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Overview of the Genetics of Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a common psychiatric illness with high levels of morbidity and mortality. Despite intensive research during the past several decades, the neurobiological basis and pathophysiology of depressive disorders remain unknown. Genetic factors play important roles in the development of MDD, as indicated by family, twin, and adoption studies, and may reveal important information about disease mechanisms. This article describes recent developments in the field of psychiatric genetics, with a focus on MDD. Early twin studies, linkage studies, and association studies are discussed. Recent findings from genome-wide association studies are reviewed and future directions discussed. Despite all efforts, thus far, no single genetic variation has been identified to increase the risk of depression substantially. Genetic variants are expected to have only small effects on overall disease risk, and multiple genetic factors in conjunction with environmental factors are likely necessary for the development of MDD. Future large-scale studies are needed to dissect this complex phenotype and to identify pathways involved in the etiology of MDD.

Keywords

Depression; Mood disorder; Linkage; Association; Genetics; SNP

Introduction

Major depressive disorder (MDD) is a common psychiatric illness with high levels of morbidity and mortality. It is estimated that 10% to 15% of the general population will experience clinical depression during their lifetime [1], and 5% of men and 9% of women will experience a depressive disorder in a given year, according to the World Health Organization [2]. Genetic factors play important roles in the development of MDD, as indicated by family, twin, and adoption studies. Twin studies suggest a heritability of 40% to 50%, and family studies indicate a twofold to threefold increase in lifetime risk of developing MDD among first-degree relatives. This degree of familial aggregation, coupled with the high heritability from twin studies, generated optimism that molecular genetic techniques would reveal genes of substantial influence on MDD risk. Unfortunately, gene localization and identification has been a slow, labor-intensive process. Genetic investigators have encountered similar frustrations with other common complex traits (eg, asthma, hypertension, and diabetes mellitus).

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The major impediments to mood disorder gene localization and identification are as follows: 1) no single gene is necessary and sufficient for MDD; 2) each susceptibility gene contributes a small fraction of the total genetic risk; and 3) complex genetic heterogeneity, meaning that multiple partially overlapping sets of susceptibility genes (which interact with the environment) can predispose individuals to similar syndromes that are indistinguishable on clinical grounds. This article provides an overview of the current efforts to identify genetic risk factors for MDD.

Twin and Family Studies

Evidence for a genetic component to mood disorders has been documented consistently using family, twin, and adoption studies. The first genetic studies of mood disorders were conducted more than 70 years ago and included assessment of concordance rates for monozygotic and dizygotic twins with mood disorders [3]. These early studies did not distinguish between bipolar depression and MDD-recurrent unipolar (MDD-RU). A recent review of twin studies in MDD-RU estimated heritability at 37%, with a substantial component of unique individual environmental risk but little shared environmental risk [4].

Family studies of MDD-RU have shown that first-degree relatives of MDD-RU probands are at increased risk of MDD-RU disorders compared with first-degree relatives of control probands [5]. There was a twofold to fourfold increased risk of MDD-RU among the first-degree relatives of MDD-RU probands. Characteristics of MDD-RU disorders that yield a more heritable phenotype include early onset (ie, before age 30 years) and a high degree of recurrence. A third characteristic that may identify a separate group of disorders is the presence of psychosis. Additional genetic subtypes of MDD-RU may be identified through examination of comorbidities with panic disorder, other anxiety disorders, and alcoholism.

Linkage Studies

Because of the epidemiologic evidence for a genetic component of MDD, the field had hoped that the identification of genetic risk factors would be straightforward. The first wave of comprehensive investigations of the genetic origins of MDD used linkage studies. Linkage studies have proven to be successful in identifying genetic risk factors for rare mendelian disorders with high penetrance, such as autosomal-dominant inherited forms of epilepsy or cystic fibrosis. The term *linkage* refers to the observation that two genetic loci found near each other on the same chromosome tend to be inherited together more often than expected by chance within families. Two such loci are said to be *linked*. The key concept of linkage is that chromosomal fragments that might harbor vulnerability genes are inherited with an illness more often then expected by chance in families.

Although some linkage studies in MDD have suggested several regions in the genome that might harbor risk alleles, findings have been inconsistent, and thus far, no established universal genetic risk factor or causative gene for depression has been identified. Although these initial results from linkage studies in MDD seem rather disappointing, they emphasize that MDD is a complex disorder with a complex mode of inheritance, that multiple genes with small effects likely are involved, and that identifying genetic factors is complicated by a significant gene–environment component.

Several MDD linkage scans have been conducted during the past several years and are reviewed in detail elsewhere [6]; however, only a few studies had a sufficient number of affected individuals (>100). Holmans et al. [7] reported on the first phase of a multisite collaborative effort (Recurrent Early-Onset Depression [GenRED] sample). The sample consisted of 297 informative multiplex families (containing 685 informative affected relative pairs, 555 sibling pairs, and 130 other pair types). Affected cases had MDD-RU

with onset before 31 years of age for probands or 41 for other affected relatives. The mean age at onset was 18.5 years, and the mean number of depressive episodes was 7.3, indicating a highly recurrent form of illness. Families were excluded if there was a first-degree or second-degree relative with bipolar disorder (BPD) [7]. Linkage was observed on chromosome 15q25.3-26.2 (empiric genome-wide P=0.023). The linkage was not sex specific. This was the sole significant linkage peak observed by this group. In the complete sample of 656 families, genome-wide suggestive linkage was confirmed on chromosome 15q and also observed on chromosomes 17p and 8p in a planned second analysis accounting for the sex of each pair of relatives [8]. Fine mapping of the 15q region demonstrated further evidence of linkage [9].

Abkevich et al. [10] reported a genome scan on 110 Utah pedigrees (each with at least four affected individuals), in which there were 784 individuals with MDD-RU, 161 with single-episode MDD, and 162 with BPD who were also considered affected. They observed a highly significant linkage signal at 12q23 [10], confirming a previously identified BPD locus. No other linkage peaks approached statistical significance. It is probable that this study detected the same BPD 12q23 locus, even though the families were ascertained from an MDD-RU proband, because most kindreds probably did have at least one BPD individual. These results confirm the findings of family and twin studies suggesting genetic overlap between BPD and MDD-RU disorders, and this study identifies the 12q23 region as a locus that increases risk of both BPD and MDD-RU disorders.

Camp et al. [11] reanalyzed the large Utah pedigrees and excluded relatives with BPD. They considered three alternative phenotypes (MDD age at onset earlier than 31 years of age, MDD or anxiety, MDD and anxiety) and identified regions with at least suggestive genome-wide evidence for linkage on chromosomes 3centr, 7p, and 18q [11]. Interestingly, the region identified on 18q with MDD and anxiety is also a well-replicated linkage finding in BPD.

Another recent genome-wide linkage scan was carried out using 497 sibling pairs concordant for recurrent depression, excluding BPD. The advantage of affected sibling pair design is that it does not require knowledge of mode of inheritance and increased power under certain conditions. Suggestive evidence of linkage was observed on chromosomes 1p36, 12q23.3-q24.11, and 13q31.1-q31.3 [12]. The 12q locus was previously implicated in linkage studies of unipolar [10] and bipolar disorders, while the 13q peak lies within a region previously linked strongly to panic disorder [13]. Middeldorp et al. [14] used 110 Australian and 23 Dutch MDD pedigrees with at least two affected siblings. The scan identified a region on chromosome 17 that includes the gene encoding the serotonin transporter (*SLC6A4*). Follow-up genotyping failed to identify the previously implicated promoter length polymorphism in *SLC6A4* to be associated with MDD, suggesting that another *SLC6A4* variant or a polymorphism in a different gene might contribute to this signal. Interestingly, they reported chromosome 8 as their most promising finding because this region has also been implicated in two previous linkage studies of personality traits, including harm avoidance [15] and neuroticism [16]. Although linkage efforts in MDD have not identified universal risk genes yet, they have provided insights into the genomic regions that might harbor genetic susceptibility factors.

Candidate Gene Studies

Candidate gene studies of unipolar depression traditionally have received less attention in the past compared with those of BPD and schizophrenia. Likely reasons for this discrepancy might be practical limitations given the much smaller expected effect size and a more heterogeneous clinical phenotype. However, with increasing sample sizes, the literature is

developing rapidly. As with other complex psychiatric disorders, there is no universal susceptibility gene for MDD. It can be expected that multiple genes with small effect sizes contribute to depression. Several candidate genes show promising preliminary results and are worth mentioning. Most candidate genes are studied using a case-control association study design. The basic principle of genetic association studies is that a genetic variant(s) is investigated in a group of cases and controls. By determining the allele or genotype frequencies and comparing them statistically, the probability that a genetic polymorphism is more frequent in one group than the other can be investigated. Hypotheses are generated based on the concept that specific variants increase or decrease risk of a certain phenotype. Genetic variants for study are usually selected based on an *a priori* hypothesis, such as neurobiologic plausibility (eg, serotonin transporter for antidepressants) or genomic location of a candidate gene (eg, in a linkage peak). More recently, "hypothesis-free" designs have been promoted with the advance of genome-wide association studies (GWAS), which space genetic markers across the whole genome based on linkage disequilibrium patterns and are discussed later; however, the resources required to conduct GWAS, including technological and clinical resources, are considerable and remain prohibitive in many instances. It is important to note that candidate gene association studies have several limitations. Such limitations include clinical and diagnostic heterogeneity, low statistical power if sample sizes are small, often-limited biological evidence of candidate gene selection, and unknown functional relevance of tested single nucleotide polymorphisms (SNPs), as well as population stratification within the sample leading to spurious positive findings or false-negative associations. Despite these obstacles, several candidate genes deserve mention, as they have been suggested repeatedly to be implicated in MDD.

Serotonin Transporter (*5HTT/SLC6A4*) and Serotonin Receptor 2A (*HTR2A*)

The serotonin transporter gene and genes involved in the serotonergic system are candidate genes for susceptibility to depression given that many antidepressant medications act on these systems. Several studies have implicated the serotonin transporter gene (*SLC6A4*) in MDD [17–19]. A 44-bp repeat polymorphism in the promoter region of the gene (*5-HTTLPR*) has been shown to influence expression levels of the serotonin transporter in vitro [20], thus making this functional variant a logical candidate for investigation in MDD. This polymorphism is the most studied genetic variant in psychiatric genetics to date. Similar to candidate gene studies in other complex psychiatric disorders, there have been some positive reports and some negative findings; additional studies are needed to dissect the exact role of this gene variant in the etiology of depressive disorders [21,22•,23].

Because the serotonin transporter gene encodes a direct target for antidepressant medications, there has been great interest in correlating genetic variation with pharmacologic treatment response [24], and the field of pharmacogenetics is rapidly developing. Results have been similarly mixed, with some studies showing a statistically significant effect of the polymorphism and others failing to do so. A recent meta-analysis of 15 published studies concluded that there was a significant association between the L allele and better treatment response to selective serotonin reuptake inhibitors [25]. Interestingly, the association between the L allele and early antidepressant treatment response was the most robust finding in this meta-analysis, suggesting that the *5-HTTLPR* might predict not only treatment response but also the time course of response and remission. A recent large-scale study using DNA samples from 1,953 patients with MDD who were treated with citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) trial investigated genetic predictors of treatment response [26]. The authors could not find evidence for *5HTT* variation influencing treatment response; however, they reported a significant effect with a marker in the serotonin receptor gene *HTR2A* and treatment outcome. As expected for a single gene, the clinical impact of *HTR2A* on treatment outcome

is modest. Although these studies face similar complexities and obstacles as disease candidate gene studies, this pharmacogenetic approach likely will yield robust results in the near future. Case-control association studies of the serotonin receptor gene *HTR2A* and major depression have yielded similar mixed results as for the serotonin transporter gene [23]. The European consortium project Genome-based Therapeutic Drugs for Depression (GENDEP) recently published its initial results. This is the first large-scale, multicenter human pharmacogenomics study focused on the prediction of therapeutic response to antidepressant drugs and adverse effects [27]. This open-label, flexible-dose, multicenter trial included 760 patients with MDD who were treated with citalopram or nortriptyline for 12 weeks. Initial analysis of ten candidate genes involved in serotonin, norepinephrine, neurotrophic, and glucocorticoid signaling revealed an association between treatment response to escitalopram and several variants in the serotonin receptor gene (*HTR2A*), with one marker (rs9316233) explaining 1.1% of the response variance. SNPs in the norepinephrine transporter gene (*SLC6A2*) predicted response to nortriptyline, and variants in the glucocorticoid receptor gene (*NR3C1*) predicted response to both antidepressants [28]. These data further support a role for the influence of genetic variants on treatment response to antidepressant drugs. Because single-marker analysis only explains a small fraction of the variance, future studies will have to use a multiple variant approach to find clinically meaningful genetic prediction algorithms.

Gene–environment interaction studies have received increasing attention, particularly for MDD, given the robust correlation between stressful life events and risk of developing depressive symptoms [17,29]. In a population-based study, Caspi and colleagues [21] noted that individuals with one or more copies of the short allele of the *5HTT* promoter variants were at increased risk of depression depending on the occurrence of adverse life events. This article describes a plausible gene–environment interaction that may help explain the conflicting results for the *5HTT* promoter variant noted above. Positive and negative replication studies have demonstrated the complexity of detecting these effects. Similar gene–environment interactions have been demonstrated for variants in the *HTR2A* gene and childhood maternal nurturance and depressive symptoms in adulthood [30]. Future genetic studies of depression will need to pay close attention to these gene–environment interactions.

Brain-Derived Neurotrophic Factor

Growing evidence suggests an important role for brain-derived neurotrophic factor (BDNF) in affective disorder [31,32]. Preclinical animal studies have consistently documented a role of BDNF in neurogenesis [33], and animal models of depression further substantiate a role of BDNF in mood disorders. Decreased BDNF levels in the hippocampus have been reported in animals exposed to chronic stress [34]. Interestingly, administration of anti-depressants increased hippocampal BDNF, preventing the stress-induced decrease [35]. These findings are intriguing given the hippocampal volume loss observed in mood disorders and decreased BDNF serum levels in individuals with mood disorders or depressive personality traits [32]. Based on these convergent preclinical and clinical data, the *BDNF* gene represents a logical target for genetic investigations of mood disorders.

Although there is stronger literature support for a genetic association between the Val66Met polymorphism in the *BDNF* gene and BPD, several studies have also investigated this SNP in MDD. Results have been similarly mixed, as with most other candidate genes for depression. Schumacher et al. [36] examined 465 individuals with MDD but did not find a significant association with the Val66Met polymorphism. However, there was evidence of a haplotypic association [36]. Surtees and colleagues [37] failed to detect an association of the Val66Met polymorphism in 1,214 individuals with a history of MDD, while studies of this polymorphism in Asian populations yielded inconsistent results. Despite these mixed and

negative results, interpretation of these data should be carried out with caution given the complex structure of the gene and the fact that most studies have only investigated the Val66Met SNP. It is likely that other variation in the *BDNF* gene influences susceptibility to depression [38].

Tryptophan Hydroxylase

Tryptophan hydroxylase is the rate-limiting enzyme in brain serotonin synthesis. The discovery of a new brain-specific isoform of the tryptophan hydroxylase (*TPH2*) has generated new interest in the connection between serotonergic systems and depression [39]. The *TPH2* gene is located on chromosome 12q, a region previously implicated in linkage studies of BPD.

Zill et al. [40] reported the first evidence of an association of variants in the *THP2* gene and major depression. Zhang et al. [41] identified a functional polymorphism (Arg441His) that results in about 80% loss of function in serotonin production when expressed in a cell system. The authors also reported that this rare mutation was not seen in 219 healthy controls but was seen in 9 of 87 individuals with major depression [41]. However, subsequent replication attempts by other groups for this rare variant were negative. Haplotypic associations of sets of markers across the *TPH2* gene have yielded positive results [42] and, interestingly, variants were associated with suicidal behavior [43,44]. Deficits in brain serotonin synthesis secondary to genetic variation in the *TPH2* gene might represent an important risk factor for unipolar depression.

In light of these multiple positive and negative reports for various candidate genes, several recent meta-analyses have tried to dissect the genetic factors of depression. The hope was that by combining several underpowered small studies into one large study, the meta-analysis would have sufficient power to detect risk alleles. One of the most comprehensive meta-analyses in depression was recently published and included 183 articles covering 393 polymorphisms in 102 genes [45]. The study showed a potential role for variants in the genes *APOE* (apolipoprotein E), *GNB3* (guanine nucleotide-binding protein β-3), *MTHFR* (methylene tetrahydrofolate reductase), and *SLC6A4* (serotonin transporter). Lopez-Leon et al. [45] observed that the S allele of the *5-HTTLPR* conferred a small increase of risk of MDD, with an OR of 1.11; however, another meta-analytic study focusing only on the *5-HTTLPR* variant recently yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or both sexes combined [22•]. Although several limitations exist in the interpretation of genetic meta-analyses (eg, publication bias and which studies are included and excluded), the overall picture is that no strong susceptibility gene or set of genetic markers for MDD could be identified.

Genome-Wide Association Studies

With the rapid development of technological advances in genomics, it is now possible to genotype 500,000 to 1 million SNPs across the genome in cases and healthy controls. This GWAS design has the advantage that no genes are preselected (as is the case in candidate gene studies), and robust findings might identify new pathways involved in mood disorders. Limitations of this approach are the immense amount of data, costs, and issues regarding multiple testing [46]. The stringent statistical correction for multiple testing might mask true signals from genes that confer only modest risk of disease [47,48]. Currently, the genome-wide significance level is set ($P<10^{-7}$ to $P<10^{-8}$). Despite these obstacles, the first results in complex medical disorders such as Crohn's disease, diabetes, and rheumatoid arthritis have emerged from GWAS [49], and several GWAS have been published for psychiatric disorders [50].

Thus far in depression, five large GWAS have been published [51•,52–55]. Sullivan et al. [51•] used a semi–community-based sample of 1,738 cases and 1,802 controls with MDD collected through the Genetic Association Information Network and conducted a GWAS of 435,291 SNPs. There was no genome-wide significant finding; however, they found 11 SNPs associated with MDD that are localized to a 167-kb region overlapping the gene piccolo (*PCLO*), a presynpatic protein also known as *aczonin* that is important in monoaminergic neurotransmission in the brain. A replication attempt of the initial finding failed to reach the significance threshold in five independent samples (6,079 MDD independent cases, 5,893 controls). Additional studies are needed to investigate the role of *PCLO* in MDD and central nervous system neurotransmission. The second published GWAS of MDD used a German clinic-based sample of 1,022 recurrent depression cases and 1,000 controls and investigated 494,678 SNPs [53]. Similar to the Sullivan et al. [51•] study, none of the SNPs were statistically significant after correction for multiple testing. The authors then performed a meta-analysis combining their first sample with a second sample of Swiss origin (494 cases, 1,052 controls) and found their best signal at rs4238010, 260 kb from the closest gene (*CCND2*, or cyclin D2); however, they still did not achieve genome-wide significance. Another recent GWAS of recurrent, early-onset MDD (GenRED) with onset before 31 years of age investigated 671,424 SNPs in 1,020 cases and 1,636 controls [56]. Again, no genome-wide significant evidence for association was observed. The strongest evidence for association was observed on chromosome 18q22.1 (rs17077540) in a region previously implicated in linkage scans in BPD. Recently, an additional GWAS of MDD was published that included the STAR*D sample of 1221 MDD cases [55]. In addition, the authors conducted a meta-analysis using three samples (Genetic Association Information Network, GenRED, STAR*D) with a total of 3,956 cases and 3,428 controls. There were no genome-wide significant findings in the primary analysis or any of the secondary analyses. Some intronic markers in the meta-analysis were close to genome-wide significance levels (ie, $P<10^{-6}$) and included the genes *ATP6V1B2*, *GRM7*, and *SP4*. The SNP in the *ATP6V1B2* gene is in close proximity to the adjacent gene *VMAT1* (vesicular monoamine transporter 1), previously implicated in BPD [56]. *GRM7* encodes a cell surface receptor and might be an interesting new target for drug development. Interestingly, weak signals were also observed by Muglia et al. [53] and Sullivan and colleagues [51•] for this gene. The gene *SP4* encodes a brain-specific zinc finger transcription factor, and several studies have shown an association between *SP4* and an *SP4*-binding site in *GRK3* (G-protein receptor kinase 3) and BPD [57]. The most recently published GWAS of MDD by Lewis et al. [52] also failed to identify genome-wide significant genetic variants contributing to major depression. The authors included 1636 cases of depression ascertained in the United Kingdom and 1594 controls. One SNP in the *BICC1* gene achieved suggestive evidence for association. A meta-analysis of United Kingdom data with previously published results from Muglia et al [53] showed some evidence for association near neuroligin-1 (*NLGN1*) on chromosome 3 but did not support findings at *BICC1*.

Although the results of these five GWAS in MDD were all essentially negative, they do suggest interesting candidate genes that may be worthwhile to follow up in future studies. It is becoming increasingly clear that individual genetic susceptibility factors for depression are likely to have only minor effects, and very large pooled analyses of cases and controls will be necessary to identify them [50]. One of the first attempts of these large-scale analyses recently yielded interesting results. A meta-analysis that used GWAS data from BPD and MDD cohorts, including more than 13,600 individuals, identified six SNPs at 3p21.1 associated with major mood disorders (rs2251219; $P = 3.63 \times 10^{-8}$; OR, 0.87) [58•]. Supportive evidence for association was observed in two of three independent replication cohorts. These results provide an example of a shared genetic susceptibility locus for BPD and MDD and point out that perhaps our current dichotomous conceptualization of mood disorders is incorrect.

Conclusions and Future Directions

The field of psychiatric genetics in general has been disappointing given that the initial hope to find common gene variants of large effect in the pathogenesis of mental illnesses has been unsuccessful. In most psychiatric illnesses, the phenotype seems too complex, with the patient cohorts too small, and no findings have been consistently replicated. This is also the case for MDDs. In addition, the phenotypic effects of genetic variants identified to date are weak, with ORs of 1.0 to 1.2. The picture is further complicated when comparing the magnitude of the impact of gene variation on disease susceptibility with the impact of lifestyle and environmental factors, which is likely to be large [59]. Despite these obstacles, the field of psychiatric genetics is rapidly growing, and several new technological advances (eg, whole-genome sequencing) will be soon available for large-scale studies. It is important to remember that genetic information will only provide additional information on one aspect of the complex and personal history of psychiatric patients. It is the sum of inside and outside factors that contributes and influences mental pathology and well-being.

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