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Genetic basis of depressive disorders

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Depression is a common mental disorder being one of the main causes of disability and mortality worldwide. Despite an intensive research during the past decades, the etiology of depressive disorders (DDs) remains incompletely understood; however, genetic factors are significantly involved in the liability to depression. The present review is focused on the studies based on a candidate gene approach, genome-wide association studies (GWAS) and whole exome sequencing (WES), which previously demonstrated associations between gene polymorphisms and DDs. According to the first approach, DD development is affected by serotonergic (*TPH1*, *TPH2*, *HTR1A*, *HTR2A*, and *SLC6A4*), dopaminergic (*DRD4*, *SLC6A3*) and noradrenergic (*SLC6A2*) system genes, and genes of enzymatic degradation (*MAOA*, *COMT*). In addition, there is evidence of the involvement of HPA-axis genes (*OXTR*, *AVPR1A*, and *AVPR1B*), sex hormone receptors genes (*ESR1*, *ESR2*, and *AR*), neurotrophin (*BDNF*) and methylenetetrahydrofolate reductase (*MTHFR*) genes, neuronal apoptosis (*CASP3*, *BCL-XL*, *BAX*, *NPY*, *APP*, and *GRIN1*) and inflammatory system (*TNF*, *CRP*, *IL6*, *IL1B*, *PSMB4*, *PSMD9*, and *STAT3*) genes in DD development. The results of the second approach (GWAS and WES) revealed that the *PCLO*, *SIRT1*, *GNL3*, *GLT8D1*, *ITIH3*, *MTNR1A*, *BMP5*, *FHIT*, *KSR2*, *PCDH9*, and *AUTS2* genes predominantly responsible for neurogenesis and cell adhesion are involved in liability to depression. Therefore, the findings discussed suggest that genetic liability to DD is a complex process, which assumes simultaneous functioning of multiple genes including those reported previously, and requires future research in this field.
Key words: depressive disorder; serotonin; hypothalamic-pituitary adrenal axis; neurotrophin; apoptosis; cytokines; GWAS; whole-exome sequencing.

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Генетические основы предрасположенности к депрессивным расстройствам

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Депрессия – это распространенное психическое расстройство, которое является одной из ведущих причин нетрудоспособности и смертности в мире. Несмотря на интенсивные исследования, проводимые в течение последних десятилетий, этиология депрессивных расстройств все еще остается не до конца изученной, однако генетические факторы, безусловно, играют важную роль в предрасположенности к депрессии. Настоящий обзор сфокусирован на результатах работ, основанных на генно-кандидатном подходе, полногеномных (Genome-Wide Association Studies, GWAS) и полноэкзомных (Whole Exome Sequencing, WES) исследованиях, продемонстрировавших связь полиморфных локусов генов с депрессивными расстройствами. Согласно первому подходу, формирование депрессивной симптоматики находится под влиянием генов серотонинергической (*TPH1*, *TPH2*, *HTR1A*, *HTR2A*, *SLC6A4*), дофаминергической (*DRD4*, *SLC6A3*) и норадренергической (*SLC6A2*) систем, а также генов ферментов их метаболизма (*MAOA*, *COMT*). Кроме того, имеются данные об участии генов гипоталамо-гипофизарной системы (*OXTR*, *AVPR1A*, *AVPR1B*) и рецепторов половых гормонов (*ESR1*, *ESR2*, *AR*), генов нейротрофического фактора мозга (*BDNF*) и фермента метилентетрагидрофолатредуктазы (*MTHFR*), нейронального апоптоза (*CASP3*, *BCL-XL*, *BAX*, *NPY*, *APP*, *GRIN1*) и воспалительной системы (*TNF*, *CRP*, *IL6*, *IL1B*, *PSMB4*, *PSMD9*, *STAT3*) в развитии депрессивных расстройств. Результаты второго подхода

(GWAS и WES) демонстрируют, что гены белков пикколо (*PCLO*) и сиртуина (*SIRT1*), фактора пролиферации стволовых клеток (*GNL3*), гликозилтрансферазы (*GLT8D1*), α-трипсинового ингибитора (*ITIH3*), мелатонинового рецептора (*MTNR1A*), костного морфогенного белка (*BMP5*), ломкой гистидиновой триады (*FHIT*) и киназного супрессора (*KSR2*), протокадгерина (*PCDH9*) и активатора транскрипции *AUTS2*, преимущественно участвующие в процессах нейрогенеза и клеточной адгезии, вовлечены в развитие депрессии. Таким образом, эти и другие литературные данные подтверждают, что формирование генетической предрасположенности к депрессивным расстройствам – сложный процесс, затрагивающий функционирование большого числа генов, в том числе тех, которые ранее не обсуждались в связи с депрессией, что требует обратить особое внимание на них в дальнейших исследованиях.
Ключевые слова: депрессивное расстройство; серотонин; гипоталамо-гипофизарная система; нейротрофин; апоптоз; цитокины; GWAS; полноэкзомное секвенирование.

Inroduction

According to the World Health Organization (WHO), unstable social, economic and ecological factors in the modern society result in the constant increase in the distribution frequency of socially significant diseases with a specific attention given to depressive disorders (DDs). Primarily, such attention is caused by a high distribution of depression among the population, the annual increase in morbidity, the difficulties of diagnosis, prevention and treatment of this disease (Smulevich, 2015). Moreover, depression is one of the leading causes of disability worldwide. To date more than 322 million of individuals with DDs differing in age were registered and the total number of individuals with depressive disorders increased by more than 18.4 % over the last decade. Suicidal behavior (SB) represents an increasing depression-associated problem being the second leading cause of mortality among individuals aged 15–29 years (WHO, 2017).

Depression is a mental disorder characterized by a pathologically reduced mood, inhibited intellectual and motor activity, reduced vital impulses with individual pessimistic assessment and future (Smulevich, 2015). Different medical classifications are based on a variety of diagnostic criteria of depression. The international classification of diseases (ICD-10) diagnoses depression (F32 − depressive episode) depending on the number and severity of symptoms including reduced mood, anhedony, strength decline and fatigue, psychomotor retardation or arousal, guilt and humiliation ideas, suicidal thoughts, decreased attention concentration and sexual motivation, impaired sleep and appetite (Smulevich, 2015; ICD-10, 2018).

Nowadays, the most common validated scales for DDs diagnostics include the Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MADRS), which are used in clinical practice by psychiatrists for the assignment of treatment strategy (Cusin et al., 2010).

The multifactorial nature of depressive disorders

Depression is a multifactorial mental disorder caused by a wide range of psychological, social, neurochemical, and hereditary factors and their interaction (Smulevich, 2015). According to the results of twin studies, the coefficient of inheritance of depression is 29–46 % differing for various DDs (Kendler et al., 2006). The psychosocial predictors of DDs distinguish a special style of individual negative thinking, which is characterized by a focus on the negative aspects of life, conflict child-parent relationships in childhood, maternal depression or a large number of stressful life events (Daches et al., 2018). The results of numerous studies suggest that the development of depression may be related to the individual reaction on diagnosed psychiatric disorder (Kim et al., 2018) causing social disadaptation. DDs are widely assumed to cause or be caused by suppressed anger and aggression (Sahu et al., 2014).

Interestingly, DDs appear to be sex-specific. It was reported that the frequency of depression was twice higher in women than in men (WHO, 2017). This sexual dimorphism is related to the differences in nervous and endocrine systems functioning and to the sex-specific transcription profiles of the genes (Gerhard, Duman, 2018). Moreover, such frequency is assumed by fact that men with depression symptoms less likely seek for the medical help than women (Girgus, Yang, 2015).

Neurophysiological studies of depressive disorders

The neurophysiological approach used for DD study suggests an important role of the detection of the primary impairments in the brain structures involved in the regulation of emotional processes and motivation. However, the data on such neurophysiological markers are scarce to date due to the significant clinical and etiological heterogeneity of DDs.

Functional, structural and post-mortem studies evidence that abnormalities in the subgenual part of the cingulate gyrus are the most stable neurophysiological markers of DDs. A decreased volume or increased metabolic activity of the subgenual part was observed in patients at the early stages of the disease and in individuals with a family history of depression (Hajek et al., 2008). Magnetic resonance imaging demonstrated reduced volumes of the frontal areas, especially the anterior cingulate gyrus, orbitofrontal and prefrontal cortex, as well as a decrease in the volume of the hippocampus, putamen and caudate nucleus in DD patients (Koolschijn et al., 2009). Moreover, temporal and insular lobes together with cerebellum, which demonstrate a decreased activity, are involved in DD pathophysiology (Fitzgerald et al., 2008).

Significant impairments in the activity of the hypothalamic-pituitary-adrenal (HPA) axis have been detected more than in a half of DD patients. Namely, the hypothalamus of patients was characterized by an increase in the number of neurons producing corticotropin-releasing hormone, which chronic

increase results in the enhancement of the toxic damage of monoaminergic neurons thus reducing their number in depressive states (Naughton et al., 2014).

Molecular genetic studies of depressive disorders

Monoaminergic systems genes. The hypothesis of monoaminergic neurotransmission deficiency in DDs proposed in the 60s of the last century, triggered the study of gene polymorphisms involved in neurotransmitter turnover and affecting serotonin, dopamine and norepinephrine synthesis, degradation and neurotransmission (Gatt et al., 2015; Shadrina et al., 2018). Inconsistent findings revealed in multiple studies of DDs were subsequently systematized in meta-analyses (Kishi et al., 2013; Zhao et al., 2014; Liu et al., 2016; Wang et al., 2016; Bleys et al., 2018; Culverhouse et al., 2018; Rui et al., 2018; Taylor, 2018), which allowed to confirm or deny initial hypotheses on the involvement of certain monoaminergic system genes in the development of DDs (Table). According to the results of the meta-analyses, increased risk for developing depression was associated with polymorphic loci located in the serotonin transporter (*SLC6A4*) and receptors (*HTR1A*, *HTR2A*), tryptophan hydroxylase (*TPH2*), dopamine transporter (*SLC6A3*) and receptor (*DRD4*), norepinephrine transporter (*SLC6A2*), monoamine oxidase A (*MAOA*), and catechol-O-methyltransferase genes (*COMT*).

The role of the methylenetetrahydrofolate reductase gene. Methylenetetrahydrofolate reductase (MTHFR) is one of the key enzymes involved in the metabolism of folate and methionine, which, in turn, play an important role in the regulation of gene expression. The methylenetetrahydrofolate reductase gene (*MTHFR*; 1p36.22) was considered as a candidate one in the study of affective and bipolar disorders, schizophrenia, and depression (Gatt et al., 2015). The activity of this enzyme is known to decrease as a result of nucleotide substitutions in the *MTHFR* gene. One of these SNPs include *677C > T* (*rs1801133*) resulting in *Ala222Val* substitution in the catalytic domain of the enzyme and causing decreased enzymatic activity to 35 % (Weisberg et al., 1998). Subsequently, a number of meta-analyses confirmed the association of *rs1801133*T* allele and DD risk (Rai, 2017).

The role of brain-derived neurotrophic factor gene. Together with the study of neurotransmitter systems, analysis of the genes involved in the regulation of neurotoxic and neuroprotective responses to stress appears to be important. Neurotrophic factors (neurotrophins) represent a large group of polypeptides playing a key role in the development and maintenance of central nervous system (CNS) (Popova et al., 2017). The brain-derived neurotrophic factor encoded by the *BDNF* gene (11p14.1) is one of the most examined neurotrophic factors. According to the functional studies, Met-allele of the *BDNF Val66Met* (*196G > A*; *rs6265*) causes a reduced level of neurotrophic factor in the prefrontal cortex and brain stem and is associated with an increased risk of depression compared to *Val*-allele carriers (Youssef et al., 2018). Previously, a modulating effect of several environmental factors including chronic stress, childhood maltreatment, brain injury, and season of birth on the association of the *Val66Met* and depression (Bîlc et al., 2018) or increased anxiety (Kazantseva et al., 2015) was reported.

The role of neuronal apoptosis genes. The study of neuronal apoptosis as the mechanism underlying the maintenance of cellular homeostasis in nervous system is becoming highly important due to the increased distribution of psychiatric diseases nowadays. To date scarce studies were conducted on the model objects indicating the relationship between neuronal apoptosis and depression or stress, which can represent the primary basis for further molecular-genetic research in humans. For example, enhanced level of caspase-3 (encoded by the *CASP3* gene) – a proteolytic enzyme inducing cellular apoptosis – was observed in the cerebral cortex of rats, which experienced chronic mild stress (Bachis et al., 2008). Moreover, a prolonged exposure to stress results in a reduced expression of the antiapoptotic *BCL-XL* gene and enhanced expression of the proapoptotic *BAX* gene; whereas, reduced stress exposure promoted expression of the brain-derived neurotrophic factor (*BDNF*), nerve growth factor (*VGF*) and neuropeptide (*NPY*) genes in the hippocampus (Jiang et al., 2014).

Together with above-mentioned invasive approaches to the study of molecular mechanisms of complex pathophysiological states, other methods include reconstruction and analysis of associative genetic networks describing the relationship between molecular-genetic objects associated with neuronal apoptosis. Thus, the analysis of neuronal apoptosis genes conducted via gene prioritization approach revealed that neuronal apoptosis was regulated by the proteins encoded by the *BDNF* (with the highest priority), glutamate receptor (*GRIN1*), amyloid beta precursor protein (*APP*), coagulation factor II thrombin receptor (*F2R*), tumor necrosis factor superfamily ligand (*FASLG*), and transcriptional co-activator of steroid and nuclear receptors (*PPARGC1A*) genes. Most of these genes have not been previously discussed with respect to DDs thus providing the field of their examination in the future studies of depressive states (Yankina et al., 2017).

The role of hypothalamic-pituitary-adrenal axis genes. The functioning of the hypothalamic-pituitary-adrenal (HPA) axis represents another key mechanism regulating mental functions. Notably, the concentration balance between oxytocin and vasopressin, as the components of HPA axis, regulates various types of emotional reactions, while an impaired balance accompanied anxiety, autism and depression (Neumann, Landgraf, 2012). The oxytocin action is mediated by its interaction with oxytocin receptor (OXTR). One of the most studied the *OXTR* gene polymorphisms is the G > A (rs53576) substitution in the intron 3, which was reported to be associated with social behavior and depression (Kushner et al., 2018). Namely, *OXTR G/G*-genotype carriers demonstrated a significant increase in depressive symptoms (Kushner et al., 2018).

The data on the vasopressin role in the development of depression are scarce. A wide range of psychological functions of vasopressin (encoded by the *AVP* gene) is realized by its binding to two types of receptors: V1A (*AVPR1A*) and V1B (*AVPR1B*), expressed in the paraventricular and supraoptic hypothalamic nuclei (Neumann, Landgraf, 2012). Post-mortem studies established that DD patients were characterized by elevated levels of *AVP* and *AVPR1A* gene expression (Wang et al., 2008), whereas association studies of the *AVPR1B* gene polymorphisms and affective-related traits showed conflicting results (Kazantseva et al., 2014).

Meta-analyses based on associations of monoaminergic systems genes and depressive disorders

Gene	SNP/VNTR	Comparison groups	Number of studies (N)[1]	OR[2] (*p*)[3]	Risk allele/genotype	Reference
TPH2 (12q21.1)	*rs4570625*	*G* vs. *T*	6 (2754)	0.83 (0.001)	*G*	Gatt et al., 2015
	rs17110747	*A* vs. *G*	5 (2536)	0.84 (0.02)	*A*	
HTR1A (5q12.3)	*rs6295*	*C* vs. *G*	15 (9732)	0.87 (0.007)	*C*	Kishi et al., 2013
	rs878567	*C* vs. *T*	5 (4775)	0.83 (0.0002)	*C*	
HTR2A (13q14.2)	*rs6311*	*A* vs. *G/G*	15 (5539)	1.20 (0.03)	*A*	Zhao et al., 2014
SLC6A4 (17q11.2)	*5-HTTLPR*	*S* vs. *L*	51 (51449)	1.18 (< 0.0001)	*S*	Bleys et al., 2018
			31 (38802)	1.25 (0.02)		Culverhouse et al., 2018
DRD4 (11p15.5)	*VNTR 48* bp	*2R* vs. (*3R*, *4R*, *5R*, *6R*, *7R*)	5 (1132)	1.73 (0.0003)	*2R*	Gatt et al., 2015
SLC6A3 (5p15.33)	*VNTR 40* bp	9/10 vs. 10/10	3 (423)	2.06 (< 0.01)	*9/10*	»
SLC6A2 (16q12.2)	*rs5569*	*A/A* vs. *G*	18 (8798)	1.19 (0.02)	*A/A*	Rui et al., 2018
MAOA (Xp11.3)	*VNTR 30* bp	*L* vs. *S*	9 (4223)	1.23 (0.03)	*L*	Gatt et al., 2015
	rs1137070	*T* vs. *C*	39 (18824)	1.26 (0.0006)	*T*	Liu et al., 2016
COMT (22q11)	*rs4680*	*Val* vs. *Met/Met*	17 (5308)	1.18 (0.02)	*Val*	Wang et al., 2016
		Val vs. *Met*	49 (10925)	0.98 (0.68)	–	Taylor, 2018

Notes: [1] N – number of individuals included in meta-analysis; [2] OR – odds ratio; [3] *p* – significance level (*p*-value).

The role of sex hormone genes and their receptors. As noted above there is a strong evidence of depression sex-specificity (Girgus et al., 2015; Gerhard, Duman, 2018). Therefore, the study of the effects of sex hormones on the human behavior is becoming increasingly popular. Estrogens represent a group of female sex hormones, which affect CNS activity via genomic and non-genomic mechanisms due to their interaction with estrogen receptors ERα and Erβ encoded by the *ESR1* and *ESR2* genes, respectively. The majority of association studies of these genes is focused on four SNPs, namely, *rs2234693* (*–397T > C*) and *rs9340799* (*–351 A > G*) in the *ESR1* gene and *rs1256049* (*1082G > A*) and *rs4986938* (*1730 G > A*) in the *ESR2* gene, which are assumed to affect gene expression and are associated with DD development (Keyes et al., 2015).

Androgens are male sex hormones also involved in the regulation of CNS activity. Testosterone as a main androgen demonstrates a number of physiological functions including the regulation of the psycho-emotional sphere in men. A decreased testosterone level due to age-related andropause was reported to significantly increase DD risk (Dreval, 2017). Moreover a reduced expression of the androgen receptor gene (*AR*, Xq12) associated with the presence of extended polyglutamine $[CAG]_n$ repeats in the exon 1 correlated with a higher risk of depression (Sankar, Hampson, 2012); however, others failed to detect such association (Gardiner et al., 2017).

The role of inflammatory genes. Recently, the hypothesis of inflammation as a DD predictor has being widely developed, which is evidenced by the data on increased expression of proinflammatory cytokines, in particular, C-reactive protein in the acute phase of inflammation (encoded by the *CRP* gene), tumor necrosis factor alpha (*TNF* gene), interleukin-1β (*IL1B* gene) and interleukin-6 (*IL6* gene) (Liu et al., 2012; Köhler et al., 2017) in patients with depressive episode. This observation could be explained by the fact that any stress is accompanied by an increased blood cytokines level and permeability of the blood-brain barrier. Such changes result in the ability of circulating cytokines to penetrate into the brain, trigger neuroinflammatory reactions, which can contribute to the development of DDs and other psychopathologies. Meanwhile, a strong evidence of a reduced synaptic availability of monoamines caused by inflammatory mediators, which is known to be one of the main mechanisms in DD pathogenesis, exists (Miller, Raison, 2016).

T-cells dysfunction and impaired immune response are also considered in the context of the inflammatory theory of depression. Thus, M.L. Wong et al. (2008) revealed that 47.8 % of the population risk of depression was caused by genetic variations in the *PSMB4* gene (*rs2296840*), which encodes β4-proteasome subunit, and in the *TBX21* gene (*rs17244587*) encoding transcription factor and involved in T-lymphocytes differentiation. Moreover, T-cells functioning and response to antidepressant therapy was significantly related to the activity of genes encoding ε-subunit of T-lymphocytes co-receptor (*CD3E*), β-subunit of glycosidase II (*PRKCSH*), signal protein (*STAT3*) and proteasome protein (*PSMD9*) (Wong et al., 2008). Therefore, they are considered as candidates in DD study.

Genome-wide association study (GWAS)

Nowadays genome-wide association study (GWAS) represents one of the most prospective approaches for the study of complex behavioral traits, which includes simultaneous examination of thousands of single nucleotide polymorphisms (SNPs) in genes involved even in unknown pathogenetic mechanisms causing DD development. One of the first GWAS demonstrated an association of the *rs2522833* in the

PCLO gene ($p = 6.4 \times 10^{-8}$) with an increased depression risk; however, it remained statistically insignificant under the appropriate level of statistical significance ($p < 5 \times 10^{-8}$) (Sullivan et al., 2009). Subsequent study confirmed the role of this protein in DD regulation, since *PCLO rs2715157* was associated with DD ($p = 2.91 \times 10^{-8}$) (Mbarek et al., 2017). The *PCLO* gene encodes the protein located in presynaptic terminals and plays a key role in monoaminergic neurotransmission of the brain (Sullivan et al., 2009), which fits into the contemporary ideas of neurotransmitter theory of depression.

As a result of Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (PGC-MDD) in 2013, 15 SNPs residing 3p21.1 were associated with a combined phenotype including the *PBRM1* gene involved in chromatin remodeling, G-protein nucleolar 3 gene (*GNL3*), glycosyltransferase 8 domain containing 1 gene (*GLT8D1*), *ITIH1-ITIH3-ITIH4* genes cluster, etc. (Major Depressive Disorder Working Group…, 2013). The association of *rs2535629* neighboring the *ITIH3* gene (inter-alpha-trypsin inhibitor heavy chain 3) and DD was the most significant ($p = 5.9 \times 10^{-9}$); however, it requires additional study.

According to the subsequent genome-wide association studies, SNPs residing the genes involved in circadian rhythms regulation such as sirtuin 1 (*SIRT1*), melatonin receptor 1A gene (*MTNR1A*), fragile histidine triad (*FHIT*) (CONVERGE consortium, 2015; Demirkan et al., 2016; Direk et al., 2017) are of interest. These findings suggest a significant role of circadian rhythms in the regulation of individual psycho-emotional sphere and point to the necessity to consider them in the DD research for the understanding of biological mechanisms causing this affective disorder.

Other GWAS based on the combined sample of CONVERGE, PGC and 23andMe demonstrated that *rs7973260* ($p = 1.8 \times 10^{-9}$), *rs62100776* ($p = 8.5 \times 10^{-9}$) and *rs9540720* ($p = 1.69 \times 10^{-8}$) located in the *KSR2* (12q24.22–q24.23), *DCC* (18q21.2) and *PCDH9* (13q21.32) genes, respectively, were associated with DD (Okbay et al., 2016). Notably, the proteins encoded by the protocadherin 9 (*PCDH9*) and kinase suppressor of ras 2 genes (*KSR2*) interacting with DCC netrin 1 receptor (*DCC*) are involved in synaptic plasticity, cellular adhesion, and axonal guidance (Guo et al., 2016; Xiao et al., 2018). Moreover, an increased expression of the *DCC* gene in prefrontal cortex resulted in a depressive-like behavior in mice (Torres-Berrío et al., 2017), while an increased expression of the *PCDH9* gene was observed in hippocampus and frontal lobe of depressed individuals, which represents a marker of enhanced risk of depression in humans (Xiao et al., 2018).

A whole-genome association study conducted by D.M. Howard et al. (2018) based on the UK Biobank cohort demonstrated the association of 17 SNPs and depression risk, including *rs10127497* (*SGIP1*), *rs6424532* (*LOC105378800*), *rs7548151* (*ASTN1*), *rs6699744* (*LOC105378797*), *rs112348907* (*KCNQ5*), *rs3132685* (*HCG9*), *rs5011432* (*TMEM106B*), *rs2402273*, *rs1554505* (*MAD1L1*), *rs3807865* (*TMEM106B*), *rs263575* (*LOC105375983*), *rs10929355* (*NBAS*), *rs40465* (*LOC105379109*), *rs1021363* (*SORCS3*), *rs10501696* (*GRM5*), *rs9530139* (*B3GLCT*), and *rs28541419*. These genes were suggested to be responsible for synaptic plasticity and neurogenesis (Howard et al., 2018). Another neurogenesis-related gene (*AUTS2*) was also involved in developing DD, which was reported in GWAS examining response efficacy to antidepressant therapy (*rs7785360* and *rs12698828*, $p = 1.60 \times 10^{-8}$) (Myung et al., 2015).

Therefore, the results obtained under GWAS evidence in the involvement of multiple genes in depression development (including those previously unexamined in psychopathologies) involved in different stages of neurogenesis, synaptic plasticity and circadian rhythms regulation. This is congruent with the existing theory of polygenic architecture of DD and demonstrates the direction for the future molecular-genetic research in this field.

Whole-exome sequencing (WES)

The development of next generation sequencing (NGS) technologies resulted in a trend for the sequencing of genetic regions containing only coding parts (i.e. exons). The total length of exons is known to be about 1% of the genome: however, it is assumed that the majority of pathogenic mutations are exon-specific. Hence, whole-exome sequencing (WES) represents one of the important approaches to solve a number of diagnostic and research tasks.

To date several whole-exome studies of DDs were conducted. The first WES study on the pharmacogenetics of antidepressants (Tammiste et al., 2013) was carried out by a group of scientists from the University of Tartu ($n = 510$). Tammiste et al. demonstrated the association of *rs41271330* in bone morphogenetic protein 5 (*BMP5*) gene with response to antidepressant therapy. Another WES study based on the RS (the Rotterdam Study) and ERF (Erasmus Rucphen Family) studies revealed a missense mutation *rs77960347* (*Asn396Ser*) observed with a population frequency of 1% in the *LIPG* gene encoding endothelial lipase, which was associated with depressive symptoms ($p = 5.2 \times 10^{-8}$) (Amin et al., 2017b). This enzyme is assumed to be involved in the metabolism of steroids, cholesterol and thyroid hormones, while *Asn396Ser* substitution caused reduced enzymatic activity (Amin et al., 2017b). In addition, subsequent WES analysis performed by the same group of scientists in DD patients detected mutation in the *NKPD1* gene ($p = 3.7 \times 10^{-8}$), which is involved in sphingolipids synthesis (Amin et al., 2017a), and in the *RCL1* gene ($p = 1.0 \times 10^{-4}$) (Amin et al., 2018). The sphingolipids are known to be widely present in the nervous tissue and are involved in myelination, which impairment could result in neuronal degeneration. At the same time, the *RCL1* gene is widely expressed in astrocytes and neurons in the cerebral cortex; however, its effect on their functioning and the potential role in DD pathogenesis remain incompletely studied and require additional studies.

Conclusion

Numerous results of genome-wide and whole-exome analyses summarized in the present review conclude that the key processes involved in developing DDs include neurogenesis, cell adhesion, axonal guidance and synaptic plasticity, which modifications have been considered as the main pathogenetic factors of cognitive impairments and neurodegenerative disorders. Moreover, the data on the association of genes encoding the proteins involved in the regulation of circadian rhythms, inflammation and hormonal regulation with an increased risk

of depression were discussed. These observations suggest that DD development is a highly complex process caused by impairments in a whole cascade of reactions and genes functioning with a small contribution of each of them in depression pathogenesis.

The studies of epigenetic factors including methylation and modifications of histones, microRNAs, and long non-coding RNAs examined in details in the previous review (Mustafin et al., 2018) are expected to make a significant contribution to unravel the nature of DDs. The role of gene-environmental interactions, ethnicity-geographic and socio-cultural factors in manifestation of depressive symptoms via epigenetic mechanisms of gene expression regulation representing a particular interest in further research in this field could not be excluded.

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