ISSN 1022-7954, Russian Journal of Genetics, 2020, Vol. 56, No. 8, pp. 903–915. © Pleiades Publishing, Inc., 2020.
Russian Text © The Author(s), 2020, published in Genetika, 2020, Vol. 56, No. 8, pp. 878–892.

REVIEWS
AND THEORETICAL ARTICLES

Genetics of Depressive Disorders: Candidate Genes and Genome-Wide Association Studies

E. I. Rafikova[a], *, A. P. Ryskov[a], and V. A. Vasilyev[a]

[a] *Institute of Gene Biology, Russian Academy of Sciences, Moscow, 119334 Russia*

**e-mail: kat.rafikov@gmail.com*

Received October 2, 2019; revised November 13, 2019; accepted December 12, 2019

Abstract—The search for molecular genetic markers of depression has been going on for more than two decades, and it began with molecular studies of the genes of the neurotransmitter systems, primarily serotonin and dopamine. However, for most genes, the results of such studies remain contradictory. In the last decade, a new approach has been used to study the genetics of multifactorial diseases—a genome-wide search for associations. This method made it possible to supplement the list of potential genetic risk factors for depression with new genes that require additional research. The review describes two different approaches to the study of the genetics of depression, as well as current problems and recent advances in this field.

Keywords: depression, serotonergic system, dopaminergic system, GWAS, genome-wide association study, SNP
DOI: 10.1134/S1022795420080116

INTRODUCTION

Depression represents a disease characterized by a stable mood decrease, reduced activity and energy, anhedonia, impaired attention, sleep, and appetite, and other symptoms. In the literature, the terms "major depressive disorder," "major depression," "clinical depression," and "unipolar depression" exist, actually stating a rather heterogeneous disease characterized by variability in symptoms and etiology [1]. Neurobiological and molecular genetic studies of depression have to unravel its pathogenesis and to provide the development of more precise universal classification of depressive disorders and methods of therapy based on it. However, the heterogeneity of depression complicates the organization of these studies.

At present, ICD-11 (International Classification of Diseases, WHO 2018) and DSM-V (The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, 2013) can be used to obtain information on types of depressive disorders and their diagnosis. According to ICD-11, depressive disorders belong to mood disorders and include depressive episode and recurrent depressive disorder, which in turn are divided into mild, medium, and severe subtypes with or without psychotic symptoms; depressive disorders also include dysthymia (chronic depression), mixed depressive and anxiety disorder, premenstrual dysphoric disorder, and others. According to the DSM-V, depressive disorders include major depressive disorder (MDD), which identifies single and recurrent episode, which can also be classified by the severity and the presence or absence of psychotic symptoms and the stage of disease (complete or partial remission, current episode). In addition, according to DSM-V, depressive disorders also include chronic depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorders related to other clinical states; in turn, they are classified by the current stage of the disease, age at onset, and other additional characteristics. Moreover, DSM-V identifies the following symptoms that may accompany depression: psychotic, melancholic, anxious, catatonic, and atypical, as well as seasonal or postpartum manifestations of the disease. Other characteristics of depression, such as therapy response (for instance, resistance) and etiology, i.e., the presence of previous life events, do not comprise distinct categories in these classifications of depressive disorders, although they are used in clinical practice [2]. In addition, ICD-11 has a separate category of stress-related disorders, including prolonged grief disorder, which represents atypically prolonged and severe experience of loss. DSM-V attributes adaptation disorder, including that with depressive mood, to stress-related disorders.

Therefore, both classifications differentiate depressive disorders primarily by the specificity of the course of disease. At the same time, diversity of symptoms indicates a heterogeneous state of the "depression disorder" term, while depressive symptoms also accompany other diseases.

According to twin and family studies, the heritability of depression is about 37% [3]. The majority of studies devoted to the search for hereditary causes of depression are designed as "case–control" studies,

where "cases" are patients with depression and "controls" are a general population sample or respondents whose absence of depressive symptoms was determined by a questionnaire. "Cases" frequently include patients diagnosed with "major depressive disorder," while the use of a certain type of depression, such as recurrent depression, is rare. The studies of depression with different distinct symptoms, such as anxiety, melancholy, and others, are rarely conducted. Some studies are focused not on the diagnosis, but on the severity of depressive symptoms in a presumably mentally healthy population or in patients with other diseases.

The search for genetic variants associated with depression is conducted in two directions. First includes candidate gene studies, i.e., the genes presumably associated with the disease. Such studies often consider childhood trauma or recent stressful events as additional factors in order to assess the role of genes and environment in development of disease. The second approach involves whole genome search (GWAS—Genome-Wide Association Studies). In this case, millions of genetic variants are compared between healthy individuals and patients with depression. The review describes the results obtained by the two main approaches in the largest and latest studies on depression genetics, related to the analysis of candidate genes and the search for novel genes via association analysis of polymorphic genomic markers.

CANDIDATE GENE STUDIES

The search for molecular genetic markers associated with depression was initiated more than two decades ago with the study of genes related to metabolism of biogenic amines. According to the monoamine theory, the main cause of depression is an impaired regulation of neurotransmitter systems, primarily serotonergic and dopaminergic ones. These systems represent the targets for the majority of antidepressants, such as MAO inhibitors and selective serotonin reuptake inhibitors (SSRIs). Moreover, the genes related to neuronal growth and development, regulation of transcription, immune system functioning, and stress response are actively studied. The most examined candidate genes associated with depression are shown in Table 1.

Serotonergic System Genes

Serotonin is one of the most studied neurotransmitters involved in the pathogenesis of depression. Caspi et al. [4] demonstrated the effect of polymorphism in the promoter region (*5-HTTLPR*) of the serotonin transporter gene (*SLC6A4*) and stressful life events on the risk of developing depression. The VNTR (variable number of tandem repeats) polymorphism is located in the promoter region of the *SLC6A4* gene, whose allelic variants differ in the number of GC-rich repeats 20–23 bp in length. The *S* allele contains 14 tandem repeats in the promoter region, and the *L* allele contains 16 repeats. The short allele is associated with a lower level of expression and, hence, with a reduced reuptake and prolonged serotonin action in the synaptic cleft [5, 6]. Caspi et al. [4] reported that carriers of at least one *S* allele (i.e., *SS* and *SL* genotypes) had a higher risk of developing depression as a response to stressful life events and/or childhood abuse and a higher suicide risk than *LL* genotype carriers.

Studies conducted after the publication of Caspi et al. [4] have extremely contradictory results. Two meta-analyses including 54 and 23 studies confirmed that the *S* allele increased the risk of depression [7, 8]. At the same time, two other smaller scale meta-analyses failed to confirm a statistically significant association [9, 10]. A recent meta-analysis combining data from 31 studies also did not confirm higher vulnerability to depression in *S*-allele carriers under the influence of stressful life events compared to *L*-allele carriers [11]. In contrast to the study of Caspi et al., this meta-analysis included only those results that were obtained from samples exceeding 300 individuals.

Ten years after the detection of VNTR polymorphism, SNP (single-nucleotide polymorphism) rs25531 was detected in the sixth repeat in the same region of the *SLC6A4* gene, which represents adenine exchange to guanine, affecting gene expression. This polymorphism is more frequent in the *L* allele, although it may also be present in the *S* allele. The L_G allele together with *S* allele was reported to be associated with a decreased expression compared to the L_A allele. A difference in expression levels is explained by a close proximity of polymorphism to the binding site of AP2 transcription factor, which inhibits expression of the L_G allele. Therefore, the L_GL_G, L_GS, and *SS* genotypes are distinguished by a low level of serotonin transporter expression [12].

The inconsistency of results with respect to the effect of *5-HTTLPR* polymorphism on liability to depression might be due to the fact that the impact of rs25531 in gene expression was not considered in these studies. However, recent sex-specific studies considering this SNP confirmed its role together with *5-HTTLPR* on risk of neuroticism, anxiety, and depression only in men [13]. The study comprised 1139 mentally healthy individuals, whose anxiety and depression levels were assessed via questionnaire. Two other studies involving war veterans confirmed that carriers of the *S* and L_G alleles demonstrated more problems with adaptation after participating in military conflicts and higher liability to anxiety disorders [14, 15]. Obviously, additional research of serotonin transporter gene polymorphism is required, which would be based on a three-allele model (*S*, L_G, and L_A alleles) and involve larger samples of patients with diagnosed depression and a control group.

Table 1. Candidate genes associated with depression

Gene	Polymorphism	Location	Allelic variant			
			increases gene expression or protein activity	decreases gene expression or protein activity	enhances depression risk	References
SLC6A4 (*5-HTT*)	uVNTR (*5-HTTLPR*) 20–23 bp	Promoter	*L* (16 repeats)	*S* (14 repeats)	*S*	[4, 7, 8]
	SNP A/G rs25531	As above	L_A	L_G	L_G	[12, 13]
HTR1B	SNP G861C rs6296	"	*G*	*C*	*C*	[22, 24]
HTR1A	SNP C1019G rs6295	"	*C* at postsynaptic membrane	*C* at presynaptic membrane	*G*	[18, 19]
HTR2A	SNP A1438G rs6311	"	*A*	*G*	–	[20, 21]
	SNP T102C rs6313	Exon 1	*T*	*C*	–	[21]
DRD4	VNTR 48 bp	Exon 3	–	*7R* (7 repeats)	–	[42–44, 47]
DRD2	SNP T/C rs1800497 Taq1A	3'-Untranslated region	*C* (*A2*)	*T* (*A1*)	*T* (*A1*)	[36–40]
SLC6A3 (DAT1)	VNTR 40–45 bp	As above	*10R*	*9R*	*9R*	[48, 49]
COMT	SNP G472A rs4680	Exon 4	*G* (Val)	*A* (Met)	–	[50–52]
MAO-A	VNTR 30 bp	Promoter region	*4R*	*3R*	*3R*	[29, 30, 34]
BDNF	SNP Val66Met	Exon	Val	Met	Met	[56, 60]
FKBP5	SNP C/T rs1360780	Intron	*T*	*C*	*T*	[63–65]
CRHR1	SNP C/T rs7209436	"	–	–	*C*	[66–68]
	SNP G/A rs110402	"	–	–	*G*	
SIRT1	SNP T/A rs2236318	"	–	–	*T*	[72]

Dashes indicate no data.

Several studies were directed to the analysis of serotonin receptor genes *HTR1B*, *HTR1A*, and *HTR2A*. Single nucleotide polymorphism C1019G (rs6295) was detected in the promoter region of the *HTR1A* gene, which affected gene expression. Transcription factor NUDR binds only to the *C* allele [16]. Binding of this factor may enhance or weaken gene expression depending on localization at a pre- or postsynaptic membrane [17]. It was demonstrated that *G*-allele carriers had higher liability to depression and affective disorders [18, 19]. Allelic variants of *HTR2A* gene polymorphisms have been described, the most examined of which are A1438G (rs6311) and T102C (rs6313). However, no recent meta-analyses reported statistically significant associations of these variants with risk of depression [20, 21].

According to post mortem studies, G861C (rs6296) polymorphism in the *HTR1B* gene affects the density of receptors via increased activity of gene expression, and the density of receptors was higher in *G*-allele carriers [22, 23]. Recent studies demonstrated that the *C* allele, associated with a decreased gene expression, could be related to enhanced risk of developing depression [24]; however, no association with suicidal behavior was observed [25].

The *MAOA* gene is actively studied as a possible molecular genetic marker of depression, since it encodes monoamine oxidase A. *MAOA* is responsible for degradation of biogenic amines, including serotonin, and, hence, reduces the period of their action in a synaptic cleft. Allelic polymorphism in the promoter gene region representing VNTR polymorphism with 30 bp repeats was first described by Sabol et al. [26]. The authors detected four allelic variants containing 3, 3.5, 4 and 5 repeats and demonstrated that variants with three and five repeats were characterized by a reduced expression level compared to alleles with 3.5 and 4 repeats. This may indicate the optimal length of promoter region, whose deviations result in a decreased gene expression [26]. *MAOA* is of interest for sex-specific studies of depression because of its location on chromosome X. Several studies point to the association of more active alleles with depression in women [27] and bipolar disorder in men [28]. However, the majority of other studies indicate the association between a low-activity allele and depression [29–31].

One of the meta-analyses demonstrated the role of *MAOA* VNTR polymorphism in risk of depression only in an Asian population in both men and women; however, no association was observed in Caucasians [32]. Another meta-analysis failed to confirm the association of *MAOA* polymorphism with the risk of developing depression [33]. The studies considering the interaction of *MAOA* with other genes and environmental factors confirmed its involvement in the risk of depression. For instance, it was reported that a combination of allelic variants of the *MAOA* gene associated with a reduced expression and the *5-HTTLPR S* allele could enhance risk of depression in adolescent girls, whereas boys were characterized by risk of depression associated with a weakened *MAOA* expression combined with *5-HTTLPR L* allele [34]. Moreover, epigenetic factors, including methylation of the CpG site located within exon 1 and intron 1, were also reported to affect *MAOA* expression. Hypermethylation in this region was associated with depression in women [35].

Probably, additional research examining a combined effect of serotonergic system genes in pathogenesis of depressive disorders is required.

Dopaminergic System Genes

Among dopaminergic system genes, the genes encoding dopamine receptors *DRD2* and *DRD4* and dopamine transporter *SLC6A3* (*DAT1*) are the most studied.

The 3'-untranslated region of the *DRD2* gene includes SNP representing C to T exchange (rs1800497 or restriction fragment length polymorphism Taq1A), which affects gene expression. Post mortem studies revealed that carriers of the *T* allele (or *A1*) had a lower density of *DRD2* receptors in the brain compared to carriers of the *C* allele (*A2*) [36]. It was reported that the *T* allele was related to early manifestation of anxiety and depression in preschoolers [37] and was associated with higher vulnerability to stressful life events in adolescents and increased risk of depression as a response to maltreatment or stress in childhood [38]. According to the results of a meta-analysis including five studies of this SNP, individuals bearing the homozygous *TT* genotype were associated with higher risk of mood disorders compared to *TC* and *CC* genotype carriers; the association was significant in a mixed sample rather than in Europeans [39]. Another large-scale meta-analysis also confirmed the effect of rs1800497 on risk of depression, but only in an Asian population, not in Europeans and a mixed sample [40].

The *DRD4* gene is one of the most variable genes. Multiple variants of the *DRD4* gene represent the result of a different number of 48 bp tandem repeats (2–11 repeats, *2R–11R* alleles, respectively), also differing in nucleotide sequence [41]. The *2R*, *4R*, and *7R* alleles are the most frequent. In vitro studies demonstrated that expression level of the *7R* variant of the gene was lower compared to *2R* and *4R* alleles [42]. According to the results of a meta-analysis combining data of 12 studies, the *2R* allele may represent a risk factor for mood disorders, including unipolar depression and bipolar disorder [43]. Other researchers demonstrated the association of alleles with seven or more repeats with depression with comorbid marijuana abuse [44], behavioral problems in children caused by a reduced level of maternal sensitivity [45], and severe posttraumatic stress disorder in adults [46].

At the same time, cortisol measurement as a response to stress in healthy individuals demonstrated that *7R*-allele carriers had lower cortisol response to stress. The same study observed interaction between the *DRD4* and *5-HTTLPR* genotypes: carriers of the L_AL_A genotype had lower cortisol release compared to carriers of the *S* and L_G alleles only in the case of the presence of at least one copy of the *7R* allele [47].

The expression of the dopamine transporter gene (*DAT1*) is caused by VNTR polymorphism in the 3'-untranslated region of the gene. VanNess et al. [48] demonstrated in vitro that the *10R* allele (10 repeats) had 50% higher expression compared to the *9R* allele. A recent study demonstrated association between the *9R* allele and severity of depression in patients of both sexes [49].

Dopamine metabolism is also related to the *COMT* gene, whose product catechol-O-methyltransferase is responsible for degradation of catecholamines, including dopamine. Single nucleotide polymorphism G/A (Val/Met) in exon 4 affects enzyme activity. The G (Val) variant correlates with higher activity [50] and, according to a recent study, may be associated with early onset depression; this association is especially significant for homozygote carriers [51]. At the same time, a large meta-analysis including 21 studies failed to confirm association between Val/Met polymorphism and any type of depression in men, women, and a total sample [52].

Since depression is a polygenic disorder, the studies involving several genes simultaneously are of interest. One such study was based on the use of a ten-point scale to assess a combined effect of five genes of the dopaminergic system: *DRD1*, *DRD2*, *DRD3*, *COMT*, and *DAT1*. Each individual scored from 0 to 2 for each gene: one point for each allele enhancing dopamine transfer. The study revealed that reduced dopamine transfer was associated with increased risk of depression and that dopaminergic system genes enhance the effect of each other in modulating mental health [53].

Other Candidate Genes

Searches for genetic variants responsible for liability to depression were conducted also among the genes related to neuronal development and growth, functioning of the hypothalamic-pituitary-adrenal system responsible for stress with transcription regulation, and many other processes.

The BDNF (brain-derived neurotrophic factor) is a protein involved in growth and development of dendrites and axons, formation of synapses, and defense of neurons. The BDNF plays an important role at different stages of neurogenesis within both prenatal development and adulthood [54]. The brain-derived neurotrophic factor is encoded by the *BDNF* gene, which is characterized by the presence of exonic SNP (Val66Met) resulting in valine exchange to methionine. Polymorphism is located in a domain responsible for molecules binding controlling intracellular transport of both mRNA and protein. The presence of methionine instead of valine results in a reduced secretion of BDNF [55]. It was demonstrated that Val66Met polymorphism could affect the risk of depression. According to the results of a recent post mortem study, the level of brain-derived neurotrophic factor was lower in depressed patients and in individuals with severe stress at early age and/or with suicide attempts [56]. In this study, a conclusion that the *66Met* allele was associated with increased risk of depression was made. A study comprising 2000 individuals reported that the allelic variant of *66Met* was associated with enhanced risk of neuroticism [57]. Other studies demonstrated the effect of this polymorphism on depression symptoms in schizophrenia [58] and Alzheimer's disease [59]. Another study based on 2679 individuals examined a combined effect of *5-HTTLPR* and Val66Met in the *BDNF* gene together with childhood maltreatment. The results indicated that individuals who reported any type of childhood abuse had a significantly higher risk of depression in the case of simultaneous presence of the *S* allele in the serotonin transporter gene and *66Met* allele in the *BDNF* gene [60].

The *FKBP5* gene is involved in hypothalamic-pituitary-adrenal system functioning and its expression is enhanced as a response to stress. The *FKBP5* gene encodes protein reducing receptor sensitivity to cortisol, thus providing a rapid decrease in cortisol effect via negative feedback [61]. The gene intron consists of single nucleotide polymorphism C/T (rs1360780). The *T* allele results in increased gene expression after activation of glucocorticoid receptors, impaired regulation of stress response, and prolonged cortisol release [62]. The data that the *T* allele might be related to depression have been published [63–65]. The *CRHR1* (corticotropin-releasing hormone receptor 1) gene is also related to the cascade of reactions initiated by stress. One study examined 15 SNPs and two of them (rs110402 and rs7209436) appeared to be associated with depression. Depression severity was increased in homozygous genotype carriers of the more frequent allelic variant (*CC* in rs7209436 and *GG* in rs110402) who reported childhood abuse. At the same time, homozygous carriers of rare allelic variants (*TT* and *AA*, respectively) with reported childhood trauma had lower predisposition to developing depression in adulthood. No statistically significant differences were detected in a group of patients without psychological trauma. This makes it possible to suggest a defense effect of rare allelic variants of the *CRHR1* gene [66]. Later, these results were confirmed in analogous studies [67, 68].

The *SIRT1* (silent information regulator-1) gene encodes deacetylase, whose substrates include histones, transcription factors, and some other proteins. Deacetylase modifies the affinity of these proteins for

DNA, thus regulating transcription activity [69]. Moreover, *SIRT1* is involved in inflammation, apoptosis, and cell growth [70, 71].

One of the last studies, which included 20 SNPs located in this gene, detected that rs2236318 (T/A) was the most statistically significant. Individuals bearing the homozygous *TT* genotype were prevailing among depression patients compared to the control group [72].

GENOME-WIDE ASSOCIATION STUDIES

In recent decades, the development of genetic technologies provided a wide use of GWAS for the search for genetic factors of different diseases, including psychopathologies. In contrast to candidate gene studies, genome-wide research has no initial hypothesis on the involvement of certain genes in disease pathogenesis. A standard GWAS scheme represents a comparison of sequence of the patient's genome with a distinct diagnosis with genomic sequences of a control group in order to determine allelic variants more frequent in this disease. The criteria of statistical significance for GWAS results are corrected for the study with multiple independent tests; therefore, the p-value has to be under 5×10^{-8} (in the standard level of significance, p-value < 0.05) [73].

A recent review described the results of GWAS of depression published in the period from 2009 to 2018 [74]. The first study (2009) failed to detect genetic risk factors under the level of statistical significance. The CIDI (Composite International Diagnostic Interview) was used for depression diagnosis. Nevertheless, the findings of this study made it possible to conclude that the *PCLO* (Piccolo presynaptic cytomatrix protein) gene was associated with depression, since 11 of 200 most significant SNPs were located within a region 167 kb in length containing this gene [75].

In 2013, the PGC (Psychiatric GWAS Consortium) conducted a meta-analysis of nine GWAS of clinical depression with a total group containing 9240 patients and a control group of 9519 subjects. This analysis failed to detect any statistically significant findings. The most significant SNPs were rs11579964 neighboring the *CNIH4*, *NVL*, and *WDR26* genes and rs7647854 near *C3orf70* and *EHHADH* [76].

Hek et al. [77] carried out a meta-analysis (n = 34549) of GWAS of depressive symptoms (CHARGE—Cohorts for Heart and Aging Research in Genomic Epidemiology). The severity of symptoms was assessed with CESD (Center for Epidemiologic Studies Depression Scale). On the basis of the results, rs8020095 ($p = 1.05 \times 10^{-7}$) was the most significant, which is located in the intronic region of the *GPHN* gene, mutations in which were associated with epilepsy [77, 78]. Nevertheless, the results of these GWAS did not achieve the required level of statistical significance and they failed to be replicated.

In 2015, the results of the CONVERGE (China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology) Consortium, which conducted GWAS on the basis of a smaller but thoroughly phenotypic sample [79]. Since the study aimed to analyze a maximally phenotypically homogenous group, the sample consisted of 5303 Chinese women with recurrent depression and a control group of 5337 individuals checked for the absence of depressive symptoms. Low-coverage sequencing was used. The data obtained were screened using an independent sample. As a result, two genetic risk factors residing chromosome 10 were identified: rs12415800 is neighboring the *SIRT1* gene ($p = 2.53 \times 10^{-10}$), and rs35936514 is located within the intronic region of the *LHPP* gene ($p = 6.45 \times 10^{-12}$). Moreover, a group of patients with melancholic depression (depression subtype was diagnosed according to DSM-IV) was examined. The significance of *SIRT1* locus association exceeded the previous one in this sample. However, the authors pointed that the identified SNPs were less frequent in European populations compared to their sample [79]. Such studies make it possible to suggest that different genes may impact the formation of the same multifactorial phenotypic trait in different ethnic groups.

The study conducted by SSGAC (Social Science Genetic Association Consortium) was based on another strategy making it possible to increase the sample size [80]. The authors combined samples with heterogeneous depression parameters. The study included the results from PGC and GERA (Resource for Genetic Epidemiology Research on Adult Health and Aging), which consisted of patients with major depressive disorder. These findings were combined with data obtained from the UK Biobank, which included patients' responses to the questions on their emotional state during the last two weeks. Therefore, the total sample comprised both patients with clinical depression and depressive symptoms. As a result, the sample included 180866 individuals. The authors succeeded in detecting two significant SNPs: rs7973260 ($p = 1.8 \times 10^{-9}$) located in the intronic region of the *KSR2* gene and rs62100776 ($p = 8.5 \times 10^{-9}$) located in the intronic region of the *DCC* gene [80].

In 2016, another large-scale search for associations was performed by 23andMe using 15 million SNPs [81]. Genomic data obtained from 75607 individuals who indicated the presence of major depressive disorder in their interview and 231747 respondents without diagnosed depression serving as a control group were used in the analysis. The study identified two distinct regions containing SNPs with p-value $< 1 \times 10^{-8}$ and five loci with p-value $< 5 \times 10^{-8}$. The most significant was rs12552 ($p = 1.23 \times 10^{-12}$) located in the 3'-untranslated region of the *OLFM4* (olfactomedin 4) gene. The *OLFM4* gene regulates various functions beyond the CNS: differentiation of cells, immune

response, and inflammation; its expression is increased in different cancers [82]. This gene is known to be also expressed in the amygdala and temporal lobe [83]. This gene is involved in development of neurons and formation of synapses [83].

Another SNP rs10514299 ($p = 4.35 \times 10^{-12}$) is located in the region between the *MEF2C* and *TMEM161B* genes. Both genes are also expressed in the brain. All results under the significance criteria were compared to data obtained in the previous PGC study. The subsequent analysis included only those SNPs which were detected in both studies. The remaining SNPs were additionally examined in another sample with similar demographic characteristics (45773 patients and 106354 individuals from the control group). The findings from three studies (the first study of 23andMe, PGC, and replication study of 23andMe) were combined to determine the total statistical significance of each SNP, which resulted in 17 significant SNPs, 15 of which were located in gene-containing regions [81].

A recent large-scale meta-analysis of GWAS containing 130664 patients and 330470 individuals from the control group identified several significant SNPs and confirmed the impact of several previously reported SNPs [84]. The main group for meta-analysis included 29 studies which diagnosed depression using standard approaches (direct interview with a psychotherapist). In addition, six studies which diagnosed depression via other methods, for instance, questionnaires, were conducted. All seven groups were focused on the cases of "clinical depression." As a result of the study, 44 loci were detected, 33 of which were novel, while 14 coincided with previous findings in studies of clinical depression or depressive symptoms. One of the most significant SNPs (rs12552) is located in the 3'-untranslated region of the *OLFM4* gene, which has been previously mentioned in the 23andMe study. The second SNP (rs1432639) is proximal to the *NEGR1* gene (neuronal growth regulator 1). *NEGR1* affects axonal length and synaptic plasticity in the cortex, hippocampus, and hypothalamus [85, 86] and regulates formation of synapses in the hippocampus [87].

New associations were reported with the *RBFOX1* (Fox-1 family of RNA-binding proteins) and *LRFN5* (Leucine-rich repeat and fibronectin type-III domain-containing protein 5) genes. Interestingly, two independent significant SNPs (rs8063603 and rs7198928) are simultaneously localized in the intronic region of the *RBFOX1* gene. This gene encodes the protein regulating transcription of multiple proteins, the majority of which are expressed in neurons. *Fox-1* is responsible for the alternative splicing of the PACAP receptor (peptide activating adenylate cyclase in hypophysis) and is involved in the regulation of corticotropin-releasing hormone release as a response to stress [88].

The *LRFN5* gene contains a depression-related SNP in the intronic region (rs4904738). This gene encodes a protein involved in formation of synapses [89] and in inhibition of neuroinflammation [90]. Therefore, reduced expression of *LRFN5* may cause enhanced neuroinflammatory response.

The data of all discussed GWAS are shown in Table 2.

CONCLUSIONS

The results of the aforementioned studies demonstrate the achievements that have been made in understanding the pathogenesis of depression. Several assumptions regarding genetic risk factors have been confirmed, although the results of single gene studies remain contradictory. The monoamine theory still remains the most studied one in depression pathogenesis. However, the meta-analyses did not always confirm the association of serotonergic and dopaminergic system genes.

Contradictory findings of molecular genetic markers of depression may be caused by several factors. First, the "cases" group usually includes patients with both anxiety and melancholic and other subtypes of clinical depression. Considering a significant difference in symptoms and therapy of various subtypes of depression, the mechanisms of their development and, hence, genetic risk factors may be different. Second, the search for associations usually is based on the inclusion of functionally significant loci, i.e., those affecting gene expression or gene product activity. However, several genes were reported to have a complex mechanism of expression regulation. For instance, the expression of the serotonin transporter gene is affected by both VNTR polymorphism in the promoter region and SNP in the same region located in one of the repeats [12]. Therefore, it is reasonable to use a multiallelic model which would consider the impact of polymorphisms affecting gene expression.

However, the main reason for the inconsistency of results is probably a polygenic nature of depression. Multiple factors affect the risk of developing depression. Many genes with different molecular functions may be associated with depression liability, while the contribution of each individual gene is rather small [84]. Therefore, the study of combinations of allelic variants of different genes can become especially informative.

Moreover, associations of both neurotransmitter system genes and genes related to the development, growth, and protection of neurons, inflammation, transcription, and other important processes have been observed. Genetically determined impairments in these processes can also contribute to the pathogenesis of depressive disorders.

Frequently, genome-wide association studies fail to confirm the results of candidate gene studies. This may be relevant to both previously described reasons

Table 2. The results of genome-wide association studies of depression

Diagnosis	Sample	SNP and *p*-value	Comment	References
Major depressive disorder diagnosed with DSM-VI using CIDI	1738 patients and 1802 controls of European origin	No statistically significant SNPs were detected. 11 of 200 most significant SNPs are located within the region 167 kb in length containing the *PCLO* gene. The most significant SNPs: rs2715148 ($p = 7.7 \times 10^{-7}$) and rs2522833 ($p = 1.2 \times 10)^{-6}$	In addition, 75 candidate genes were examined. Statistically significant association was observed with *NOS1* gene	[75]
Major depressive disorder diagnosed with standard technique: direct interview or inventories	9 independent samples including 9240 patients and 9519 controls of European origin	No statistically significant SNPs were detected. The most significant SNPs: rs11579964 ($p = 1.0 \times 10^{-7}$) neighboring *CNIH4*, *NVL*, and *WDR26* genes and rs7647854 ($p = 6.5 \times 10^{-7}$) located in a close proximity to *C3orf70* and *EHHADH*	Moreover, comorbid psychopathology and other factors (sex, age, early onset and type of depression) were analyzed. The trends identified in a replication sample in general were congruent to the initial sample	Psychiatric GWAS Consortium [76]
17 population studies including 34549 individuals of European origin	Depressive symptoms diagnosed with CESD	No statistically significant SNPs were detected. The most significant SNP is rs8020095 ($p = 1.05 \times 10^{-7}$)	A meta-analysis of 22 studies was conducted ($n = 51\,258$); rs40465 achieved a level of statistical significance ($p = 4.78 \times 10^{-8}$). The functions of genes with the most significant SNPs were analyzed, the majority of which are involved in release of neurotransmitters, transport of vitamins, and synaptic transfer	CHARGE [77]
5303 patients and 5337 controls, women from China	Recurrent sample	Two significant SNPs located both on chromosome 10: rs12415800 near *SIRT1* gene ($p = 2.53 \times 10^{-10}$) and rs35936514 located in the intronic region of *LHPP* gene ($p = 6.45 \times 10^{-12}$)	A sample homogenous by several parameters (sex, ethnicity, depression type) was analyzed. In addition, a melancholic type of depression was examined, which demonstrated that SNP in the *SIRT1* gene was statistically significant at a higher level in patients of this group. However, detected SNPs are rare in Europeans	CONVERGE [79]
180866 individuals	Major depressive disorder and depressive symptoms	The most significant SNPs: rs7973260 ($p = 1.8 \times 10^{-9}$) in the intronic region of *KSR2* gene and rs62100776 ($p = 8.5 \times 10^{-9}$) in the intronic region of *DCC* gene	Combined data from PGC, GERA, and UK BioBank. The sample consists of both patients with clinical depression and respondents with depressive symptoms	SSGAC [80]
75607 patients and 231747 controls	Major depressive disorder whose presence or absence was reported by respondents	The most significant SNPs: rs12552 ($p = 1.23 \times 10^{-12}$) located in *OLFM4* gene and rs10514299 ($p = 4.35 \times 10^{-12}$) located in the region between *MEF2C* and *TMEM161B* genes	The results of the study were examined in a replication sample (45773 patients and 106354 controls) and compared to PGC results with a subsequent meta-analysis of obtained data. Meta-analysis detected 15 statistically significant SNPs located in gene-containing regions	23andMe [83]
29 independent studies including 130664 patients and 330470 controls	Major depressive disorder determined via different diagnostic instruments	44 SNPs were detected, 14 of which are congruent to previous research. The most significant SNPs: rs12552 ($p = 6.1 \times 10^{-19}$) in the *OLFM4* gene and rs1432639 ($p = 4.6 \times 10^{-15}$) in the *NEGR1* gene	Two independent significant SNPs, rs8063603 and rs7198928 located within intronic region of *RBFOX1* gene	[84]

and to the specificity of the method itself, which allows search for associations with SNPs rather than with VNTR polymorphism [74]. The first GWAS did not result in statistically significant findings; however, later it was possible to identify several associations and to confirm them in replication samples. To increase the GWAS efficacy, it is recommended to use large samples. It is expected that in 2020 the data of a sample of one million individuals would become available [84]. The results also depend on the study design. Groups of patients diagnosed with "clinical depression" can be valuable for the search for allelic variants common to all types of depression. At the same time, the use of groups being homogeneous by diagnosis and other phenotypic parameters can make it possible to identify allelic variants characteristic of a certain subtype of depression and help to detect ethnic, gender, and other specific parameters of development of disease.

In this regard, the development of new approaches to the study of depression is discussed. For instance, the data on the association of genomic polymorphic markers or candidate gene variants with antidepressant effect in samples of patients with certain depression subtypes remain insignificant. Such studies could be informative for both assessment of the significance of certain genotypes in the development of this pathology and for the development of personalized medicine.

Therefore, more thorough and precise understanding of the nature of depression will help to personalize the diagnosis and treatment of the disease. In addition, further research of the mechanisms of development of disease can serve as a basis for the search for new targets in pharmacotherapy, which is especially relevant in consideration of a high percentage of patients with recurrent depression.

FUNDING

The present study was supported by the Russian Foundation for Basic Research (project nos. 19-04-00383, 17-29-02203-ofi-m) and the Program "Postgenomic Technologies and Prospective Solutions in Biomedicine."

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

REFERENCES

1. Kessing, L.V. and Bukh, J.D., The clinical relevance of qualitatively distinct subtypes of depression, *World Psychiatry*, 2017, vol. 16, no. 3, pp. 318—319. https://doi.org/10.1002/wps.20461
2. *In Depression: The Treatment and Management of Depression in Adults*, Leicester (UK), 2010, updated ed.
3. Sullivan, P.F., Neale, M.C., and Kendler, K.S., Genetic epidemiology of major depression: review and meta-analysis, *Am. J. Psychiatry*, 2000, vol. 157, no. 10, pp. 1552—1562. https://doi.org/10.1176/appi.ajp.157.10.1552
4. Caspi, A., Sugden, K., Moffitt, T.E., et al., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene, *Science*, 2003, vol. 301, no. 5631, pp. 386—389. https://doi.org/10.1126/science.1083968
5. Heils, A., Teufel, A., Petri, S., et al., Allelic variation of human serotonin transporter gene expression, *J. Neurochem.*, 1996, vol. 66, no. 6, pp. 2621—2624. https://doi.org/10.1046/j.1471-4159.1996.66062621.x
6. Lesch, K.P., Bengel, D., Heils, A., et al., Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region, *Science*, 1996, vol. 274, no. 5292, pp. 1527—1531. https://doi.org/10.1126/science.274.5292.1527
7. Karg, K., Burmeister, M., Shedden, K., et al., The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation, *Arch. Gen. Psychiatry*, 2011, vol. 68, no. 5, pp. 444—454. https://doi.org/10.1001/archgenpsychiatry.2010.189
8. Oo, K.Z., Aung, Y.K., Jenkins, M.A., et al., Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: a systematic review and meta-analysis, *Aust. N. Z. J. Psychiatry*, 2016, vol. 50, no. 9, pp. 842—857. https://doi.org/10.1177/0004867416637920
9. Risch, N., Herrell, R., Lehner, T., et al., Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression a meta-analysis, *Jama-J. Am. Med.* Assoc., 2009, vol. 301, no. 23, pp. 2462—2471. https://doi.org/10.1001/jama.2009.878
10. Munafo, M.R., Durrant, C., Lewis, G., et al., Gene × environment interactions at the serotonin transporter locus, *Biol. Psychiatry*, 2009, vol. 65, no. 3, pp. 211—219. https://doi.org/10.1016/j.biopsych.2008.06.009
11. Culverhouse, R.C., Saccone, N.L., Horton, A.C., et al., Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression, *Mol. Psychiatry*, 2018, vol. 23, no. 1, pp. 133—142. https://doi.org/10.1038/mp.2017.44
12. Hu, X.Z., Lipsky, R.H., Zhu, G., et al., Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder, *Am. J. Hum. Genet.*, 2006, vol. 78, no. 5, pp. 815—826. https://doi.org/10.1086/503850
13. Chang, C.C., Chang, H.A., Fang, W.H., et al., Gender-specific association between serotonin transporter polymorphisms (5-HTTLPR and rs25531) and neuroticism, anxiety and depression in well-defined healthy Han Chinese, *J. Affective Disord.*, 2017, vol. 207, pp. 422—428. https://doi.org/10.1016/j.jad.2016.08.055

14. Kimbrel, N.A., Morissette, S.B., Meyer, E.C., et al., Effect of the 5-HTTLPR polymorphism on posttraumatic stress disorder, depression, anxiety, and quality of life among Iraq and Afghanistan veterans, *Anxiety Stress Coping*, 2015, vol. 28, no. 4, pp. 456—466. https://doi.org/10.1080/10615806.2014.973862

15. Telch, M.J., Beevers, C.G., Rosenfield, D., et al., 5-HTTLPR genotype potentiates the effects of war zone stressors on the emergence of PTSD, depressive and anxiety symptoms in soldiers deployed to Iraq, *World Psychiatry*, 2015, vol. 14, no. 2, pp. 198—206. https://doi.org/10.1002/wps.20215

16. Lemonde, S., Turecki, G., Bakish, D., et al., Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide, *J. Neurosci.*, 2003, vol. 23, no. 25, pp. 8788—8799. https://doi.org/10.1523/JNEUROSCI.23-25-08788.2003

17. Czesak, M., Lemonde, S., Peterson, E.A., et al., Cell-specific repressor or enhancer activities of Deaf-1 at a serotonin 1A receptor gene polymorphism, *J. Neurosci.*, 2006, vol. 26, no. 6, pp. 1864—1871. https://doi.org/10.1523/JNEUROSCI.2643-05.2006

18. Lenze, E.J., Shardell, M., Ferrell, R.E., et al., Association of serotonin-1A and 2A receptor promoter polymorphisms with depressive symptoms and functional recovery in elderly persons after hip fracture, *J. Affective Disord.*, 2008, vol. 111, no. 1, pp. 61—66. https://doi.org/10.1016/j.jad.2008.02.005

19. Molina, E., Cervilla, J., Rivera, M., et al., Polymorphic variation at the serotonin 1-A receptor gene is associated with comorbid depression and generalized anxiety, *Psychiatr. Genet.*, 2011, vol. 21, no. 4, pp. 195—201. https://doi.org/10.1097/YPG.0b013e3283457a48

20. Jin, C., Xu, W., Yuan, J., et al., Meta-analysis of association between the −1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder, *Neurol. Res.*, 2013, vol. 35, no. 1, pp. 7—14. https://doi.org/10.1179/1743132812Y.0000000111

21. Zhao, X., Sun, L., Sun, Y.H., et al., Association of HTR2A T102C and A-1438G polymorphisms with susceptibility to major depressive disorder: a meta-analysis, *Neurol. Sci.*, 2014, vol. 35, no. 12, pp. 1857—1866. https://doi.org/10.1007/s10072-014-1970-7

22. Huang, Y.Y., Grailhe, R., Arango, V., et al., Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue, *Neuropsychopharmacology*, 1999, vol. 21, no. 2, pp. 238—246. https://doi.org/10.1016/S0893-133X(99)00030-5

23. Duan, J., Sanders, A.R., Molen, J.E., et al., Polymorphisms in the 5'-untranslated region of the human serotonin receptor 1B (HTR1B) gene affect gene expression, *Mol. Psychiatry*, 2003, vol. 8, no. 11, pp. 901—910.

24. Kao, W.T., Yang, M.C., and Lung, F.W., Association between HTR1B alleles and suicidal ideation in individuals with major depressive disorder, *Neurosci. Lett.*, 2017, no. 638, pp. 204—210.

25. Bani-Fatemi, A., Howe, A., Zai, C., et al., Differential allelic expression of HTR1B in suicide victims: genetic and epigenetic effect of the cis-acting variants, *Neuropsychobiology*, 2016, vol. 74, no. 3, pp. 144—149.

26. Sabol, S.Z., Hu, S., and Hamer, D., A functional polymorphism in the monoamine oxidase A gene promoter, *Hum. Genet.*, 1998, vol. 103, no. 3, pp. 273—279. https://doi.org/10.1007/s004390050816

27. Yu, Y.W., Tsai, S.J., Hong, C.J., et al., Association study of a monoamine oxidase a gene promoter polymorphism with major depressive disorder and antidepressant response, *Neuropsychopharmacology*, 2005, vol. 30, no. 9, pp. 1719—1723. https://doi.org/10.1038/sj.npp.1300785

28. Lin, Y.M., Davamani, F., Yang, W.C., et al., Association analysis of monoamine oxidase A gene and bipolar affective disorder in Han Chinese, *Behav. Brain Funct.*, 2008, no. 4, p. 21. https://doi.org/10.1186/1744-9081-4-21

29. Aklillu, E., Karlsson, S., Zachrisson, O.O., et al., Association of MAOA gene functional promoter polymorphism with CSF dopamine turnover and atypical depression, *Pharmacogenet. Genomics*, 2009, vol. 19, no. 4, pp. 267—275. https://doi.org/10.1097/FPC.0b013e328328d4d3

30. Doornbos, B., Dijck-Brouwer, D.A., Kema, I.P., et al., The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2009, vol. 33, no. 7, pp. 1250—1254. https://doi.org/10.1016/j.pnpbp.2009.07.013

31. Huang, S.Y., Lin, M.T., Lin, W.W., et al., Association of monoamine oxidase A (MAOA) polymorphisms and clinical subgroups of major depressive disorders in the Han Chinese population, *World J. Biol. Psychiatry*, 2009, vol. 10, no. 4, pp. 544—551. https://doi.org/10.1080/15622970701816506

32. Fan, M., Liu, B., Jiang, T., et al., Meta-analysis of the association between the monoamine oxidase-A gene and mood disorders, *Psychiatr. Genet.*, 2010, vol. 20, no. 1, pp. 1—7. https://doi.org/10.1097/YPG.0b013e3283351112

33. Liu, Z., Huang, L., Luo, X.J., et al., MAOA variants and genetic susceptibility to major psychiatric disorders, *Mol. Neurobiol.*, 2016, vol. 53, no. 7, pp. 4319—4327. https://doi.org/10.1007/s12035-015-9374-0

34. Priess-Groben, H.A. and Hyde, J.S., 5-HTTLPR X stress in adolescent depression: moderation by MAOA and gender, *J. Abnorm. Child Psychol.*, 2013, vol. 41, no. 2, pp. 281—294. https://doi.org/10.1007/s10802-012-9672-1

35. Melas, P.A., Wei, Y., Wong, C.C., et al., Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities, *Int. J. Neuropsychopharmacol.*, 2013, vol. 16, no. 7, pp. 1513—1528. https://doi.org/10.1017/S1461145713000102

36. Noble, E.P., Blum, K., Ritchie, T., et al., Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism, *Arch. Gen. Psychiatry*, 1991, vol. 48, no. 7, pp. 648—654. https://doi.org/10.1001/archpsyc.1991.01810310066012

37. Hayden, E.P., Klein, D.N., Dougherty, L.R., et al., The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: associations and evidence for gene-environment correlation and gene-environment interaction, *Psychiatr. Genet.*, 2010, vol. 20,

no. 6, pp. 304—310.
https://doi.org/10.1097/YPG.0b013e32833adccb

38. Zhang, W., Cao, Y., Wang, M., et al., The dopamine D2 receptor polymorphism (DRD2 TaqIA) interacts with maternal parenting in predicting early adolescent depressive symptoms: evidence of differential susceptibility and age differences, *J. Youth Adolesc.*, 2015, vol. 44, no. 7, pp. 1428—1440.
https://doi.org/10.1007/s10964-015-0297-x
39. Zou, Y.F., Wang, F., Feng, X.L., et al., Association of DRD2 gene polymorphisms with mood disorders: a meta-analysis, *J. Affective Disord.*, 2012, vol. 136, no. 3, pp. 229—237.
https://doi.org/10.1016/j.jad.2010.11.012
40. Zhang, L., Hu, L., Li, X., et al., The DRD2 rs1800497 polymorphism increase the risk of mood disorder: evidence from an update meta-analysis, *J. Affective Disord.*, 2014, no. 158, pp. 71—77.
https://doi.org/10.1016/j.jad.2014.01.015
41. Ding, Y.C., Chi, H.C., Grady, D.L., et al., Evidence of positive selection acting at the human dopamine receptor D4 gene locus, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, vol. 99, no. 1, pp. 309—314.
https://doi.org/10.1073/pnas.012464099
42. Schoots, O. and Van Tol, H.H., The human dopamine D4 receptor repeat sequences modulate expression, *Pharmacogenomics J.*, 2003, vol. 3, no. 6, pp. 343—348.
https://doi.org/10.1038/sj.tpj.6500208
43. Lopez Leon, S., Croes, E.A., Sayed-Tabatabaei, F.A., et al., The dopamine D4 receptor gene 48-base-pair-repeat polymorphism and mood disorders: a meta-analysis, *Biol. Psychiatry*, 2005, vol. 57, no. 9, pp. 999—1003.
https://doi.org/10.1016/j.biopsych.2005.01.030
44. Bobadilla, L., Vaske, J., and Asberg, K., Dopamine receptor (D4) polymorphism is related to comorbidity between marijuana abuse and depression, *Addict. Behav.*, 2013, vol. 38, no. 10, pp. 2555—2562.
https://doi.org/10.1016/j.addbeh.2013.05.014
45. King, A.P., Muzik, M., Hamilton, L., et al., Dopamine receptor gene DRD4 7-repeat allele × maternal sensitivity interaction on child externalizing behavior problems: independent replication of effects at 18 months, *PLoS One*, 2016, vol. 11, no. 8. e0160473. .
https://doi.org/10.1371/journal.pone.0160473
46. Dragan, W.L. and Oniszczenko, W., The association between dopamine D4 receptor exon III polymorphism and intensity of PTSD symptoms among flood survivors, *Anxiety Stress Coping*, 2009, vol. 22, no. 5, pp. 483—495.
https://doi.org/10.1080/10615800802419407
47. Armbruster, D., Mueller, A., Moser, D.A., et al., Interaction effect of D4 dopamine receptor gene and serotonin transporter promoter polymorphism on the cortisol stress response, *Behav. Neurosci.*, 2009, vol. 123, no. 6, pp. 1288—1295.
https://doi.org/10.1037/a0017615
48. Van Ness, S.H., Owens, M.J. and Kilts, C.D., The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density, *BMC Genet.*, 2005, no. 6, p. 55.
https://doi.org/10.1186/1471-2156-6-55
49. Bielinski, M., Jaracz, M., Lesiewska, N., et al., Association between COMT Val158Met and DAT1 polymorphisms and depressive symptoms in the obese population, *Neuropsychiatr. Dis. Treat.*, 2017, no. 13, pp. 2221—2229.
https://doi.org/10.2147/NDT.S138565
50. Lachman, H.M., Papolos, D.F., Saito, T., et al., Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders, *Pharmacogenetics*, 1996, vol. 6, no. 3, pp. 243—250.
51. Danzi, B.A., and La Greca, A.M., Genetic pathways to posttraumatic stress disorder and depression in children: investigation of catechol-O-methyltransferase (COMT) Val158Met using different PTSD diagnostic models, *J. Psychiatr. Res.*, 2018, no. 102, pp. 81—86.
https://doi.org/10.1016/j.jpsychires.2018.03.014
52. Klein, M., Schmoeger, M., Kasper, S., et al., Meta-analysis of the COMT Val158Met polymorphism in major depressive disorder: the role of gender, *World J. Biol. Psychiatry*, 2016, vol. 17, no. 2, pp. 147—158.
https://doi.org/10.3109/15622975.2015.1083615
53. Pearson-Fuhrhop, K.M., Dunn, E.C., Mortero, S., et al., Dopamine genetic risk score predicts depressive symptoms in healthy adults and adults with depression, *PLoS One*, 2014, vol. 9, no. 5. e93772.
https://doi.org/10.1371/journal.pone.0093772
54. Huang, E.J. and Reichardt, L.F., Neurotrophins: roles in neuronal development and function, *Annu. Rev. Neurosci.*, 2001, no. 24, pp. 677—736.
https://doi.org/10.1146/annurev.neuro.24.1.677
55. Egan, M.F., Kojima, M., Callicott, J.H., et al., The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, *Cell*, 2003, vol. 112, no. 2, pp. 257—269.
https://doi.org/10.1016/s0092-8674(03)00035-7
56. Youssef, M.M., Underwood, M.D., Huang, Y.Y., et al., Association of BDNF Val66Met polymorphism and brain BDNF levels with major depression and suicide, *Int. J. Neuropsychopharmacol.*, 2018, vol. 21, no. 6, pp. 528—538.
https://doi.org/10.1093/ijnp/pyy008
57. Terracciano, A., Tanaka, T., Sutin, A.R., et al., BDNF Val66Met is associated with introversion and interacts with 5-HTTLPR to influence neuroticism, *Neuropsychopharmacology*, 2010, vol. 35, no. 5, pp. 1083—1089.
https://doi.org/10.1038/npp.2009.213
58. Schumacher, J., Jamra, R.A., Becker, T., et al., Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression, *Biol. Psychiatry*, 2005, vol. 58, no. 4, pp. 307—314.
https://doi.org/10.1016/j.biopsych.2005.04.006
59. Borroni, B., Grassi, M., Archetti, S., et al., BDNF genetic variations increase the risk of Alzheimer's disease-related depression, *J. Alzheimers Dis.*, 2009, vol. 18, no. 4, pp. 867—875.
https://doi.org/10.3233/JAD-2009-1191
60. Gutierrez, B., Bellon, J.A., Rivera, M., et al., The risk for major depression conferred by childhood maltreatment is multiplied by BDNF and SERT genetic vulnerability: a replication study, *J. Psychiatry Neurosci.*,

2015, vol. 40, no. 3, pp. 187—196.
https://doi.org/10.1503/jpn.140097

61. Gillespie, C.F., Phifer, J., Bradley, B., et al., Risk and resilience: genetic and environmental influences on development of the stress response, *Depress. Anxiety*, 2009, vol. 26, no. 11, pp. 984—992.
https://doi.org/10.1002/da.20605

62. Zannas, A.S. and Binder, E.B., Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism, *Genes, Brain Behav.*, 2014, vol. 13, no. 1, pp. 25—37.
https://doi.org/10.1111/gbb.12104

63. Appel, K., Schwahn, C., Mahler, J., et al., Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the general population, *Neuropsychopharmacology*, 2011, vol. 36, no. 10, pp. 1982—1991.
https://doi.org/10.1038/npp.2011.81

64. Lahti, J., Ala-Mikkula, H., Kajantie, E., et al., Associations between self-reported and objectively recorded early life stress, FKBP5 polymorphisms, and depressive symptoms in midlife, *Biol. Psychiatry*, 2016, vol. 80, no. 11, pp. 869—877.
https://doi.org/10.1016/j.biopsych.2015.10.022

65. Tozzi, L., Carballedo, A., Wetterling, F., et al., Single-nucleotide polymorphism of the FKBP5 gene and childhood maltreatment as predictors of structural changes in brain areas involved in emotional processing in depression, *Neuropsychopharmacology*, 2016, vol. 41, no. 2, pp. 487—497.
https://doi.org/10.1038/npp.2015.170

66. Bradley, R.G., Binder, E.B., Epstein, M.P., et al., Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene, *Arch. Gen. Psychiatry*, 2008, vol. 65, no. 2, pp. 190—200.
https://doi.org/10.1001/archgenpsychiatry.2007.26

67. Ressler, K.J., Bradley, B., Mercer, K.B., et al., Polymorphisms in CRHR1 and the serotonin transporter loci: gene × gene × environment interactions on depressive symptoms, *Am. J. Med. Genet., Part B*, 2010, vol. 153B, no. 3, pp. 812—824.
https://doi.org/10.1002/ajmg.b.31052

68. Ludwig, B., Kienesberger, K., Carlberg, L., et al., Influence of CRHR1 polymorphisms and childhood abuse on suicide attempts in affective disorders: A G × E approach, *Front. Psychiatry*, 2018, no. 9, p. 165.
https://doi.org/10.3389/fpsyt.2018.00165

69. Hsu, W.W., Wu, B., and Liu, W.R., Sirtuins 1 and 2 are universal histone deacetylases, *ACS Chem. Biol.*, 2016, vol. 11, no. 3, pp. 792—799.
https://doi.org/10.1021/acschembio.5b00886

70. Donmez, G. and Outeiro, T.F., SIRT1 and SIRT2: emerging targets in neurodegeneration, *EMBO Mol. Med.*, 2013, vol. 5, no. 3, pp. 344—352.
https://doi.org/10.1002/emmm.201302451

71. Tang, L., Chen, Q., Meng, Z., et al., Suppression of sirtuin-1 increases IL-6 expression by activation of the akt pathway during allergic asthma, *Cell Physiol. Biochem.*, 2017, vol. 43, no. 5, pp. 1950—1960.
https://doi.org/10.1159/000484119

72. Aftanas, L.I., Anisimenko, M.S., Berdyugina, D.A., et al., SIRT1 allele frequencies in depressed patients of European descent in Russia, *Front. Genet.*, 2018, no. 9, p. 686.
https://doi.org/10.3389/fgene.2018.00686

73. Pearson, T.A. and Manolio, T.A., How to interpret a genome-wide association study, *JAMA*, 2008, vol. 299, no. 11, pp. 1335—1344.
https://doi.org/10.1001/jama.299.11.1335

74. Shadrina, M., Bondarenko, E.A., and Slominsky, P.A., Genetics factors in major depression disease, *Front. Psychiatry*, 2018, vol. 9, p. 334.
https://doi.org/10.3389/fpsyt.2018.00334

75. Sullivan, P.F., de Geus, E.J., Willemsen, G., et al., Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo, *Mol. Psychiatry*, 2009, vol. 14, no. 4, pp. 359—375.
https://doi.org/10.1038/mp.2008.125

76. Ripke, S., Wray, N.R., Lewis, C., et al., A mega-analysis of genome-wide association studies for major depressive disorder, *Mol. Psychiatry*, 2013, vol. 18, no. 4, pp. 497—511.
https://doi.org/10.1038/mp.2012.21

77. Hek, K., Demirkan, A., Lahti, J., et al., A genome-wide association study of depressive symptoms, *Biol. Psychiatry*, 2013, vol. 73, no. 7, pp. 667—678.
https://doi.org/10.1016/j.biopsych.2012.09.033

78. Rees, M.I., Harvey, K., Ward, H., et al., Isoform heterogeneity of the human gephyrin gene (GPHN), binding domains to the glycine receptor, and mutation analysis in hyperekplexia, *J. Biol. Chem.*, 2003, vol. 278, no. 27, pp. 24688—24696.
https://doi.org/10.1074/jbc.M301070200

79. CONVERGE Consortium, Sparse whole-genome sequencing identifies two loci for major depressive disorder, *Nature*, 2015, vol. 523, no. 7562, pp. 588—591.
https://doi.org/10.1038/nature14659

80. Okbay, A., Baselmans, B.M., De Neve, J.E., et al., Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses, *Nat. Genet.*, 2016, vol. 48, no. 6, pp. 624—633.
https://doi.org/10.1038/ng.3552

81. Hyde, C.L., Nagle, M.W., Tian, C., et al., Identification of 15 genetic loci associated with risk of major depression in individuals of European descent, *Nat. Genet.*, 2016, vol. 48, no. 9, pp. 1031—1036.
https://doi.org/10.1038/ng.3623

82. Liu, W. and Rodgers, G.P., Olfactomedin 4 expression and functions in innate immunity, inflammation, and cancer, *Cancer Metastasis Rev.*, 2016, vol. 35, no. 2, pp. 201—212.
https://doi.org/10.1007/s10555-016-9624-2

83. Hawrylycz, M.J., Lein, E.S., Guillozet-Bongaarts, A.L., et al., An anatomically comprehensive atlas of the adult human brain transcriptome, *Nature*, 2012, vol. 489, no. 7416, pp. 391—399.
https://doi.org/10.1038/nature11405

84. Wray, N.R., Ripke, S., Mattheisen, M., et al., Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major de-

pression, *Nat. Genet.*, 2018, vol. 50, no. 5, pp. 668—681. https://doi.org/10.1038/s41588-018-0090-3

85. Sanz, R., Ferraro, G.B., and Fournier, A.E., IgLON cell adhesion molecules are shed from the cell surface of cortical neurons to promote neuronal growth, *J. Biol. Chem.*, 2015, vol. 290, no. 7, pp. 4330—4342. https://doi.org/10.1074/jbc.M114.628438
86. Lee, A.W., Hengstler, H., Schwald, K., et al., Functional inactivation of the genome-wide association study obesity gene neuronal growth regulator 1 in mice causes a body mass phenotype, *PLoS One*, 2012, vol. 7, no. 7. e41537. https://doi.org/10.1371/journal.pone.0041537
87. Hashimoto, T., Maekawa, S., and Miyata, S., IgLON cell adhesion molecules regulate synaptogenesis in hippocampal neurons, *Cell Biochem. Funct.*, 2009, vol. 27, no. 7, pp. 496—498. https://doi.org/10.1002/cbf.1600
88. Amir-Zilberstein, L., Blechman, J., Sztainberg, Y., et al., Homeodomain protein otp and activity-dependent splicing modulate neuronal adaptation to stress, *Neuron*, 2012, vol. 73, no. 2, pp. 279—291. https://doi.org/10.1016/j.neuron.2011.11.019
89. Choi, Y., Nam, J., Whitcomb, D.J., et al., SALM5 trans-synaptically interacts with LAR-RPTPs in a splicing-dependent manner to regulate synapse development, *Sci. Rep.*, 2016, no. 6, p. 26676. https://doi.org/10.1038/srep26676
90. Zhu, Y., Yao, S., Augustine, M.M., et al., Neuron-specific SALM5 limits inflammation in the CNS via its interaction with HVEM, *Sci. Adv.*, 2016, vol. 2, no. 4. e1500637. https://doi.org/10.1126/sciadv.1500637

Translated by A. Kazantseva