Unipolar depression: Genetics

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INTRODUCTION

Unipolar depression is a major public health problem associated with increased functional disability and mortality. The illness likely represents a group of heterogeneous disorders that are phenotypically similar [1]. Depression can thus be considered the final common pathway of different disease processes that occur across a biopsychosocial continuum. Efforts to understand the pathogenesis of depression, including its genetic basis, are intended to discern these different diseases or subtypes.

This topic reviews the genetic basis of unipolar depression. Other aspects of the pathogenesis of unipolar depression are discussed separately, as are the neurobiology, clinical features, assessment, diagnosis, and initial treatment of unipolar depression:

- (See "Unipolar depression: Pathogenesis".)
- (See "Unipolar depression: Neurobiology".)
- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)

DEFINITIONS OF DEPRESSION

The term "depression" can be used in multiple ways, which can be confusing; depression may refer to a [2,3]:

- Mood state, as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement, or hopelessness; having no feelings; or appearing tearful. Depressed (dysphoric) mood may be normal or a symptom of a psychopathological syndrome or a general medical disorder.

- Syndrome, which is a constellation of symptoms and signs that may include depressed mood. Depressive syndromes that are typically encountered include major depression, minor depression, or dysthymia (persistent depressive disorder).

- Mental disorder that identifies a distinct clinical condition. As an example, the syndrome of major depression can occur in several disorders, such as unipolar major depression (also called "major depressive disorder"), bipolar disorder, schizophrenia, substance/medication-induced depressive disorder, and depressive disorder due to another (general) medical condition.

GENETICS OF UNIPOLAR DEPRESSION

Unipolar major depression is likely due to genetic effects as well as environmental influences specific to the individual, with altered gene expression occurring during brain development and in response to stress [4-9]. Genes probably contribute vulnerability toward depression that requires additional nongenetic environmental factors to produce the disorder.

Evidence of genetic effects — Evidence that genetic effects are involved in the pathogenesis of unipolar depression includes the following:

- In a meta-analysis of six twin studies involving more than 21,000 individuals [6] and a subsequent study of more than 15,000 twin pairs [4], the concordance rate for major depression in monozygotic twins was 37 and 38 percent. Thus, environmental factors accounted for most of the risk for major depression.

- A national registry study identified monozygotic and dizygotic twin pairs, full siblings who were reared together or apart, and half siblings who were reared together or apart (total n >1.7 million pairs), to estimate the proportion of risk for unipolar major depression that was due to genetic factors or variation (heritability) [10]. The relative contribution of genetic factors to major depression in males was 36 to 41 percent and in females was 49 to 51 percent; the remaining contribution was attributable to either nonshared or shared environmental factors.

In addition, it appears that the genetic basis of major depression stems from multiple small genetic effects. A genome-wide association meta-analysis of seven studies included patients with unipolar depressive syndromes (n >130,000) and nondepressed controls (n >340,000) and found 44 independent and significant loci; 30 were newly discovered and 14 were previously identified [11]. Gene expression patterns in the prefrontal cortex and anterior cingulate, areas involved in executive functions and emotion, differed between cases and controls.

Although some studies have failed to identify genes associated with major depression [12-16], these failures may be due to the heterogeneity of the disorder [17]. A genome-wide association study (GWAS) minimized heterogeneity by examining only Chinese women (n >5000) with recurrent episodes of major depression and no substance use disorders prior to onset of major depression; the controls (n >5000) were individuals who had no personal or family psychiatric history [18]. Two loci on chromosome 10 were associated with major depression, and the findings were replicated in a separate sample of Chinese cases and controls.

Another reason that some studies have failed to identify causal loci for unipolar major depression is that their small effects necessitate large samples. Relatively large studies that have identified genes associated with depression include the following:

- A meta-analysis of three GWAS data sets, which included more than 130,000 patients with a history of depressive syndromes and more than 340,000 controls, identified 15 independent loci (17 single nucleotide polymorphisms) associated with depression [19]. Some of these variants were replicated in a subsequent study [20].

- A genome-wide association meta-analysis of seven studies found 44 significant loci, utilizing data from more than 130,000 patients with unipolar depressive syndromes and more than 340,000 controls [11].

- A meta-analysis of three GWAS data sets required more than 160,000 individuals to identify two genetic variants associated with depressive symptoms [21].

However, the validity of the results may be limited because several studies identified cases of depression based upon self-report data rather than administering structured interviews [8].

Some studies have focused upon both genes and environmental factors, and how their interaction causes depression; however, the findings have not been consistently replicated [22,23]. As an example, several studies reported that an interaction between the short allele of the serotonin transporter gene and stressful life events increased the risk for depression [24-26]. However, a meta-analysis of 14 studies (n >14,000 participants) found that the serotonin transporter genotype did not add anything to the prediction of increased risk of depression

associated with stressful life events and thus failed to confirm this association [27]. One plausible mechanism by which gene-environment interactions may lead to depression is epigenetic changes [28]. (See 'Epigenetics' below.)

General information about genetics and medical illnesses is discussed separately. (See "Basic genetics concepts: DNA regulation and gene expression".)

Sex differences — Multiple studies suggest that the genetic factors involved in unipolar depression differ between females and males:

- Genetic factors seem to play a larger role for depression in females than males [10]. As an example, one twin study found that the heritability of major depression was higher in women compared with men (42 versus 29 percent) [4].

- The interaction between genetic effects and environmental influences may differ between females and males. A study of adolescents (n >1000) found that in females, the *5-HTTLPR* SL genotype was associated with a decreased risk of depressive symptoms independent of social context [29]. However, among males, the protective effect occurred only in the context of socioeconomic deprivation.

- Gene expression (transcription) appears to differ between females and males with depression:

  - A meta-analysis of three studies examined gene expression across three brain regions, using postmortem brains from subjects with unipolar major depression (24 females and 26 males) and from sex-matched controls [30]. Among depressed females and female controls, there were 882 differentially expressed genes (524 upregulated and 358 downregulated). Among depressed males and male controls, there were 706 genes that were differentially expressed (252 upregulated and 454 downregulated). Only 73 differentially expressed genes were shared by both females and males with depression, and 52 of these were changed in the opposite direction.

  - A study examined gene expression in six brain regions, using postmortem brains from people with unipolar major depression (n = 13 males and 13 females) and control subjects (n = 13 males and 9 females) [31]. Gene expression in all six regions differed between female depressed subjects and female controls, and differed between male depressed subjects and male controls. In addition, the overlap between female and male depressed subjects was only 5 to 10 percent, depending upon the brain region. The findings were largely replicated in a second set of subjects (n = 50).

The sexual dimorphism in the genetics of depression is consistent with differences between women and men in the prevalence of unipolar major depression, which occurs twice as often in women. (See "Unipolar depression in adults: Epidemiology", section on 'Sex'.)

Age of onset — Genetic factors may be involved in age of onset of major depression.

A twin study suggests that familial/genetic loading for major depression is high in depressed patients with an early age of onset (eg, age 18 years) [32]. Among patients with a late age of onset of major depression (eg, age 60 years), familial/genetic loading for vascular disease appears to be high, which is consistent with multiple studies that found late-life depression is associated with vascular dysfunction. (See "Unipolar depression: Neurobiology", section on 'Vascular function'.)

Gene expression — Ribonucleic acid sequencing of postmortem tissue from patients with unipolar major depression and healthy controls indicates that gene expression (transcription) is altered in unipolar major depression:

- A study of gene expression in the postmortem dorsolateral prefrontal cortex of patients with unipolar major depression (n = 69) and nonpsychiatric controls (n = 286) found that expression of the gene neuregulin 3 was greater in patients [33].

- A study analyzed gene expression patterns in the cerebral cortex of postmortem brains (n = 700) from patients with unipolar major depression, alcoholism, autism, bipolar disorder, or schizophrenia, as well as matched healthy controls (n = 293) [34]. Differential gene expression in the patients overlapped between major depression and schizophrenia, and between major depression and bipolar disorder.

Epigenetics — Epigenetic changes refers to modifications of chromosomes that do not alter the nucleotide base sequence, but nevertheless increase or decrease gene expression. Examples include methylation of DNA or acetylation of histones. These modifications may occur in response to environmental factors such as adverse life events or chronic stress, and may thus serve as a mechanism by which adversity increases the risk of mental illness [35,36]. The changes are heritable in that they are passed down from one cell to another and in some cases may be passed onto offspring. In contrast to DNA sequence variation, epigenetic changes are reversible. Additional information about epigenetics is discussed separately. (See "Principles of epigenetics".)

Different epigenetic changes are associated with unipolar depression, and may contribute to differential gene expression in depression. Although a causal role for epigenetic changes in the

pathophysiology of depression has not been demonstrated, evidence that implicates epigenetic factors includes the following:

- A study examined six monozygotic twin pairs (12 individuals) who were discordant for a lifetime history of an anxiety or depressive disorder; most of the largest methylation differences between the twins were found in genes previously associated with neuropsychiatric disorders, including depression [37].

- A prospective study enrolled pregnant women with a lifetime history of depression (current or past, n = 29) and pregnant women with no history of psychiatric disorder (n = 15), and examined DNA methylation of T lymphocytes from neonatal cord blood [38]. The analyses found 145 differentially methylated CG-sites in T lymphocytes of offspring from the depression group, compared with controls.

- A prospective study of 132 adolescents found that adversity in the form of lower socioeconomic status at baseline was associated with greater methylation of the serotonin transporter gene two years later and greater methylation was associated with larger increases in amygdala reactivity to fearful facial expression [39]. Increases in threat-related amygdala reactivity were subsequently associated with greater increases in depressive symptoms one year later in adolescents with a family history of depression.

- A meta-analysis of 10 studies assessed blood sample methylation levels and depressive symptoms in more than 11,000 individuals; after controlling for potential confounding variables (eg, age, sex, and smoking status), the analyses found that three methylated sites were associated with increased depressive symptoms [28].

DNA methylation may represent accelerated aging, and can be used as a marker of biological age by generating a score that correlates with chronologic age. A prospective study enrolled 811 subjects with a lifetime diagnosis of major depression and 319 controls with no history of depressive disorders, and examined all methylation sites in blood samples [40]. After adjusting for potential confounding factors (eg, sex, body mass index, alcohol use, and number of chronic diseases), the analyses showed that epigenetic aging was higher in depressed subjects. In addition, a dose-response effect was observed, such that greater epigenetic aging was associated with greater levels of depressive symptoms. Epigenetic aging was also associated with a history of childhood trauma. The difference in epigenetic aging between depressive cases and controls was replicated in postmortem brain tissue from a separate sample of 74 depressed subjects and 64 controls [40].

PHARMACOGENETICS

Genetic factors in patients with unipolar depression may influence response to antidepressants:

- A meta-analysis of five studies (n = 544 White patients) reported that polymorphisms related to expression of the serotonin transporter gene (5-HTTLPR, located on chromosome 17) were associated with remission of depression in patients treated with selective serotonin reuptake inhibitors (odds ratio 2.4, 95% CI 1.6-3.6) [41].

- A subsequent meta-analysis found that besides 5-HTTLPR, two genes located on chromosome 11 were associated with efficacy of antidepressant treatment [42]. These were TPH1 (seven studies, 754 patients of mixed ancestry, odds ratio 1.6), which is involved in serotonin synthesis, and brain-derived neurotrophic factor (four studies, 490 patients, odds ratio 1.6). There were also associations between polymorphisms of different genes and side effects.

- A subsequent genome-wide association study of 706 patients of European ancestry found that other genes were also associated with therapeutic response to antidepressants [43]. Polymorphisms of the uronyl 2-sulphotransferase gene, which is involved in neurogenesis and is located on chromosome 6, were associated with response to the tricyclic nortriptyline. Response to the selective serotonin reuptake inhibitor escitalopram was best predicted by a gene that encodes the cytokine interleukin-11 and is located on chromosome 19. In addition, an intergenic region on chromosome 1 and another on 10 were associated with response to either antidepressant (these regions do not code for genes but may influence the expression of certain genes).

Information about the role of genetic factors in antidepressant pharmacokinetics, as well as general information about genetic factors and drug metabolism and response, are discussed separately. (See "Overview of pharmacogenomics".)

GENETIC OVERLAP WITH OTHER MENTAL DISORDERS

Different studies suggest that many of the genes putatively involved in the pathogenesis of unipolar major depression may have pleiotropic effects and confer risk for other types of psychopathology [19,44]. Patients with shared risk genes may develop different psychiatric disorders because of other genes that are not shared, as well as environmental influences and epigenetic factors. However, some authorities think that the overlap in genetic risk factors, along with the lack of distinct genetic and clinical boundaries between psychiatric patients and

normal individuals, indicates that psychiatric nosology is not composed of discrete disorders and needs to be reconceptualized [45-47].

Evidence of shared heritability among psychiatric disorders includes the following:

- A study pooled meta-analyses of genome-wide association study (GWAS) data sets for 10 psychiatric disorders (cases >150,000 and controls >360,000) to look for genetic variants associated with the disorders [46]. The analyses found shared genetic variants across the disorders, especially unipolar major depression, attention deficit-hyperactivity disorder (ADHD), bipolar disorder, and schizophrenia. In addition, positive genetic correlations were found for unipolar major depression and neuroticism (marked by fearfulness, worrying, and irritability), and between depression and smoking initiation. A negative correlation was identified for depression and years of education.

- In a genome-wide association meta-analysis of seven studies, which included patients with unipolar depressive syndromes (n >130,000) and controls (n >340,000), 44 independent and significant loci were identified, six of which are also associated with schizophrenia [11]. In addition, there were positive genetic correlations between major depression and anorexia nervosa, anxiety disorders, ADHD, autism spectrum disorder (ASD), and bipolar disorder.

- A meta-analysis of GWAS data sets included patients with unipolar major depression, ADHD, ASD, bipolar disorder, or schizophrenia (total n >33,000), as well as healthy controls (and 27,000 controls); one single nucleotide polymorphism on chromosome 3 and two on chromosome 10 were each associated with all five disorders [48].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Unipolar depression likely represents a group of heterogeneous disorders that are phenotypically similar. Efforts to understand the pathogenesis of depression, including its genetic basis, are intended to discern these different diseases or subtypes. (See 'Introduction' above and "Unipolar depression: Pathogenesis".)

- Unipolar major depression is likely due to multiple small genetic effects as well as environmental influences specific to the individual. Different studies suggest that the relative contribution of genetic factors to major depression ranges from approximately 35 to 50 percent. (See 'Genetics of unipolar depression' above and 'Evidence of genetic effects' above.)

- Genetic factors involved in unipolar depression appear to play a larger role in females than males, and gene expression (transcription) appears to differ between females and males with depression. (See 'Sex differences' above.)

- Gene expression (transcription) is altered in unipolar major depression. (See 'Gene expression' above.)

- Epigenetic changes refers to modifications of chromosomes that do not alter the nucleotide base sequence, but nevertheless increase or decrease gene expression. Different epigenetic changes are associated with unipolar depression, and may contribute to differential gene expression in depression. These modifications may occur in response to environmental factors such as adverse life events or chronic stress, and may thus serve as a mechanism by which adversity increases the risk of mental illness. (See 'Epigenetics' above.)

- Genetic factors in patients with unipolar depression may influence response to antidepressants. (See 'Pharmacogenetics' above.)

- Many of the genes putatively involved in the pathogenesis of unipolar major depression may have pleiotropic effects and confer risk for other types of psychopathology. (See 'Genetic overlap with other mental disorders' above.)

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