko GS, Scheftner WA, Crowe RR, Depaulo JR Jr, et al. Genetics of recurrent early-onset major depression (GenRED): final genome scan report. Am J Psychiatry 2007;164(2):248–258. [PubMed: 17267787]
31. Middeldorp CM, Sullivan PF, Wray NR, Hottenga JJ, de Geus EJ, van den Berg M, et al. Suggestive linkage on chromosome 2, 8, and 17 for lifetime major depression. Am J Med Genet B Neuropsychiatr Genet 2009;150B(3):352–358. [PubMed: 18615541]
32. Verma R, Holmans P, Knowles JA, Grover D, Evgrafov OV, Crowe RR, et al. Linkage disequilibrium mapping of a chromosome 15q25–26 major depression linkage region and sequencing of NTRK3. Biol Psychiatry 2008;63(12):1185–1189. [PubMed: 18367154]
33. Cloninger CR, Van Eerdewegh P, Goate A, Edenberg HJ, Blangero J, Hesselbrock V, et al. Anxiety proneness linked to epistatic loci in genome scan of human personality traits. Am J Med Genet 1998;81(4):313–317. [PubMed: 9674977]
34. Fullerton J, Cubin M, Tiwari H, Wang C, Bomhra A, Davidson S, et al. Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. Am J Hum Genet 2003;72 (4):879–890. [PubMed: 12612864]
35. Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, Del-Favero J, Claes SJ, Oostra BA, et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry 2008;13(8):772–785. [PubMed: 17938638]
36. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261(5123):921–923. [PubMed: 8346443]
37. Slifer MA, Martin ER, Gilbert JR, Haines JL, Pericak-Vance MA. Resolving the relationship between ApolipoproteinE and depression. Neurosci Lett 2009;455(2):116–119. [PubMed: 19368858]
38. Gaysina D, Cohen S, Craddock N, Farmer A, Hoda F, Korszun A, et al. No association with the 5,10-methylenetetrahydrofolate reductase gene and major depressive disorder: results of the depression case control (DeCC) study and a meta-analysis. Am J Med Genet B Neuropsychiatr Genet 2008;147B (6):699–706. [PubMed: 18165972]
39. Chen L, Lawlor DA, Lewis SJ, Yuan W, Abdollahi MR, Timpson NJ, et al. Genetic association study of BDNF in depression: finding from two cohort studies and a meta-analysis. Am J Med Genet B Neuropsychiatr Genet 2008;147B(6):814–821. [PubMed: 18205169]
40. Chen C, Glatt SJ, Tsuang MT. The tryptophan hydroxylase gene influences risk for bipolar disorder but not major depressive disorder: results of meta-analyses. Bipolar Disord 2008;10(7):816–821. [PubMed: 19032713]
41. Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, et al. Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. Neuron 2005;45(1):11–16. [PubMed: 15629698]

42. Glatt CE, Carlson E, Taylor TR, Risch N, Reus VI, Schaefer CA. Response to Zhang et al. (2005): loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. Neuron 45, 11–16. *Neuron* 2005; 48(5): 704–705; author reply 705–706.
43. Van Den Bogaert A, De Zutter S, Heyrman L, Mendlewicz J, Adolfsson R, Van Broeckhoven C *et al*. Response to Zhang et al (2005): loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major Depression. Neuron 45, 11–16. *Neuron* 2005; 48(5): 704; author reply 705–706.
44. Zhou Z, Peters EJ, Hamilton SP, McMahon F, Thomas C, McGrath PJ *et al.* Response to Zhang et al. (2005): loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. Neuron 45, 11–16. *Neuron* 2005; 48(5): 702–703; author reply 705–706.
45. International HapMap Consortium. The International HapMap Project. Nature 2003;426(6968):789–796. [PubMed: 14685227]
46. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996;273 (5281):1516–1517. [PubMed: 8801636]
47. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447(7145):661–678. [PubMed: 17554300]
48. Sullivan PF, de Geus EJ, Willemsen G, James MR, Smit JH, Zandbelt T, et al. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Mol Psychiatry 2009;14(4):359–375. [PubMed: 19065144]
49. Cen X, Nitta A, Ibi D, Zhao Y, Niwa M, Taguchi K, et al. Identification of Piccolo as a regulator of behavioral plasticity and dopamine transporter internalization. Mol Psychiatry 2008;13(4):349–363. [PubMed: 18195717]
50. Leal-Ortiz S, Waites CL, Terry-Lorenzo R, Zamorano P, Gundelfinger ED, Garner CC. Piccolo modulation of Synapsin1a dynamics regulates synaptic vesicle exocytosis. J Cell Biol 2008;181(5): 831–846. [PubMed: 18519737]
51. Tokoro T, Higa S, Deguchi-Tawarada M, Inoue E, Kitajima I, Ohtsuka T. Localization of the active zone proteins CAST, ELKS, and Piccolo at neuromuscular junctions. Neuroreport 2007;18(4):313–316. [PubMed: 17435594]
52. Shibasaki T, Sunaga Y, Fujimoto K, Kashima Y, Seino S. Interaction of ATP sensor, cAMP sensor, Ca2+ sensor, and voltage-dependent Ca2+ channel in insulin granule exocytosis. J Biol Chem 2004;279(9):7956–7961. [PubMed: 14660679]
53. Muglia P, Tozzi F, Galwey NW, Francks C, Upmanyu R, Kong XQ, et al. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. Mol Psychiatry. 2008 in press.
54. Shi J, Potash JB, Knowles JA, Weissman MM, Coryell W, Scheftner WA, et al. Genomewide association study of recurrent early-onset major depressive disorder. Mol Psychiatry. 2009 in press.
55. Shyn SI, Shi J, Potash JB, Knowles JA, Slager SL, Holmans P, et al. Novel loci for major depression identified by genome-wide association study of STAR*D and meta-analysis of three studies. Mol Psychiatry. 2009 in press.
56. Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, et al. Whole-genome association study of bipolar disorder. Mol Psychiatry 2008;13(6):558–569. [PubMed: 18317468]
57. Zhou R, Yuan P, Wang Y, Hunsberger JG, Elkahloun A, Wei Y, et al. Evidence for selective microRNAs and their effectors as common long-term targets for the actions of mood stabilizers. Neuropsychopharmacology 2009;34(6):1395–1405. [PubMed: 18704095]
58. Palucha A, Klak K, Branski P, van der Putten H, Flor PJ, Pilc A. Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. Psychopharmacology (Berl) 2007;194(4):555–562. [PubMed: 17622518]
59. Wieronska JM, Klak K, Palucha A, Branski P, Pilc A. Citalopram influences mGlu7, but not mGlu4 receptors' expression in the rat brain hippocampus and cortex. Brain Res 2007;1184:88–95. [PubMed: 17976546]
60. Zhou X, Tang W, Greenwood TA, Guo S, He L, Geyer MA, et al. Transcription factor SP4 is a susceptibility gene for bipolar disorder. PLoS ONE 2009;4(4):e5196. [PubMed: 19401786]
61. Zhou X, Barrett TB, Kelsoe JR. Promoter variant in the GRK3 gene associated with bipolar disorder alters gene expression. Biol Psychiatry 2008;64(2):104–110. [PubMed: 18359007]

62. Zhou X, Qyang Y, Kelsoe JR, Masliah E, Geyer MA. Impaired postnatal development of hippocampal dentate gyrus in Sp4 null mutant mice. Genes Brain Behav 2007;6(3):269–276. [PubMed: 16899055]
63. Zhou X, Long JM, Geyer MA, Masliah E, Kelsoe JR, Wynshaw-Boris A, et al. Reduced expression of the Sp4 gene in mice causes deficits in sensorimotor gating and memory associated with hippocampal vacuolization. Mol Psychiatry 2005;10(4):393–406. [PubMed: 15558077]
64. Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 2000;5(3):262–269. [PubMed: 10889528]
65. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40(8):955–962. [PubMed: 18587394]
66. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008;40(9):1056–1058. [PubMed: 18711365]
67. Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, et al. Psychiatric GWAS Consortium Coordinating Committee. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. Am J Psychiatry 2009;166(5):540–556. [PubMed: 19339359]
68. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301(5631):386–389. [PubMed: 12869766]
69. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, et al. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 2008;65(2):190–200. [PubMed: 18250257]
70. Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, et al. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry. 2009
71. Munafo MR, Durrant C, Lewis G, Flint J. Gene X environment interactions at the serotonin transporter locus. Biol Psychiatry 2009;65(3):211–219. [PubMed: 18691701]
72. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 2009;301(23):2462–2471. [PubMed: 19531786]
73. Nash MW, Huezo-Diaz P, Williamson RJ, Sterne A, Purcell S, Hoda F, et al. Genome-wide linkage analysis of a composite index of neuroticism and mood-related scales in extreme selected sibships. Hum Mol Genet 2004;13(19):2173–2182. [PubMed: 15351774]
74. Zubenko GS, Maher B, Hughes HB 3rd, Zubenko WN, Stiffler JS, Kaplan BB, et al. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet B Neuropsychiatr Genet 2003;123B (1):1–18. [PubMed: 14582139]
75. Camp NJ, Lowry MR, Richards RL, Plenk AM, Carter C, Hensel CH, et al. Genome-wide linkage analyses of extended Utah pedigrees identifies loci that influence recurrent, early-onset major depression and anxiety disorders. Am J Med Genet B Neuropsychiatr Genet 2005;135B(1):85–93. [PubMed: 15806581]
76. Abkevich V, Camp NJ, Hensel CH, Neff CD, Russell DL, Hughes DC, et al. Predisposition locus for major depression at chromosome 12q22–12q23.2. Am J Hum Genet 2003;73(6):1271–1281. [PubMed: 14606042]

Table 1

Summary of published MDD linkage results

A number of the studies shown here included secondary analyses which utilized covariates, sex-specific linkage, and/or alternative phenotypic definitions. For simplicity, only the primary analysis results of these studies are shown below.

chr	region (cM)[&]		LOD	phenotype	analysis model	sample size	author
1	43–70		2.2	neuroticism	non-parametric	297 sib-pairs	Nash et al[73]
1	126	*	4.0	neuroticism	non-parametric	561 sib-pairs	Fullerton et al[34]
2	237		~2	MDD-R	non-parametric	81 families	Zubenko et al[74]
3	105		3.8	MDD-REO or anxiety	parametric, dominant	611 indivs, 112 pedigrees	Camp et al[75]
4	176	*	3.8	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
5	108		~2	MDD-REO	non-parametric	81 families	Zubenko et al
5	130		~2	MDD-R	non-parametric	81 families	Zubenko et al
6	34–63		2.7	neuroticism	non-parametric	297 sib-pairs	Nash et al
7	0.1		2.9	MDD-REO or anxiety	parametric, dominant	718 indivs, 78 pedigrees	Camp et al
7	42	*	3.9	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
8	8	*	2.9	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
8	17		3.2	harm avoidance	non-parametric	758 sib-pairs	Cloninger et al[33]
11	2		4.2	MDD-R	non-parametric	81 families	Zubenko et al
11	85		2.5	MDD-REO	non-parametric	81 families	Zubenko et al
11	99	*	3.7	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
12	105	*	4.7	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
13	64	*	3.8	neuroticism	non-parametric	561 sib-pairs	Fullerton et al
15	36		2.0	MDD-R	non-parametric	81 families	Zubenko et al
15	105		2.1	MDD-REO	non-parametric	1,494 affected relative pairs	Holmans et al[30]
18	73		3.8	MDD-REO and anxiety	parametric, dominant	96 indivs, 21 pedigrees	Camp et al

[&]centimorgan (cM) map distances given in Marshfield units

*denotes -logP instead of LOD score

MDD-R = recurrent, MDD.

MDD-REO = recurrent, early-onset MDD.

Abkevich et al[76] is not tabulated above since Camp et al utilized the same Utah pedigree resource.

Camp et al used an a priori pedigree-splitting algorithm to address potential intra-familial heterogeneity in large, multi-generational pedigrees; this accounts for the varied sample sizes at different loci.

Table 2

Summary of published MDD GWAS results

None of the studies below achieved genome-wide significant findings (i.e., p-value $\leq 5 \times 10^{-8}$). Abbreviations: GWAS (genome-wide association study), ctrls (controls), GAIN (Genetic Association Information Network), GSK (GlaxoSmithKline), GenRED (Genetics of Recurrent Early-onset Depression), STAR*D (Sequenced Treatment Alternatives to Relieve Depression).

GWAS	authors	Sample	cases	ctrls	platform	markers	top findings
GAIN	Sullivan et al	semi- community- based	1,738	1,820	Perlegen Illumina 550 (1st sample), Affymetrix	435,291	*PCLO*
GSK	Muglia et al	mix of clinic- & community- based	[a]1,516	[a]2,052	5.0 (2nd sample)	[b]494,678	*CCND2*; [c]*GRM7*
GAIN, GenRED, STAR*D	Shyn et al	---	[d]3,956	[d]3,428	---	2,391,203	*ATP6V1B2*, *GRM7*, & *SP4*
meta- analysis GenRED- MGS[e]	Shi et al	Clinical	1,020	1,636	Affymetrix 6.0	662,206	[f] BC053410
STAR*D- MGS[e]	Shyn et al	Clinical	1,221	1,636	Affymetrix 500K, Affymetrix 5.0, Affymetrix 6.0	260,474	intergenic regions in 19q12, 2q23.3

[a] The Muglia et al study was a 2-stage study; case and control tallies represent the sum across their two samples.

[b] This figure represents the total number of markers analyzed across both platforms, after quality control and imputation.

[c] This was the top finding among a panel of mood disorder-related candidate genes suggested by previous literature.

[d] These figures are the sum totals for cases and controls across the three MDD GWAS studies; of note, because Sullivan et al was not yet published at the time of this meta-analysis, the exact numbers of cases and controls retained for analysis from GAIN diverged modestly. Also, with respect to controls, there were 805 individuals in common between MGS and NIMH.

[e] MGS refers to the Molecular Genetics of Schizophrenia control sample. A portion of these controls were retained (after screening-out MDD) for the GenRED and STAR*D MDD GWAS'.

[f] putative mRNA identified from pooled brain samples; no annotated gene.