Review Article

Genetic biomarkers of depression

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Depression is a term that has been used to describe a variety of ailments, ranging from minor to incapacitating. Clinically significant depression, termed as major depression, is a serious condition characterized not only by depressed mood but also by a cluster of somatic, cognitive, and motivational symptoms. Significant research efforts are aimed to understand the neurobiological as well as psychiatric disorders, and the evaluation of treatment of these disorders is still based solely on the assessment of symptoms. In order to identify the biological markers for depression, we have focused on gathering information on different factors responsible for depression including stress, genetic variations, neurotransmitters, and cytokines and chemokines previously suggested to be involved in the pathophysiology of depression. The present review illustrates the potential of biomarker profiling for psychiatric disorders, when conducted in large collections. The review highlighted the biomarker signatures for depression, warranting further investigation.

Key words: Cytokines, depression, genetic variability, neurotransmitters, stress

Introduction

Depression is a term that has been used to describe a variety of ailments, ranging from minor to incapacitating. Clinically significant depression, termed as major depression, is a serious condition characterized not only by depressed mood but also by a cluster of somatic, cognitive, and motivational symptoms. Major depression can be differentiated from a normal and transient sad mood by several factors, such as intensity, as major depression causes impairment in social or occupational functioning and persists across time and situations.

Relationship to antecedent events, as major depression either occurs without any identifiable antecedent event or, is clearly in excess of what would be considered an expected reaction. Emotion being different from that experienced in a normal sad mood. Associated features are the mood co-occurs with a group of other cognitive and somatic symptoms. Individuals who are suffering from major depression often report feeling overwhelmed, helpless, despairing, suffocated, or numb.

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Factors responsible for depression

Stress

Stress is a term that means different things to different people, but generally has a negative connotation.[1] Stress is a familiar aspect of modern life and is a stimulant for some individuals, but a problem for many others. Stress has been defined as a constellation of events, which begins with a stimulus (stressor) that precipitates a reaction in the brain (stress perception), which subsequently activates physiologic systems in the body (stress response).[2,3] The physiologic stress response results in the release of neurotransmitters and hormones that serve as the brain's messengers to the rest of the body. The consequences of this physiologic response are generally adaptive in the short run, but can be damaging when stress is chronic and long lasting.[4,5] Chronic stress is long-term, negative stress that has become detrimental to the individual, while acute stress is short-term, positive stress that is relatively harmless to the individual and

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often gives an extra burst of energy that is needed during the stressful period. An important marker of the deleterious effects of chronic stress is a breakdown in the regulation of the circadian corticosterone rhythm in rodents and cortisol rhythm in humans.[6] Chronic stress seems to be linked to the etiology of many diseases. A number of studies have shown that stress can be immunosuppressive and hence that it can be detrimental to health. Moreover, glucocorticoid stress hormones are regarded widely as immunosuppressive[7] and are used clinically as anti-inflammatory agents.[8]

Genetic variability

Genetic factors have been implicated in the etiology of depression and many studies have determined that changes in protein structure correlate with a predisposition to specific conditions. More than 10 million single nucleotide polymorphisms (SNPs) have been identified in humans; however, the importance of most SNPs for health and disease is not understood. Most SNPs are indeed unimportant and because of often inadequately powered studies, many observations on SNP effects cannot be repeated by other researchers. SNPs are at best shown to influence protein function or level, rarely to influence risk of disease, and almost never to influence total mortality, the ultimate endpoint. However, specific genes or relevant DNA sequence variations involved in the pathogenesis of depression have not yet been identified.

Major depressive disorder (MDD) is common and moderately heritable. Recurrence and early age at onset characterize cases with the greatest familial risk. MDD and the neuroticism personality trait have overlapping genetic susceptibilities. Most genetic studies of MDD have considered a small set of functional polymorphisms relevant to monoaminergic neurotransmission. Meta-analyses suggest small positive associations between the polymorphism in the serotonin transporter promoter region (5-HTTLPR) and bipolar disorder, suicidal behavior, and depression-related personality traits but not yet to MDD itself. This polymorphism might also influence traits related to stress vulnerability. Newer hypotheses of depression neurobiology suggest closer study of genes related to neurotoxic and neuroprotective (neurotrophic) processes and to overactivation of the hypothalamic–pituitary axis, with mixed evidence regarding association of MDD with polymorphisms in one such gene brain-derived neurotrophic factor (BDNF).[9]

MDD has been a growing public health concern due to its recurrent, deliberate, and lethal nature. According to projections, MDD will become the second leading cause of disability worldwide by the year 2020.[10] By the year 2030, it is estimated to be the highest cause of disability in high-income countries and still the second cause of burden of disease globally. Having been recognized as a multifactorial disease, the total contribution of genetic factors in the origin of disease, the heritability, is estimated at nearly 40%.[11] Notably, the mode of inheritance is complex and ambiguous. Thus, relevant DNA sequence variations in potential candidate genes contributing to the susceptibility to MDD remain to be explored. Studies on norepinephrine and serotonin pathways have highlighted the molecular role of these neurotransmitter systems in the pathophysiology of MDD. Nevertheless, the role of dopamine (DA) neurotransmission in MDD has gained increasing attention since the earliest report in the mid-1970s.[12] Clinically, changes in both serotonergic and dopaminergic activity have been observed in patients with MDD receiving long-term treatment with antidepressants.[13] Also, therapy using dopaminergic agents in treatment-resistant patients with MDD has been demonstrated to enhance the action of antidepressant medications.[14] Furthermore, antidepressants with direct dopaminergic effects have been well documented.[15] Research findings have consistently emphasized the molecular connection between genes associated with dopaminergic activity and the pathophysiology of MDD.[16,17] The dopaminergic system, which consists of DA-producing cells, DA receptors and DA transporters (DAT1, also referred to as SLC6A3), may play a crucial role in MDD. In particular, DAT1 proteins play a significant role in the reuptake of DA into presynaptic neurons and limit the duration of synaptic activity, thus being the key regulators of DA level in the brain. In humans, the DAT1 gene, located at chromosome 5q35.1, contains 15 exons,[18,19] and its expression occurs in all DA neurons, including those originating in the substantia nigra and ventral tegmentum.[20] Although several lines of evidence suggest an association between

DA and MDD, few studies have directly explored the molecular link between MDD and polymorphisms in such main dopaminergic gene as DAT1. Until recently, the C/T single nucleotide polymorphism (SNP) in intron 14 of the DAT1 gene, also referred to as rs40184, has been demonstrated to moderate the effect of perceived maternal-rejection on the onset of MDD, as well as on suicidal ideation, thus signifying a gene-by-environment (G x E) interaction in the etiology of MDD.[21] This particular SNP has also been found to play a genetic role in certain neuropsychiatric and neurological illnesses such as attention deficit hyperactivity disorder, bipolar disorder,[22] and migraine with aura.[23]

The norepinephrine transporter (NET), a Na/Cl-dependent substrate specific transporter, terminates noradrenergic signaling by rapid reuptake of neuronally released norepinephrine into presynaptic terminals. NET exerts a fine regulated control over norepinephrine-mediated physiological effects such as depression. As the 50 flanking promoter region of the NET gene, NET T-182C, contains several *cis* elements that play a critical role in transcription regulation,[24,25] changes in this promoter DNA structure may lead to an altered transcriptional activity responsible for a predisposition to MDD.[26] Although a silent G1287A polymorphism, located at exon 9 of the NET gene, is not an important factor in susceptibility to depression in a Japanese population,[27] but it cannot be denied that it may be an important candidate. BDNF is a nerve growth factor that has antidepressant-like effects in animals and may be implicated in the etiology of mood-related phenotypes. However, genetic association studies of the BDNF Val66Met polymorphism (SNP rs6265) in MDD have produced inconsistent results. Meta-analysis of studies compared the frequency of the BDNF Val66Met-coding variant in depressed cases (MDD) and non-depressed controls. MDD is more prevalent in women and in Caucasians and because BDNF allele frequencies differ by ethnicity. BDNF Val66Met polymorphism is of greater importance in the development of MDD in men than in women.[28] In order to further clarify the impact of BDNF gene variation on major depression as well as antidepressant treatment response, association of three BDNF polymorphisms [rs7103411, Val66Met (rs6265) and rs7124442] with major depression and antidepressant treatment response was investigated.[29] All SNPs had main effects on antidepressant treatment response. Results do not support an association between genetic variation in BDNF and antidepressant treatment response or remission. Preliminary studies suggest a potential minor role of genetic variation in BDNF and antidepressant treatment outcome in the context of melancholic depression.[30] Identification of novel genetic polymorphisms in the BDNF gene and assessment of their frequencies and associations with MDD or antidepressant response. Novel single-nucleotide polymorphisms (SNPs), untranslated regions, in coding sequences, in introns, and upstream regions; 3 of 4 rare novel coding SNPs were non synonymous. Association analyses of patients with MDD and controls showed that 6 SNPs were associated with MDD (rs12273539, rs11030103, rs6265, rs28722151, rs41282918, and rs11030101) and two haplotypes in different blocks (one including Val66, another near exon VIIIh) were significantly associated with MDD. One recently reported 5' untranslated region SNP, rs61888800, was associated with antidepressant response after adjusting for age, sex, medication, and baseline score on the 21-item Hamilton Depression Rating Scale.[31]

Alterations in BDNF-signaling pathways may play an important role in the pathophysiology of MDD. Five SNPs in three BDNF signal-transduction pathway genes (BDNF, GSK3B, and AKT1) were used in association analyses. An allelic association between the GSK3B SNP rs6782799 and MDD was found in our samples. Further gene-gene interaction analyses showed a significant effect of a two-locus BDNF/GSK3B interaction with MDD (GSK3B rs6782799 and BDNF rs7124442) and also for a three-locus interaction (GSK3B rs6782799, BDNF rs6265, and BDNF rs7124442). These findings support the assertion that the GSK3B gene is an important susceptibility factor for MDD in a Han Chinese population.[32]

Mounting evidence shows that brain-derived neurotrophic factor (BDNF) plays a crucial role in synaptic plasticity. Normally, BDNF sustains the viability of brain neurons. Under stress, however, BDNF gene is repressed, leading to atrophy and possible apoptosis

of vulnerable neurons in the hippocampus when their neurotrophic factor BDNF is absent. These events in turn lead to depression and to the consequences of repeated depressive episodes, namely, more and more episodes and less and less responsiveness to treatment. Due to its potential involvement in psychiatric diseases such as depression, BDNF became a major target in research. A functional polymorphism of the BNDF Val66Met influences and reduces trafficking and secretion of BDNF protein in the brain and is thought to be associated with low BNDF levels in MDD.[33-36]

Neurotransmitters

The monoamine hypothesis proposes that depression is due to a deficiency in monoaminergic neurotransmission. Developed out of a meticulous research effort in modern psychiatry, the monoamine hypothesis is an early milestone in the field of depression. Under this hypothesis, depression is postulated to reflect a deficiency or imbalance in noradrenaline or serotonin. Several antidepressant drugs increased synaptic concentrations of noradrenaline or serotonin and that reserpine, a catecholamine-depleting drug, could cause depression-like symptoms. Catecholamine depletion by dietary methods has also been shown to induce a relapse of depressive symptoms. Subsequent variations of the monoamine hypothesis were supported by animal research, including the findings that antidepressants effectively treat learned helplessness. Currently, the evolving monoamine hypothesis considers the possibility that depression may be linked to a deficiency in signal transduction from the monoamine neurotransmitter to its postsynaptic neuron in the presence of normal amounts of neurotransmitter and receptor.

The 5-HTT gene regulates brain serotonin neurotransmission by removing the neurotransmitter from the extracellular space. Since the development of the selective serotonin reuptake-inhibitors, a putative role for 5-HTT in the etiology of depression has been explored. The discovery of a functional 5-HTT polymorphism has provided a novel tool to further scrutinize the role of serotonergic neurons in depression. A repeat of 20-23 base pairs has been observed as a motif within a polymorphic region of the 5-HTT gene and it occurs as two prevalent alleles: one consisting of 14 repeats (S allele) and another of 16 repeats (L allele). This functional polymorphism in the promoter region, termed 5-HTTLPR, alters transcription of the serotonin transporter gene. The S allele leads to less transcriptional efficiency of serotonin[37,38] and it can partly account for anxiety-related personality traits.

Two serotonin 2A receptor (HTR2A) SNPs recently reported to be associated with antidepressant treatment response in STARD (rs7997012; rs1928040) for association with treatment response in two independent Caucasian samples of patients with a Major Depressive Episode. SNP rs7997012 was significantly associated with remission after 5 weeks providing first replicative support for the initial finding, with however, an inverse allelic association as compared to the STARD sample.[39] Another common polymorphism is a variable number tandem repeat (VNTR) in intron 2 (STin2), which has three alleles consisting of either 9 (STin2.9), 10 (STin2.10), or 12 (STin2.12) repeats, were shown to be in linkage disequilibrium, with the positive association between the STin2 allele 10 and the 5-HTTLPR L allele.[40] Variation at the VNTR can also influence expression of the transporter with the polymorphic VNTR regions acting as transcriptional regulators[41] although it is likely to have no significant effect on function. Tryptophan hydroxylase (TPH) is the enzyme involved in the biosynthesis of serotonin. It catalyzes the oxygenation of tryptophan to 5-hydroxytryptophan, which is decarboxylated to serotonin.[42] It is thus the rate-limiting enzyme in the biosynthesis of serotonin. Changes in the metabolism of the essential amino acid tryptophan play an important role in the brain-endocrine-immune system interaction that is hypothesized to be involved in the pathophysiology of MDD. There are two main pathways of tryptophan metabolism: one is the serotonin pathway and the other is the kynurenine (KYN) pathway.[43] Dysfunction of the serotonergic system has been hypothesized to play an important role in depression. The higher serotonergic activity during stress leads to a higher breakdown of serotonin. Sustained stress will lead to diminution of serotonin (synthesis/degradation). Thus, chronic stress may lead to functional shortage of the supply of serotonin. Two genes have been discovered which encode for the TPH isoforms

(TPH1 and TPH2). Most of the molecular genetic studies on the TPH genes so far have examined the two polymorphisms of the TPH1, A218C and A779C, which have been found to be in complete or strong linkage disequilibrium in previous studies.[44] A polymorphism in intron 7 of TPH1, A218C, has been extensively examined in association studies, and the A allele is associated with anxiety symptoms in depression.[45] There is no association between the TPH2 polymorphisms and stress-induced depression.[46,47] Catechol-O-methyltransferase (COMT) is an important enzyme involved in the degradation of catecholamine neurotransmitters. Depression is thought to involve, in part, dysregulation of serotonergic neurotransmission. A Val158Met polymorphism affects the activity of the COMT enzyme and individuals with the Val/Val genotype have a 3–4 times higher enzyme activity than those with the Met/Met genotype.[48] One of the European study reported an association between the Val/Val genotype and early onset MDD,[49] but conflicting results have been found in other studies with fewer participants.[50] As serotonin exerts its effect on specific receptors on the postsynaptic membranes, the serotonin receptor (5-HTR) genes are considered good candidates. The 5-HTRs affect the release and activity of other neurotransmitters such as glutamate, DA, and gamma-aminobutyric acid (GABA). There are seven main types of 5-HTRs. Including subtypes, there are a total of at least 14 different receptors based on their pharmacological responses to specific ligands, sequence similarities at the gene and amino acid levels, gene organization, and second messenger coupling pathways.[51] Several subtypes, including the 5-HTR1A, 5-HTR1B, 5-HTR2A, 5-HTR3, and 5-HTR4, act to facilitate neurotransmitter DA release, while the 5-HTR2C receptor mediates an inhibitory effect of serotonin on DA release. Most 5-HTR subtypes only modulate DA release when serotonin and/or DA neurons are stimulated, but the 5-HTR2C, characterized by high levels of constitutive activity, inhibits tonic as well as evoked DA release.[52] The 5-HTR1A is an important member of the large family of serotonin receptors.[53] The 5-HTR1A is located both at a postsynaptic and at a presynaptic level, in the first case, they mediate the action of serotonin on cortical and limbic neurons and in the second case, they act as serotonergic autoreceptors on serotonergic neurons in the raphe nuclei and prevent the release of serotonin by negative feedback.[54] In depressed individuals, the number of serotonin receptors, including the 5-HTR1A autoreceptors, is increased.[55] A common functional polymorphism C-1019G in the promoter region of the human 5-HT1A receptor gene has been reported, which may be useful in identifying psychopathology associated with altered function of the human 5-HT1A receptor.[56] DOPA decarboxylase is an enzyme implicated in two metabolic pathways, synthesizing two important neurotransmitters, DA and serotonin.[57] Following the hydroxylation of tyrosine to form 3,4-dihydroxy-Lphenylalanine (L-DOPA), catalyzed by tyrosine hydroxylase (TH), DDC decarboxylates L-DOPA to form DA. The TH is the initial and rate-limiting enzyme in the biosynthesis of catecholamine neurotransmitters and has been a candidate for possible involvement in the development of psychiatric illness.[58] Among polymorphisms in the TH gene identified so far, a pentaallelic polymorphism consisting of several numbers of tetranucleotide repeats [or microsatellite polymorphism (TCAT)n] in intron 1 and three SNPs, namely Val81Met, Leu205Pro, and Val468Met, may alter the functional activity of TH protein. A tetranucleotide repeat in intron 1 has been reported to play a role in psychiatric illnesses.[59-61] DA is the most abundant catecholaminergic neurotransmitter in the brain and is involved in the regulation of emotions, motivation, reward, and reinforcement behavior through the mesocorticolimbic pathway.[62] Preclinical and clinical studies incriminate the dopaminergic system in affective disorders. While hyperfunction of the dopaminergic system may lead to manic behavior, its hypofunction may lead to depressive symptoms.[63,64] DA, functioning at dopamine D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors, crucially influences both the induction and the reversal of neuroplasticity at corticostriatal synapses. These two subfamilies have different pharmacologic properties, signal transduction properties, and genomic organization. The receptors of the D1-like subfamily stimulate cAMP synthesis through coupling with Gs-like proteins, and their genes do not contain introns within their protein coding regions. The receptors of the D2-like family inhibit cAMP synthesis through their interaction with Gi-like proteins and share a similar genomic organization, which

includes introns within their protein-coding regions.[65] On the basis of sequence similarity, the G subunits have been divided into four families (Gi, Gs, Gq, and G12). Heterotrimeric guanine nucleotide-binding proteins (G proteins) are signal transducers and are attached to the cell surface plasma membrane that connects receptors to effectors and thus to intracellular signaling pathways.[66] Receptors that couple to G proteins communicate signals from a large number of hormones, neurotransmitters, chemokines, and autocrine and paracrine factors. Many important hormones and neurotransmitters, including epinephrine, acetylcholine, DA, and serotonin, use the Gi and Go pathways to evoke physiological responses. *In vitro* and *in vivo* studies suggested that the -141C Ins/Del polymorphism may be directly responsible for the regulation of DRD2 expression and DRD2 function.[67] Ser311Cys in DRD2 has been reported to be associated with a reduced ability of activating the appropriate Gi-like protein.[68] Brain imaging studies of healthy volunteers have shown that individuals with an A1 allele (C allele of C32806T) of DRD2 have a reduced number of dopamine D2 receptors.[69,70] The DRD3 Ser9Gly genotypes were reported to differ with regard to their DA-binding affinity.[71] The most widely studied polymorphism of DRD4 is a 48-bp variable number of tandem repeats (VNTRs) which encodes for the third intracytoplasmic loop and contains 2–11 repeats.[72] A 48-base pairs repeat in exon 3 of DRD4 was associated with the potency of inhibition of cAMP formation by DA.[73] The DRD4 48-base pairs repeat in the exon 3 was significantly associated with major depression while the DRD2 Ser311Cys and DRD3 Ser9Gly polymorphisms were not.[74] These polymorphisms may be hypothesized to influence MDD. These polymorphisms have been reported to increase the susceptibility to depression, although negative findings have also been reported.

GABA is the main inhibitory neurotransmitter in the mammalian central nervous system and regulates many physiological and psychological processes. Both animal and human studies associate variations in GABA in the mammalian forebrain with anxiety and depression.[75] The GABAA receptor is the site of action for anxiolytic drugs of the benzodiazepine and barbiturate classes. Also, GABA concentrations are increased with selective serotonin reuptake inhibitors (SSRIs), the other major drug class currently used to treat ANX as well as depressive disorders. Thus, GABA is strongly implicated in multiple anxiety-related processes. Although GABA acts through both GABAA and GABAB receptors to decrease neurotransmission.[76] In particular, several studies have documented altered benzodiazepine binding at cerebral GABAA receptors in panic disorder.[77,78] Functional GABAA receptors are typically constructed of five subunits drawn from eight different classes (α, β, etc.). Each subunit is encoded by a distinct gene and differentially expressed in the brain, suggesting that mutation in any one gene could, in principle, contribute to the symptoms of anxiety-related disorders. The GABAA α2 subunit, primarily expressed in the limbic system, likely mediates the anxiolytic effects of benzodiazepines.[79] The gene that encodes this protein, GABRA2, has been associated with alcohol dependence in several studies.[80,81] ANX is known to have high co morbidity rates with alcoholism, and one study suggests that part of the association of this gene with alcohol dependence may be accounted for by anxious temperament.[82] Pharmacological studies have specifically implicated the GABAA α3 subunit in anxiety.[83] Genetic studies of GABRA3 gene also support its potential role in mood disorder phenotypes. Recent studies provided evidence that mice with global deletion of the GABRA3 gene had more depression-related behaviors.[84] The human GABRA3 gene is located in Xq28 region, an area that has been linked to the genetic transmission of bipolar affective disorder.[85] Genetic association has been reported between the GABRA3 and both bipolar[86] and unipolar[87] mood disorders, although earlier studies failed to detect these associations.[88,89] GABRA6 is involved in several factors contributing to ANX pathology. Sen and colleagues (1991)[90] reported an association between a GABRA6 receptor coding polymorphism and neuroticism a personality trait related to both anxiety and depression. Variation in GABRA6 has also been associated with increased production of cortisol and increased blood pressure in response to psychological stress.[91] A broad role of GABRG2 in anxiety-related behavior was demonstrated, whereby γ2 heterozygous mice with resulting reduced GABAA receptor clustering showed increased fear of a novel environment.[92]

S100B is a neurotrophic factor that is involved in neuroplasticity. Neuroplasticity is disrupted in depression; however, treatment with antidepressants can restore neuroplasticity. S100B has previously been used as a biological marker for neuropathology and neuroplasticity. The difference in the serum S100B levels between depressive patients and normal controls and between antidepressant responders and non-responders was compared. Serum S100B level is associated with the subsequent response to antidepressants. The high baseline serum S100B level that was observed in depressive patients may enhance neuroplasticity, which results in a favorable therapeutic response to antidepressants.[93]

Nontraditional gene candidates such as PCLO and GRM7 are now emerging and beginning to change the landscape for future human and animal research on depression.[94]

Immune biomarkers

A role of inflammation in depression was first proposed by Smith (1991).[95] Since then, several studies have reported a link between MDD, or depressive symptoms, and a variety of inflammatory and immune biomarkers.[96-98] Depression may cause inflammation through altered neuroendocrine function and central adiposity.[99] However, depression may also be a consequence of inflammation, since a pathogenic role of inflammatory cytokines in the etiology of depression has been described.[100] Although given less consideration, a third possibility is that depression is a marker of some other underlying dimension that is separately linked to depression and inflammation. Recently, it has been proposed that such underlying factor could be a specific genetic makeup.[101]

MPO is an enzyme of the innate immune system, which exhibits a wide array of proatherogenic features.[102] MPO is secreted upon leukocyte activation, contributing to innate host defenses. However, it also increases oxidative stress, thereby contributing to tissue damage during inflammation and atherogenesis. MPO generates numerous reactive oxidants that cause lipid peroxidation, posttranslational modifications to target proteins, and decrease of nitricoxide bioavailability resulting into oxidation of low density lipoproteins LDL and apolipoprotein A1, protein carbamylation, and endothelial dysfunction.[103] Transgenic mice containing the human MPO gene show significantly larger atherosclerosis build up than the wild type.[104] In humans, individuals with total or subtotal MPO deficiency, a defect with a frequency of 1 in every 2000 to 4000 whites, are less likely to develop cardiovascular diseases and those harboring a promoter polymorphism associated with a 2-fold reduction in MPO expression appear cardioprotected.[103] Oxidative stress has also been linked to neuronal degeneration in the central nervous system.[105] MPO is both expressed and enzymatically active in the human brain and is associated with Alzheimer's disease.[106] Earlier studies have described abnormalities of oxidant–antioxidant systems in MDD suggestive of higher oxidative stress. For example, elevated levels of antioxidant enzymes, particularly superoxide dismutase (SOD) and biomarkers of oxidation, such as malondialdehyde, were found in plasma, red blood cells, or other peripheral tissues of acutely depressed MDD patients compared with controls. In some cases,[107] but not others, [108] these abnormalities were reduced with antidepressant treatment. SOD coenzyme concentrations are also higher in postmortem brain tissue (prefrontal cortex) of MDD patients than in control brains.[109] Overall, twins with MDD had 32% higher levels of MPO than those without MDD, an association that was not explained by other risk factors. Other inflammatory biomarkers, except TNF-α, tended to be elevated in twins with MDD, in contrast to MPO however, these associations became weaker and mostly nonsignificant after adjusting for behavioral and coronary heart disease CHD risk factors. Depressive symptoms were not correlated with MPO, and adjustment for Beck Depression Inventory BDI score in the analysis did not alter the results for any of the biomarkers. It is possible that MPO is a more specific indicator of brain immune activation than other inflammatory biomarkers. MPO is a myeloid-specific enzyme produced by activated phagocytic cells, including brain microglia. In contrast, inflammatory cytokines are produced by a variety of cell types, while acute-phase proteins such as CRP and fibrinogen are mostly secondary products in response to cytokine signaling.[110] Thus, MPO is potentially a more specific marker of microglial immune activation

and therefore more relevant for MDD and other brain disorders.

When compared with non-depressed individuals, both medically ill and medically healthy patients with major depression have been found to exhibit all of the cardinal features of inflammation, including elevations in relevant inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid (CSF), as well as elevations in peripheral blood concentrations of acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins.[111,112] Associations between inflammatory markers and individual depressive symptoms such as fatigue, cognitive dysfunction, and impaired sleep have also been described.[113,114] For example, both dysregulated sleep in depressed patients and sleep deprivation have been associated with increased interleukin (IL-6), as well as activation of nuclear factor kappa B (NF-κB), a primary transcription factor in the initiation of the inflammatory response.[114,115] Although much of the interest in inflammation and depression has been focused on cytokines, which mediate the innate immune response, including IL-1β, tumor necrosis factor TNF-α and IL-6 which appears to be one of the most reliable peripheral biomarkers in major depression,[112,116] findings of increased markers of T cell activation (e.g., soluble IL-2 receptor) in depressed patients raises the specter that both acquired (e.g., T and B cell) and innate (e.g., macrophage) immune responses may be involved.[116] Nevertheless, in contradistinction to the prominence of depression following administration of innate immune cytokines such as interferon IFN α to humans,[117,118] administration of the T cell cytokine, IL-2, is not uncommonly associated with profound changes in mental status including psychosis, delirium and agitation.[119] In addition to correlative data linking inflammatory markers with depressive symptoms, several lines of evidence demonstrate that both acute and chronic administration of cytokines or cytokine inducers such as lipopolysaccharide (LPS) or vaccination can cause behavioral symptoms that overlap with those found in major depression. For example, normal volunteers injected with LPS exhibited acute increases in symptoms of depression and anxiety[120] and administration of a *Salmonella typhi* vaccine to healthy individuals produced depressed mood, fatigue, mental confusion, and psychomotor slowing.[121] In both cases, symptom severity correlated with increases in peripheral blood cytokine concentrations. These data in humans are consistent with a large literature in laboratory animals demonstrating that cytokines and cytokine inducers can lead to a host of behavioral changes overlapping with those found in depression, including anhedonia, decreased activity, cognitive dysfunction, and altered sleep.[122] Long-term exposure to cytokines has also been shown to lead to marked behavioral alterations in humans. For example, 20-50% of patients receiving chronic IFN- α therapy for the treatment of infectious diseases or cancer develop clinically significant depression. Of note, depressive syndromes induced by IFN-α exhibit considerable overlap with idiopathic major depression and like idiopathic major depression, respond to conventional antidepressant medication.[117,118] The inflammatory signaling molecule, NF-κB, has been found to be an essential mediator at the blood–brain interface that communicates peripheral inflammatory signals to the central nervous system CNS. Central blockade of NF-κB in rodents inhibits c-fos activation in multiple brain regions following peripheral administration of IL-1β while also inhibiting IL-1β- and LPS-induced behavioral changes.[123] Data indicate that peripheral cytokine signals can also access the brain in humans and activate relevant cell types that serve to amplify central inflammatory responses. For example, peripheral administration of IFN-α to patients with hepatitis C led to increased CSF IFN-α which correlated with increased CSF concentrations of IL-6 and the chemokine, monocyte chemoattractant protein (MCP-1). Monocyte chemoattractant protein-1, which is released by astrocytes and endothelial cells, has been found to prime microglia to produce IL-1 and TNF- α in response to LPS in rodents, an effect that is reduced in MCP-1 KO animals.[124]

Once cytokine signals reach the brain, they have the capacity to influence the synthesis, release, and reuptake of mood-relevant neurotransmitters including the monoamines. Literature on animals demonstrating that administration of cytokines or cytokine inducers can profoundly affect the metabolism of serotonin,

nor-epinephrine, and DA.[125,126] Moreover, drugs (serotonin and nor-epinephrine reuptake inhibitors) and gene polymorphisms (serotonin transporter gene) that affect monoamine metabolism have been shown to influence the development of cytokine-induced depressive-like behavior in laboratory animals and humans.[127,128] Regarding the mechanisms involved, much attention has been focused on the enzyme, indoleamine 2,3 dioxygenase (IDO). Through stimulation of multiple inflammatory signaling pathways, including signal transducer and activator of transcription 1a (STAT1a), interferon regulatory factor (IRF)-1, NF-κB, and p38 mitogen-activated protein kinase (MAPK), cytokines can activate IDO.[129] Indoleamine 2,3 dioxygenase, in turn, breaks down tryptophan (TRP), the primary amino acid precursor of serotonin, into KYN. The breakdown of TRP is believed to contribute to reduced serotonin availability.[122,130] Supportive of the role of IDO in cytokine-induced depression, decreased TRP and increased KYN in the peripheral blood have been associated with the development of depression in patients administered IFN-α. Moreover, blockade of IDO has been shown to inhibit the development of LPS-induced depressive-like behavior in mice. Of note, cytokine-induced IDO activation and the generation of KYN appear to have important effects on neurotransmitters and mood independent of effects on serotonin. Administration of KYN alone has been shown to induce depressive-like behavior in mice.[131] In addition, based on the differential expression of relevant metabolic enzymes, KYN is preferentially converted to *kynurenic* acid (KA) in astrocytes and quinolinic acid (QUIN) in microglia.[130] KA has been shown to inhibit the release of glutatmate, which, by extension, may inhibit the release of DA, whose release is regulated in part by glutamatergic activity.[132] Indeed, intrastriatal administration of KA has been shown to dramatically reduce extracellular DA in the rat striatum.[133] In contrast, QUIN promotes glutamate release through activation of *N*-methyl-D-aspartate (NMDA) receptors. QUIN also induces oxidative stress, which in combination with glutamate release may contribute to CNS excitotoxicity.[134-137] Thus, the relative induction of KA versus QUIN may determine the effects of cytokines on the CNS and remains an important area for future investigation, including the therapeutic targeting of IDO and KYN enzymatic pathways. Cytokines also have been shown to influence the synthesis of DA. Intramuscular injection of recombinant, species-specific IFN-α to rats has been shown to decrease CNS concentrations of tetrahydrobiopterin (BH4) and DA in association with the stimulation of nitric oxide (NO). Tetrahydrobiopterin is an important enzyme cofactor for tyrosine hydroxylase, which converts tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) and is the rate-limiting enzyme in DA synthesis. Tetrahydrobiopterin is also required for NO synthesis, and therefore increased NO generation is associated with increased BH4 utilization (thus decreasing the availability of BH4 to support tyrosine hydroxylase activity). Treatment with an inhibitor of NO synthase was found to reverse the inhibitory effects of IFN-α on brain concentrations of both BH4 and DA.[138] Activation of microglia is associated with increased NO production suggesting that cytokine influences on BH4 via NO may be a common mechanism by which cytokines reduce DA availability in relevant brain regions. Cytokines and their signaling pathways can also influence the reuptake of monoamines. Mitogen-activated protein kinase pathways, including p38 and extracellular signal-regulated kinases (ERK) 1/2, which mediate the effects of cytokines on cell proliferation/differentiation and apoptosis, as well as gene expression of inflammatory mediators, increased the activity of membrane transporters for serotonin and DA, as well as norepinephrine.[139,140] IL-1β and TNF-α have been shown to significantly increase serotonin reuptake in rat brain synaptosomes through activation of p38 MAPK.[140] Of note, activated p38 in peripheral blood mononuclear cells has been associated with decreased CSF concentrations of the serotonin metabolite, 5-hydroxyindoleactectic acid (5-HIAA), in juvenile Rhesus monkeys that were maternally abused as infants.[141] Extending these findings, recent data in humans administered IFN-α have revealed that decreased CSF 5-HIAA was correlated not only with depressed mood but also increased CSF IL-6, which is capable of activating both MAPK and IDO pathways.[111] Taken together with the influence of cytokines on monoamine synthesis, these data suggest that cytokines may exert a “double hit” on both monoamine synthesis and reuptake, thus contributing to reduced monoamine availability.

Conclusions

It is concluded that the biomarkers such as genetic mutations, neurotransmitters, and cytokines can be used further for the identification of depressive conditions in the patients. At present, the mechanism for the development of depression is not well understood. Therefore, further research is required to understand the molecular basis at cellular level for its effective treatment.

References

1. Straub RH, Dhabhar FS, Bijlsma JW, Cutolo M. How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis. Arthritis Rheum 2005;52:16-26.
2. Dhabhar FS, McEwen BS. Acute stress enhances while chronic stress suppresses immune function *in vivo*: A potential role for leukocyte trafficking. Brain Behav Immun 1997;11:286-306.
3. Dhabhar FS, McEwen BS. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc Natl Acad Sci U S A 1999;96:1059-64.
4. Dhabhar FS, McEwen BS. Stress-induced enhancement of antigenspecific cell-mediated immunity. J Immunol 1996;156:2608-15.
5. McEwen BS. Protective and damaging effects of stress mediators: Allostasis and allostatic load. N Engl J Med 1998;338:171-9.
6. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst 2000;92:994-1000.
7. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;5:25-44.
8. Schleimer RP, Claman HN, Oronsky A, editors. Anti-inflammatory steroid action: Basic and clinical aspect. San Diego: Academic Press Inc.; 1989.
9. Levinson DF. The genetics of depression: A review. Biol Psychiatry 2006;60:84-92.
10. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436-42.
11. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. Am J Psychiatry 2000;157:1552-62.
12. Randrup A, Munkvad J, Fog R, Gerlach J. Molander L, Kjellberg B. Mania, Depression, and Brain Dopamine. In: Essman W, Valzelli L, editors. Current Developments in Psychopharmacology. Vol. 2. New York: Spectrum Publications; 1975. p. 206-48.
13. Bonhomme N, Esposito E. Involvement of serotonin and dopamine in the mechanism of action of novel antidepressant drugs: A review. J Clin Psychopharmacol 1998;18:447
14. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. J Clin Psychiatry 1998;59:60-3.
15. Robinson DS. The role of dopamine and norepinephrine in depression. Prim Psychiatry 2007;14:21-3.
16. Davidson RJ, Pizzagalli D, Nitschke JB. The Representation and Regulation of Emotion in Depression. Perspectives from Affective Neuroscience. In: Gotlib IH, Hammen CL, editors. Handbook of Depression. New York: Guilford; 2002. p. 219-44.
17. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007;64:327-37.
18. Giros B, el Mestikawy S, Godinot N, Zheng K. Cloning, pharmacological characterization, and chromosome assignment of the human dopamine transporter. Mol Pharmacol 1992;42:383-90.
19. Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA. Human dopamine transporter gene (DAT1) maps to chromosome 5p15,3 and displays a VNTR. Genomics 1992;14:1104-6.
20. Ciliax BJ, Heilman C, Demchyshyn LL, Pristupa ZB. The dopamine transporter: Immunochemical characterization and localization in brain. J Neurosci 1995;15:1714-23.
21. Haeffel GJ, Getchell M, Koposov RA, Yrigollen CM. Association between polymorphisms in the dopamine transporter gene and depression: Evidence for a gene-environment interaction in a sample of juvenile detainees. Psychol Sci 2008;19:62-9.
22. Mick E, Kim JW, Biederman J, Wozniak J. Family based association study of pediatric bipolar disorder and the dopamine transporter gene (SLC6A3). Am J Med Genet B Neuropsychiatr Genet 2008;147:1182-5.
23. Todt U, Netzer C, Toliat M, Heinze A, Goebel I, Nürnberg P, *et al*. New genetic evidence for involvement of the dopamine system in migraine with aura. Hum Genet 2009;125:265-79.
24. Cohen S, Rosa A, Corsico A, Sterne A, Owen M, Korzsun A, *et al*. The brain derived neurotrophic factor (BDNF) Val66Met polymorphism and recurrent unipolar depression. Am J Med Genet B Neuropsychiatr Genet 2004;130:37-8.
25. Kim CH, Kim HS, Cubells JF, Kim KS. A previously undescribed intron and extensive 50 upstream sequence, but not Phox2a-mediated transactivation, are necessary for high level cell type-specific expression of the human norepinephrine transporter gene. J Biol Chem 1999;274:6507-18.
26. Meyer J, Wiedemann P, Okladnova O, Bruss M, Staab T, Stober G, *et al*. Cloning and functional characterization of the human norepinephrine transporter gene promoter. J Neural Transm 1998;105:1341-50.
27. Chang CC, Lu RB, Chen CL, Chu CM, Chang HA, Huang CC. Lack of association between the norepinephrine transporter gene and major depression in a Han Chinese population. J Psychiatry Neurosci 2007;32:121-8.
28. Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vásquez A, Buitelaar JK, *et al*. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: Effects of gender and ethnicity. Mol Psychiatry 2010;15:260-71.
29. Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed

JF, *et al*. BDNF variation and mood disorders: A novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. Neuropsychopharmacol 2005;30:1353-61.
30. Domschke K, Lawford B, Laje G, Berger K, Young R, Morris P, *et al*. Brain-derived neurotrophic factor (BDNF) gene: No major impact on antidepressant treatment response. Int J Neuropsychopharmacol 2010;13:93-101.
31. Licinio J, Dong C, Wong ML. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch Gen Psychiatry 2009;66:488-97.
32. Zhang K, Yang C, Xu Y, Sun N, Yang H, Liu J, *et al*. Genetic association of the interaction between the BDNF and GSK3B genes and major depressive disorder in a Chinese population. J Neural Transm 2010;117:393-401.
33. Arias B, Catalan R, Gasto C, Gutierrez B, Fananas L. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. J Clin Psychopharmacol 2003;23:563-7.
34. Duman RS, Charney DS. Cell atrophy and loss in major depression. Biol Psychiatry 1999;45:1083-4.
35. Lee HY, Kim YK. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology 2008;57:194-9.
36. Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, *et al*. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 2003;23:8788-99.
37. Heils A, Moßner R, Lesch KP. The human serotonin transporter gene polymorphism-basic research and clinical implications. J Neural Transm 1997;104:1005-14.
38. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D. Allelic variation of human serotonin transporter gene expression. J Neurochem 1996;66:2621-4.
39. Lucae S, Ising M, Horstmann S, Baune BT, Arolt V, Müller-Myhsok B, *et al*. HTR2A gene variation is involved in antidepressant treatment response. Eur Neuropsychopharmacol 2010;20:65-8.
40. Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry 1996;1:453-60.
41. McKenzie A, Quinn J. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc Natl Acad Sci U S A 1999;96:15251-5.
42. Abbar M, Courtet P, Amadéo S, Caer Y, Mallet J, Baldy-Moulinier MC, *et al*. Suicidal behaviors and the tryptophan hydroxylase gene. Arch Gen Psychiatry 1995;52:846-9.
43. Peroutka SJ. 5-Hydroxytryptamine receptor subtypes. Ann Rev Neurosci 1988;11:45-60.
44. Nielsen DA, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M. Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatry 1994;51:34-8.
45. Du L, Bakish D, Hrdina PD. Tryptophan hydroxylase gene 218A/C polymorphism is associated with somatic anxiety in major depressive disorder. J Affect Disord 2001;65:37-44.
46. Gizatullin R, Zaboli G, Jonsson EG, Asberg M, Leopardi R. The tryptophan hydroxylase (TPH) 2 gene unlike TPH-1 exhibits no association with stress-induced depression. J Affect Disord 2008;107:175-9.
47. Jokela M, Raikkonen K, Lehtimaki T, Rontu R, Keltikangas-Jarvinen L. Tryptophan hydroxylase 1 gene (TPH1) moderatesthe influence of social support on depressive symptoms in adults. J Affect Disord 2007;100:191-7.
48. Christenson JG, Dairman W, Udenfriend S. On the identity of DOPA decarboxylase and 5-hydroxytryptophan decarboxylase (immunological titration-aromatic L-amino acid decarboxylase-serotonin-dopamine-norepinephrine). Proc Natl Acad Sci U S A 1972;69:343-7.
49. Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melén K, Julkunen I, *et al*. Kinetics of human soluble and membrane-bound catechol - O-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry 1995;34:4202-10.
50. Massat I, Souery D, Del-Favero J, Nothen M, Blackwood D, Muir W, *et al*. Association between COMT (Val158Met) functional polymorphism and early onset in patients with major depressive disorder in a European multicenter genetic association study. Mol Psychiatry 2005;10: 598-605.
51. Ohara K, Nagai M, Suzuki Y, Ohara K. Low activity allele of the catechol-O-methyltransferase gene and Japanese unipolar depression. Neuroreport 1998;9:1305-8.
52. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71:533-54.
53. Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol Ther 2007;113:296-320.
54. Pucadyil TJ, Chattopadhyay A. Cholesterol modulates the antagonist-binding function of hippocampal serotonin1A receptors. Biochim Biophys Acta 2005;1714:35-42.
55. Kapur S, Remigton G. Serotonin–Dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996;153:466-76.
56. Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, Van Heertum RL, Arango V, Mann JJ. Altered serotonin 1A binding in major depression: A (carbonyl-C-11) WAY100635 positron emission tomography study. Biol Psychiatry 2006;59:106-13.
57. Inoue K, Itoh K, Yoshida K, Higuchi H, Kamata M, Takahashi H, *et al*. No association of the G1287A polymorphism in the norepinephrine transporter gene and susceptibility to major depressive disorder in a Japanese population. Biol Pharm Bull 2007;30:1996-8.
58. Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin Psychiatry 1998;59:11-4.
59. Lim LC, Gurling H, Curtis D, Brynjolfsson J, Petursson H, Gill M. Linkage between tyrosine hydroxylase gene and affective disorder cannot be excluded in two of six pedigrees. Am J Med Genet 1993;48:223-8.
60. Serretti A, Macciardi F, Verga M, Cusin C, Pedrini S, Smeraldi E. Tyrosine hydroxylase gene associated with depressive symptomatology in mood disorder. Am J Med Genet 1998;81:127-30.
61. Souery D, Lipp O, Mahieu B, Mendelbaum K, De Bruyn A, De Maertelaer V, *et al*. Excess of tyrosine hydroxylase

restriction fragment length polymorphism homozygosity in unipolar but not bipolar patients: A preliminary report. Biol Psychiatry 1996;40:305-8.
62. Furlong RA, Rubinsztein JS, Ho L, Walsh C, Coleman TA, Muir WJ, *et al*. Analysis and metaanalysis of two polymorphisms within the tyrosine hydroxylase gene in bipolar and unipolar affective disorders. Am J Med Genet 1999;88:88-94.
63. Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 1990;347:146-51.
64. Willner P, Muscat R, Phillips G. The role of dopamine in rewarded behavior: Ability, insight, drive or incentive? Pol J Pharmacol Pharm 1991;43:291-300.
65. Willner P, Muscat R, Papp M. An animal model of anhedonia. Clin Neuropharmacol 1992;15:550-1.
66. Civelli O, Bunzow JR, Grandy DK. Molecular diversity of the dopamine receptors. Annu Rev Pharmacol Toxicol 1993;33:281-307.
67. Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet 1997;6:577-82.
68. Jönsson EG, Nöthen MM, Grünhage F, Farde L, Nakashima Y, Propping P, *et al*. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 1999;4:290-6.
69. Cravchik A, Sibley DR, Gejman PV. Functional analysis of the human D2 dopamine receptor missense variants. J Biol Chem 1996;271:26013-7.
70. Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvalahti EK, *et al*. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol Psychiatry 1998;3:256-60.
71. Jonsson EG, Flyckt L, Burgert E, Crocq MA, Forslund K, Mattila-Evenden M. Dopamine D3 receptor gene Ser9 Gly variant and schizophrenia: Association study and meta-analysis. Psychiatr Genet 2003;13:1-12.
72. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O. Multiple dopamine D4 receptor variants in the human population. Nature 1992;358:149-52.
73. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol H. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 1995;65:1157-65.
74. Manki H, Kanba S, Muramatsu T, Higuchi S, Suzuki E, Matsushita S. Dopamine D2, D3 and D4 receptor and transporter gene polymorphisms and mood disorders. J Affect Disord 1996;40:7-13.
75. Kalueff AV, Nutt DJ. Role of GABA in anxiety and depression. Depress Anxiety 2007;24:495-517.
76. Roy-Byrne PP. The GABA-benzodiazepine receptor complex: Structure, function, and role in anxiety. J Clin Psychiatry 2005;66:14-20.
77. Hasler G, Nugent AC, Carlson PJ, Carson RE, Geraci M, Drevets WC. Altered cerebral gamma-aminobutyric acid type A-benzodiazepine receptor binding in panic disorder determined by (11C) flumazenil positron emission tomography. Arch Gen Psychiatry 2008;65:1166-75.
78. Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain GABA(A)- benzodiazepine receptor binding in panic disorder: Preliminary results from a quantitative PET study. Arch Gen Psychiatry 1998;55:715-20.
79. Löw K, Crestani F, Keist R, Benke D, Brünig I, Benson JA, *et al*. Molecular and neuronal substrate for the selective attenuation of anxiety. Science 2000;290:131-4.
80. Covault J, Gelernter J, Hesselbrock V, Nellissery M, Kranzler HR. Allelic and Haplotypic Association of GABRA2 with alcohol dependence. Am J Med Genet B Neuropsychiatr Genet 2004;129:104-9.
81. Edenberg HJ, Dick DM, Xuei X, Tian H, Almasy L, Bauer LO, *et al*. Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. Am J Hum Genet 2004;74:705-14.
82. Enoch MA, Schwartz L, Albaugh B, Virkkunen M, Goldman D. Dimensional anxiety mediates linkage of GABRA2 haplotypes with alcoholism. Am J Med Genet B Neuropsychiatr Genet 2006;141:599-607.
83. Atack JR, Hutson PH, Collinson N, Marshall G, Bentley G, Moyes C, *et al*. Anxiogenic properties of an inverse agonist selective for alpha3 subunit-containing GABA a receptors. Br J Pharmacol 2005;144:357-66.
84. Fiorelli R, Rudolph U, Straub CJ, Feldon J, Yee BK. Affective and Cognitive Effects of Global Deletion of Alpha3-Containing Gamma-Aminobutyric Acid-A Receptors. Behav Pharmacol 2008;19:582-96.
85. Hayden EP, Nurnberger JI Jr. Molecular genetics of bipolar disorder. Genes Brain Behav 2006;5:85-95.
86. Massat I, Souery D, Del Favero J, Oruc L, Noethen MM, Blackwood D, *et al*. Excess of allele1 for alpha3 subunit GABA receptor gene (GABRA3) in bipolar patients: A multicentric association study. Mol Psychiatry 2002;7: 201-7.
87. Henkel V, Baghai TC, Eser D, Zill P, Mergl R, Zwanzger P, *et al*. The Gamma Amino Butyric Acid (GABA) receptor alpha-3 subunit gene polymorphism in unipolar depressive disorder: A genetic association study. Am J Med Genet B Neuropsychiatr Genet 2004;126:82-7.
88. Massat I, Souery D, Del Favero J, Oruc L, Jakovljevic M, Folnegovic V, *et al*. Lack of association between GABRA3 and unipolar affective disorder: A multicentre study. Int J Neuropsychopharmacol 2001;4:273-8.
89. Puertollano R, Visedo G, Saiz-Ruiz J, Llinares C, Fernandez-Piqueras J. Lack of association between manic-depressive illness and a highly polymorphic marker from GABRA3 Gene. Am J Med Genet 1995;60:434-5.
90. Sen S, Villafuerte S, Nesse R, Stoltenberg SF, Hopcian J, Gleiberman L, *et al*. Serotonin Transporter and GABAA Alpha 6 Receptor Variants Are Associated With Neuroticism. Biol Psychiatry Feb 1;2004 55(3):244–9.
91. Uhart M, McCaul ME, Oswald LM, Choi L, Wand GS. GABRA6 gene polymorphism and an attenuated stress response. Mol Psychiatry 2004;9:998-1006.
92. Crestani F, Lorez M, Baer K, Essrich C, Benke D, Laurent JP, *et al*. Decreased GABAA-receptor clustering results in enhanced anxiety and a bias for threat cues. Nat Neurosci 1999;2:833-9.
93. Jang BS, Kim H, Lim SW, Jang KW, Kim DK. Serum S100B Levels and major depressive disorder: Its

characteristics and role in antidepressant response. Psychiatry Invest 2008;5:193-8.
94. Shyn SI, Hamilton SP. The genetics of major depression: Moving beyond the monoamine hypothesis. Psychiatr Clin North Am 2010;33:125-40.
95. Smith RS. The macrophage theory of depression. Med Hypotheses 1991;35:298-306.
96. Empana JP, Sykes DH, Luc G, Juhan-Vague I, Arveiler D, Ferrieres J. Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: The Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2005;111:2299-305.
97. Kling MA, Alesci S, Csako G, Costello R, Luckenbaugh DA, Bonne O, *et al*. Sustained low-grade pro-inflammatory state in unmedicated, remitted women with major depressive disorder as evidenced by elevated serum levels of the acute phase proteins C-reactive protein and serum amyloid A. Biol Psychiatry 2007;62:309-13.
98. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279-83.
99. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res 2002;53:897-902.
100. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24-31.
101. McCaffery JM, Frasure-Smith N, Dube MP, Theroux P, Rouleau GA, Duan Q, *et al*. Common genetic vulnerability to depressive symptoms and coronary artery disease: A review and development of candidate genes related to inflammation and serotonin. Psychosom Med 2006;68:187-200.
102. McMillen TS, Heinecke JW, LeBoeuf RC. Expression of human myeloperoxidase by macrophages promotes atherosclerosis in mice. Circulation 2005;111:2798-804.
103. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 2005;25:1102-11.
104. Podrez EA, Schmitt D, Hoff HF, Hazen SL. Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form *in vitro*. J Clin Invest 1999;103:1547-60.
105. Koutsilieri E, Scheller C, Grunblatt E, Nara K, Li J, Riederer P. Free radicals in Parkinson's disease. J Neurol 2002;249:II1-5.
106. Green PS, Mendez AJ, Jacob JS, Crowley JR, Growdon W, Hyman BT, Heinecke JW. Neuronal expression of myeloperoxidase is increased in Alzheimer's disease. J Neurochem 2004;90:724-33.
107. Bilici M, Efe H, Koroglu MA, Uydu HA, Bekaroglu M, Deger O. Antioxidative enzyme activities and lipid peroxidation in major depression: Alterations by antidepressant treatments. J Affect Disord 2001;64:43-51.
108. Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. Major depressive disorder is accompanied with oxidative stress: Short-term antidepressant treatment does not alter oxidativeantioxidative systems. Hum Psychopharmacol 2007;22:67-73.
109. Michel TM, Frangou S, Thiemeyer D, Camara S, Jecel J, Nara K, Brunklaus A, Zoechling R, Riederer P. Evidence for oxidative stress in the frontal cortex in patients with recurrent depressive disorder--A postmortem study. Psychiatry Res 2007;151:145-50.
110. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
111. Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, Woolwine BJ. Activation of central nervous system inflammatory pathways by interferon-alpha: Relationship to monoamines and depression. Biol Psychiatry 2009;65:296-303.
112. Zorilla EP, Luborsky L, McKay JR, Roesnthal R, Houldin A, Tax A. The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun 2001;15:199-226.
113. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 2005;104:788-93.
114. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. Psychosom Med 2005;67:187-94.
115. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry 2008;64:538-40.
116. Mossner R, Mikova O, Koutsilieri E, Saoud M, Ehlis AC, Muller N. Consensus paper of the WFSBP task force on biological markers: Biological markers in depression. World J Biol Psychiatry 2007;8:141-74.
117. Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH. Neurobehavioral effects of interferon-alpha in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643-52.
118. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001;344:961-6.
119. Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer 1998;83:797-805.
120. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001;58:445-52.
121. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 2008;63:1022-9.
122. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46-56.
123. Godbout JP, Berg BM, Krzyszton C, Johnson RW. Alpha-tocopherol attenuates NFkβ activation and pro-inflammatory cytokine production in brain and improves recovery from lipopolysaccharide induced sickness behavior. J Neuroimmunol 2005;169:97-105.
124. Rankine EL, Hughes PM, Botham MS, Perry VH, Felton LM. Brain cytokine synthesis induced by an

intraparenchymal injection of LPS is reduced in MCP-1-deficient mice prior to leucocyte recruitment. Eur J Neurosci 2006;24:77-86.
125. Anisman H, Merali Z, Hayley S. Neurotransmitter; Peptide and cytokine processes in relation to depressive disorder: Co-morbidity between depression and neurodegenerative disorders. Prog Neurobiol 2008;85:1-74.
126. Felger JC, Alagbe O, Hu F, Mook D, Freeman AA, Sanchez MM, Kalin NH, Ratti E, Nemeroff CB, Miller AH.Effects of interferon-alpha on rhesus monkeys: A non-human primate model of cytokine-induced depression. Biol Psychiatry 2007;62:1324-33.
127. Bull SJ, Huezo-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. Mol Psychiatry 2009;14:1095-104.
128. Yirmiya R, Pollak Y, Barak O, Avitsur R, Ovadia H, Bette M, Weihe E, Weidenfeld J. Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. Neuropsychopharmacology 2001;24:531-44.
129. Fujigaki H, Saito K, Fujigaki S, Takemura M, Sudo K, Ishiguro H. The signal transducer and activator of transcription 1 alpha and interferon regulatory factor 1 are not essential for the induction of indoleamine 2,3-dioxygenase by lipopolysaccharide: Involvement of p38 mitogen-activated protein kinase and nuclear factor-kappaB pathways, and synergistic effect of several proinflammatory cytokines. J Biochem 2006;139:655-62.
130. Schwarcz R, Pellicciari R. Manipulation of brain kynurenines: Glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther 2002;303:1-10.
131. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N. Lipopolysaccharide induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 2009;14:511-22.
132. Borland LM, Michael AC. Voltammetric study of the control of striatal dopamine release by glutamate. J Neurochem 2004;91:220-9.
133. Wu HQ, Rassoulpour A, Schwarcz R. Kynurenic acid leads, dopamine follows: A new case of volume transmission in the brain? J Neural Transm 2007;114:33-41.
134. Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, Miller AH. Interferonalpha-induced changes in tryptophan metabolism: Relationship to depression and paroxetine treatment. Biol Psychiatry 2003;54:906-14.
135. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: A literature review. CNS Spectr 2008;13:501-10.
136. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. Mol Psychiatry 2007;12:988-1000.
137. Rios C, Santamaria A. Quinolinic acid is a potent lipid peroxidant in rat brain homogenates. Neurochem Res 1991;16:1139-43.
138. Kitagami T,. Yamada K, Miura H, Hashimoto R, Nabeshima T, Ohta T. Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: Role of nitric oxide as a signal crossing the blood-brain barrier. Brain Res 2003;978:104-14.
139. Moron JA, Zakharova I, Ferrer JV, Merrill GA, Hope B, Lafer EM, *et al*. Mitogen-activated protein kinase regulates dopamine transporter surface expression and dopamine transport capacity. J Neurosci 2003;23:8480-8.
140. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology 2006;31:2121-31.
141. Sanchez MM, Alagbe O, Felger JC, Zhang J, Graff AE, Grand AP. Activated p38 MAPK is associated with decreased CSF 5-HIAA and increased maternal rejection during infancy in rhesus monkeys. Mol Psychiatry 2007;12:895-7.

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