Genetic Markers in Psychiatry

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Abstract

Psychiatric disorders such as addiction (substance use and addictive disorders), depression, eating disorders, schizophrenia and posttraumatic stress disorder (PTSD) are severe, complex, multifactorial mental disorders that carry a high social impact, enormous public health costs, and various comorbidities as well as premature morbidity. Their neurobiological foundation is still not clear. Therefore, it is difficult to uncover new set of genes, and possible genetic markers of these disorders since the understanding of the molecular imbalance leading to these disorders is not complete. The integrative approach is needed which will combine genomics and epigenomics, evaluate epigenetic influence on genes, and their influence on neuropeptides, neurotransmitters and hormones, examine gene x gene and gene x environment interplay, and identify abnormalities contributing to development of these disorders. Therefore, novel genetic approaches, based on systems biology focused on improvement of the identification of the biological underpinnings might offer genetic markers of addiction, depression, eating disorders, schizophrenia and PTSD. These markers might be used for early prediction, detection of the risk to develop these disorders, novel subtypes of the diseases and tailored, personalized approach to therapy.

Key words: addiction; depression; eating disorders; schizophrenia; genetics; markers; PTSD

Introduction

Psychiatric disorders are among the leading causes of the disability worldwide. The classifications of psychiatric disorders, even the most recent ones such as DSM 5 [1] and ICD-10 [2], are based on clusters of symptoms, described as clinical syndromes, which have mostly unknown etiology. In the 21st century, unlike in any other fields of medicine, there is still lack of reliable diagnostic tools in psychiatry. However, strong evidence from numerous studies indicates that psychiatric disorders have a genetic background. This chapter focuses on the genetic basis of different psychiatric conditions. Various methods have been used in the studies, which investigated the association between genetic factors and the development of psychiatric disorders. Numerous family, twin and adoption studies were carried out several decades ago and provided the first evidence of the genetic background of psychiatric disorders. They revealed more frequent occurrence of psychiatric diseases in the families of affected members than in control population. This familial aggregation might be due to the shared genes which are involved in the development of the disease (nature) or shared environment (nurture). Twin studies offer an advantage over even the most sophisticated molecular genetic studies, in terms of capturing all inherited genetic effects, and thus offering the best available measure of heritability [3]. Findings obtained from family, twin and adoption studies provided strong evidence for the heritability of major psychiatric disorders. Heritability estimates the proportion of individual variation in particular trait, which is explained by

inherited factors, while the rest of variation is explained by non-inherited factors [4]. Most psychiatric disorders are moderately to highly heritable [5]. Among psychiatric disorders, bipolar disorder is one of the most heritable medical disorders, with the heritability between 59 and 87% [6,7]. Similarly, heritability estimates for schizophrenia are around 80% [8]. Some studies suggested that earlier onset of the disease is associated with increased familiar risk [6], while others did not confirm this finding [9]. Major depressive disorder (MDD) is generally considered to have moderate heritability [4]. However, recent study reported the heritability of MDD to be as high as 67% [9]. On the other hand, anxiety disorders have lower heritability rate, such as 43% for panic disorder and 32% for generalized anxiety disorder [10], while heritability estimates for obsessive compulsive disorder (OCD) ranged from 27-65% [11]. For eating disorders, such as anorexia nervosa and bulimia nervosa, heritability rates were reported to be 28% to 58% and 54 to 83%, respectively [12]. Wide variations in aforementioned heritability estimates across studies might arise from differences in methodology, such as type of population, diagnostic criteria, different endophenotypes, issues of comorbidity and statistical power. Modern methods include the field of molecular genetics. Although the development of all psychiatric disorders is influenced by both environmental and genetic factors, it is considered that the onset of such complex disorders is influenced by only small number of genes with a small effect. Namely, thousands of variants impact the risk for psychiatric disorders. Almost all psychiatric disorders are associated with potentially thousands of genes, each contributing with a very small effect, as reflected from the odds ratios mostly being between 1.01 to 1.2. Risk loci are located in both coding and non-coding portions of the genes. The human genome contains millions of loci that are commonly polymorphic. At the most polymorphic loci, hundreds of alleles may be found. They might impact gene expression, and consequently increase the risk for the development of particular disorder. Association studies are commonly used in psychiatry, including case-control and family-based designs. The former includes large samples of cases and controls and is the only possible method in the case of diseases with a late onset such as dementias, for which parents of affected individuals are no longer available. However, in case-control studies, both cases and controls need to be carefully matched demographically, given the substantial differences in allele frequencies in different populations [13, 14]. Those candidate genes are coding different structures (i.e. receptors, transporters, metabolizing enzymes, ion channels) in dopaminergic, adrenergic, serotonergic, glutamatergic, GABAergic, cannabinoid and opioid systems, neurotrophins, the hypothalamic-pituitary-adrenal (HPA) axis, and proteins involved in neuronal and synaptic functioning. In addition, association studies are typically addressing only few markers in candidate genes, which are hypothesized to be related to a particular disorder. Those limitations are overcome in genome-wide association studies (GWAS), including tens of thousands of samples and millions of different polymorphisms. GWAS including tens of thousands of participants confirmed genetic heritability and genetic correlation estimates for PTSD [3]. These studies are necessary for locating genetic effects in highly polygenic conditions such as psychiatric disorders. Majority of GWAS were focused on genetics of only one disorder. In psychiatry, however, the comorbidity is more a rule than an exception. Consequently, the cross-disorder genomics field has been recently introduced [5]. The large molecular study of cross-disorder genetics [15] reported the highest genetic correlations of common single-nucleotide polymorphisms (SNP) between schizophrenia and bipolar disorder, the prototypes of two most severe and devastating psychiatric disorders. This finding is not completely unexpected, given that two disorders share several similarities, such as the onset in early adulthood, psychotic features and the chronic course. Correlations of MDD were also significant with schizophrenia, bipolar disorder and attention deficit hyperactivity disorder (ADHD) [5]. Moreover, a high proportion of co-heritable SNPs was detected across schizophrenia and bipolar disorder, unlike for any other pair of psychiatric disorders [5]. Recent study, which included more than 100 000 subjects, confirmed the presence of shared genetic substrate between schizophrenia and bipolar disorder, but also emphasized disease-specific genetic substrate [16]. More recently, a conceptual shift in molecular

genomic studies occurred. Dimensional approach, rather than classical diagnostic criteria, holds promise for future phenotypic research [5].

The aim of this chapter is to summarize the knowledge about the role of genetic factors in the development of psychiatric disorders. For scientists and clinicians, those findings would not only improve our understanding of the biology of psychiatric disorders, but are also expected to eventually help in predicting the development of certain disorders and thus, apply appropriate preventive strategies. Moreover, it would help tailoring treatment to the individual patient, in order to maximize the chance of the most favorable outcome.

Genetics of addiction

Substance use and addictive disorders

Addiction is a chronic psychiatric disorder characterized mostly by the compulsive use of a certain drug or activity which strongly and directly activate the brain reward system leading to neglection of other activities resulting in repercussions on the individuals, their families and society [17]. According to DSM-5 [1] criteria, addictions are grouped in substance use and addictive disorders. Substance use disorders are addictions related to different types of substances including for example alcohol or stimulant use disorder, while gambling disorder is the only addictive disorder included in DSM-5 as a diagnosable condition for now [1]. Some people are more prone to become addictive which depends on several factors, including intrinsic factors (genetic background, gender, age, medical history including other addictions or mental disorders), environmental factors (availability of addictive substance or activity, peer influences, social support, childhood adversity, socioeconomic status) and the nature of the addictive substance or activity (psychoactive properties, mode of use). The impact of these factors may be different through different stages of addiction. Usually, the first exposure is mostly influenced by peers and family environment, while further development of addiction depends more on genetic factors and psychopathology [18].

Genetic background of addiction

There are family, adoption and twin studies emphasizing the importance of genetic background in the development of addictions [19-23]. Despite the fact that there are evidences indicating a role of genetic influences in the development of addiction, a sole identification of crucial genes and loci moderating vulnerability is a big challenge due to the genetic complexity of addictive disorders. During this search, scientists usually choose either candidate gene studies or genome-wide association studies (GWAS) approach.

One of the first GWAS [24] seeking to define specific genes included in the etiology of opioid use disorder (OUD) found no significant associations of 10 000 SNPs between relatively small groups of heroin dependent patients and controls of European descent. After increasing a sample size and including also patients of African ancestry, the same group of scientists found only one (rs10494334) out of 100 000 SNPs significantly associated with heroin addiction, but only in Europeans [24]. A big GWAS of OUD [26] performed on more than 12 000 subjects of either European-American or African-American ancestry implicated the strongest association of opioid dependence with genes encoding potassium voltage-gated channel subunits such as KCNC1, KCNG2, and KCNA4 genes. A study conducted on 4 cohorts [27] identified a variant on chromosome 15, rs12442183, near RGMA (repulsive guidance molecule family member A), associated with opioid dependence. Additionally, they showed on 10 brain tissues derived from 134 healthy human brains from UK Biobank that the risk T allele is correlated with higher expression

of a specific RGMA transcript variant in frontal cortex [27]. Considering the GWAS results in other addictions, the strongest association was found [28] between nicotine addiction and CHRNA5-CHRNA3-CHRNB4 gene cluster encoding for α5, α3, and β4 subunits of nicotinic acetylcholine receptors (nAChRs). On the other hand, alcohol dependence GWAS reported mostly results not reaching the genome-wide significance [29]. The most significant marker associated with alcoholism was rs6943555 in autism susceptibility candidate 2 gene (AUTS2) [30]. It seems that the GWAS results for addiction thus far defined quite small number of genes that could be a consequence of a relatively small sample sizes (<10 000) or cross-country heterogeneity.

In contrast to the non-hypothesis driven GWAS approach, the candidate gene approach focuses on discovering potential associations between specific disorder or phenotype and pre-specified genes that could be involved in certain mechanism of disease development. One of the candidate gene in case of OUD is opioid receptor mu 1 gene (OPRM1) encoding for mu-opioid receptor that becomes activated by endogenous peptides, opioid analgesics or illegal substances. Maybe the most studied SNP in OPRM1 gene is rs1799971. Since this polymorphism changes amino acid sequence of the protein, one could assume that it could also alter its expression or function. This hypothesis was confirmed in several studies [31, 32], but association studies of this SNP in OUD provided opposite findings, suggesting that this association either exists [33] or does not exist [34]. Other SNP (rs3778150) found in OPRM1 gene that does not alter the amino acid sequence was significantly associated with opioid dependence in a population of subjects from USA that were of either of African or European ancestry [35]. The same effect was found in a replication study in a population of European ancestry, while, on the other hand, this effect was not significant in a replication study with subjects of African ancestry, suggesting that, as in most genetics studies, the whole genetic background could play a crucial role. Besides mu-opioid receptor, an important role in reward system has the delta-opioid receptor encoded by opioid receptor delta 1 (OPRD1) gene. Most studied variants of OPRD1 gene were rs2236861, rs2236857 and rs3766951. Findings of studies dealing with an association of those OPRD1 variants with OUD are again opposite, a phenomenon that could be explained by the different ancestry of included subjects [36-39]. Not only opioid, but also dopamine receptors have an important role in the normal function of human brain reward system. The rs1079597 (Taq1B) variant of dopamine receptor D2 (*DRD2*) gene was found to be in high linkage disequilibrium with the rs1800497 (Taq1A) variant of a gene encoding a serine/threonine protein kinase (*ANKK1*) [40]. For both variants have found an association with opioid dependence in European [41] as well as in Han Chinese [42] subjects. Although not directly involved in the award system, the brain-derived neurotrophic factor (BDNF) is, through its role in a neuronal growth and differentiation, a gene candidate in OUD. The C allele of rs6265 (Val66Mat) BDNF variant was found to be associated with increased risk of opioid dependence in the samples from central China [43] and Taiwan [44], but, also, the lack of association between BDNF rs6265 and alcohol dependence or alcohol related endophenotypes was reported in Caucasians with alcohol dependence [45]. In the case of alcohol dependence, probably the most important candidate genes are alcohol-metabolizing genes, alcohol dehydrogenase 1B (*ADH1B*) and aldehyde dehydrogenase 2 (*ALDH2*). The rs1229984 (His48Arg) variant in *ADH1B* gene directly affects catalytic efficiency of an enzyme. Namely, His48/His48 homozygotes have increased ADH1B activity resulting in higher rates rate of oxidation of ethanol to acetaldehyde [46]. On the other hand, the Lys487 allele according to rs671 (Glu487Lys) variant of *ALDH2* gene reduces the enzyme activity causing the same result, accumulation of acetaldehyde [46]. Subsequently, acetaldehyde accumulation leads to heightened alcohol-induced responses (flushing, nausea, headache and tachycardia) which in the end makes the above mentioned alleles protective against alcohol dependence [47, 48]. Considering the role of monoamines in the modulation of emotionality, cognition and reward, it is not surprising that some of the genes encoding for monoamines are also among candidate genes for alcohol dependence. For example, the activity of dopamine metabolizing enzyme catechol-O-methyltransferase (COMT) depends

on rs4680 SNP in *COMT* gene. There are studies reporting no associations [49] between this polymorphism and addiction, but also indicating the Val158 allele as a risk allele in methamphetamine, nicotine, alcohol and polysubstance addiction [50-53]. Opposite results were found in patients with late onset alcoholism from Finland, where increased risk were associated with the Met158 allele of the *COMT* rs4680 [54].

Since such complex phenotypes as addictions arise as a result of different interacting biochemical pathways influenced by the products of numerous genes, scientists often choose a study approach in which one phenotype would be better understood by clarifying the effects of gene variants in the context of specific biochemical pathways. Also, unless there is a direct impact of a particular gene on a substance metabolism, genetic influence on the development of addiction will be more evident if environmental exposure is also considered. Besides, one should take into account possible gene x gene interactions that could have additive or masking effect. After all, it is evident that the search of genetic markers of addiction is quite demanding, but promising and important field of science.

Genetics of eating disorders

Eating disorders

Classical eating disorders include anorexia nervosa (AN), bulimia nervosa (BN) and binge-eating disorder (BED) and they are gender dependent, affecting mainly female population. These are severe mental disorders that carry a high social impact, an enormous public health cost, premature mortality in young people and increased disability-adjusted life years [55]. According to the newest classification of mental disorders (DSM 5) [1], the chapter on Feeding and Eating Disorders includes also Pica, Rumination Disorder Avoidant/Restrictive Food Intake Disorder (ARFID), Other Specified Feeding or Eating Disorder (OSFED) and Unspecified Feeding or Eating Disorder (UFED). Better understanding of the neurobiological and genetic underpinning of eating disorders might improve the treatment, since novel knowledge might point to novel therapeutic targets, and identify validated and sensitive biomarkers [56]. Namely, besides psychological interventions, only two drugs are approved by the FDA for eating disorders, fluoxetine for bulimia nervosa and lisdexamfetamine for BED [57].

Genetic background of eating disorders

Genetic background of eating disorders is confirmed by the family, twin and adoption studies showing aggregations in families and estimated high heritability, between 40-65% [55,57-59]. As in all complex psychiatric disorders, which are complicated entities, the neurobiological foundation of eating disorders is not clearly identified. Different neurotransmitters and their receptors (serotonin, dopamine, opioids), neuropeptides (BDNF) and hormones (neuropeptide Y, agouti-related peptide /AgRP/, alpha-melanocyte-stimulating hormone, orexins, proopiomelanocortin (POMC), CRH, cocaine and amphetamine regulated transcript (CART), oxytocin, ghrelin, leptin), other appetite regulators (glucagon like peptide 1, cholecystokinin, peptide tyrosine tyrosine (PYY), anandamide or N-arachidonoylethanolamine (AEA)), and many others are altered in eating disorders [55,57,58]. Serotonergic system has a role in regulation of mood and impulse control, satiety, anxious and obsessional behavior, appetite, and body weight, dopaminergic system affects feeding and addictive behavior via its reward system, opioid system via its receptors also modulate reward sensitivity and food intake, ghrelin, neuropeptide Y and AgRP possess appetite-stimulating effects and promote feeding and increase body mass index while POMC and CART have the opposite, appetite suppressing effects; melanocortin 4 receptor (MC4R) is associated with obesity; BDNF moderates energy metabolism and regulates mood, feeding behavior and weight [60];

oxytocin inhibits appetite; leptin promotes satiety and it is important regulator of energy metabolism and balance; cholecystokinin induces satiation, glucagon like peptide 1 inhibits food intake [55,57,58].

Therefore, the genetic architecture of eating disorders is complex and polygenic, making the search for the risk/protective genetic markers even more complicated. Several approaches are used to study genetic background of all psychiatric disorders including eating disorders. These are: quantitative and molecular genetic studies [57] (Breithaupt et al. 2018). Quantitative studies include family, twin and adoption studies, that shed light on the aggregation in families and heritability [55]. Molecular genetic [57] studies might be hypothesis free, such as linkage studies and GWAS, and hypothesis based, such as candidate gene association studies. Linkage studies detect specific genomic regions associated with genes related to eating disorders (i.e. AN, BN or BED), while candidate gene association studies compare the frequency of genotypes/alleles of the particular gene associated with eating disorders in affected subjects and controls. GWAS identify genetic variations of the whole genome in case/controls. However, characterization of genetic basis of eating disorders (AN, BN or BED) has been particularly challenging, and a lot of discoveries were not replicated. GWAS are large scale genomic studies, require very large samples, however due to the multiple testing corrections, rare genetic variants reach genome-wide significance [55]. To overcome these problems, meta analyses were conducted, but they still failed to confirm GWAS significant results either in AN [61-63], BN [64], or general symptoms of eating disorders [63,64].

Besides these methods, novel methods include copy number variation (changes /deletions or duplications/ in the number of copies of a genomic region), high-throughput sequencing studies, transcriptomic and epigenetic studies [65], linkage disequilibrium score regression, genetic correlations, polygenic risk scores, gene-wide analysis and pathway analysis, and rare genetic variations [57]. All these novel methods might lead to precision medicine approach to eating disorders [57]. With aim to evaluate which genetic variations contribute to a person's risk for development of particular eating disorder, a psychiatric consortium and working groups for eating disorders (especially AN) were established, resulting in large sets of data [57,65]. However, consortiums for BN and BED, and more confirmed GWAS data are still scarce.

As recently reviewed [55], few loci, genes and their polymorphisms have been reported to be associated with eating disorders (AN, BN, BED), using association studies and GWAS, but few of them were confirmed with meta-analyses [58]. These are the genes related to potassium calcium activated channel (KCNN3) and orexin receptor (HCRTR1) [66]; serotonin receptor type 2A (HTR2A) [59, 67-71], serotonin receptor type 1D (HTR1D) [62,72-74], serotonin receptor type 1B (HT1B) [75]; serotonin transporter (5-HTT) [59,76,77], tryptophan hydroxylase (TPH2) [78]; OPRD1 [73,79], dopamine receptor type 2 /ankyrin repeat and kinase domain containing 1 (DRD2/ANKK1), COMT [71,80-82]; and dopamine receptor type 4 (DRD4) [83,84]; also genes for ghrelin [85,86], ghrelin O-acyl-transferase (GOAT) [87]; AgRP [85,88]; estrogen receptor 1 (ESR1) [89]; type 1 cannabinoid receptor (CB1R) [90]; BDNF [91]; fat mass and obesity (FTO) [92]; calcium-activated potassium channel (SK3) [93]; sex determining region Y-Box 2 (SOX2) [63,65,94]; C-type lectin domain containing 5A (CLEC5A), peptidase S1 domain-containing protein (LOC136242), teashirt zinc finger homeobox 1 (TSHZ1), synaptotagmin like 5 (SYTL5) for AN, 5'-nucleotidase, cytosolic IB (NT5C1B) for BN and ATPase phospholipid transporting 8A2 (ATP8A2) for BED [64]; and RUN and FYVE domain-containing protein 1 (RUFY1), cyclin L1 (CCNL1), semaphorin 6D (SEMA6D), SHC Adaptor Protein 4 (SHC4), disks large-associated protein 1 (DLGAP1), serum deprivation-response protein (SDPR), and transcriptional repressor GATA binding 1 (TRPS1) [63]. Some of the polymorphisms significantly associated with AN (Table 1) or BN (Table 2) are shown [55,58].

However, although some of these associations were suggestive, none of them reached genome wide significance [55]. Namely, after correction for the multiple testing none of these loci, genes and polymorphisms were significantly associated with eating disorders, or were significant only at the trend level, or suggested that the existence of signal which was not significant [57,58]. Genes related to serotonergic, dopaminergic and opioid system were not confirmed, while some new genes with unknown biological function were suggested, but still not replicated in GWAS.

Until now, there are no significant genes that are associated with eating disorders [55,57,58]. The reasons for the inconsistent results in linkage, candidate gene association studies and especially GWAS lay in the fact that these studies need very narrowly defined groups (i.e. phenotypes, endophenotypes and clinical subtypes) with particular eating disorders (AN, BN or BED) and age and sex-matched control groups, a large number of subjects to increase statistical power and to detect association, and require the inclusion of patients without comorbid psychiatric disorders and symptoms, such as major depressive disorder, bipolar disorder, schizophrenia, alcohol and substance use disorders, personality disorder, obsessive-compulsive disorder, anxiety, emotional instability, suicidality, and obesity [55,57-59,100], which are frequent in eating disorders. On the other hand, some of these comorbid disorders (alcohol or substance use disorders) have been associated with eating disorders as they share similar disruptions of the control and reward systems [58,69,71]. A novel method, linkage disequilibrium score regression, merged GWAS data with genetic correlation between different phenotypes/traits, and provided the first results showing an overlap between AN and schizophrenia, AN and major depressive disorder and AN and bipolar disorder, suggesting a shared, common genetic cumulative risk [65,100]. In addition, detection of the single gene is tempered by the small effect size of genes involved in eating disorders [57,58].

Genetic markers of eating disorders

To uncover new set of genes, and possible genetic markers, the integrative approach is needed which will combine genomics and epigenomics, evaluate epigenetic influence on genes, and their influence on neuropeptides, neurotransmitters and hormones, examine gene-environment interplay, and identify biological, but also psychological, and/or environmental abnormalities contributing to development of eating disorders. The aim is to improve the understanding of the molecular imbalance leading to eating disorders [55,57,58]. Therefore, novel genetic approaches, based on systems biology focused on improvement of the identification of the biological underpinnings of eating disorders, might offer genetic markers of eating disorders such as markers for early prediction, detection of risk to develop eating disorders, novel subtypes of the diseases and tailored approach to therapy of particular eating disorders [55,57,58]. To achieve this goal, multidisciplinary teams and creation of new available databases are required.

Genetics of post-traumatic stress disorder

Post-traumatic stress disorder

Although only a subset of individuals develops post-traumatic stress disorder (PTSD) (5-10%) [101] after witnessing or being exposed to the traumatic event, its debilitating nature is manifested in subsequent trauma re-experience, avoidance, numbing, negative cognitive and mood alternations and hyperarousal symptoms (DSM-5) [1]. In addition to psychiatric, metabolic and cardiovascular comorbidities frequently present in individuals with PTSD [102] and lack of appropriate therapy, this disorder still represents a major health care challenge as well as social and financial burden. External factors such as type of trauma, early life adversity, sex and age influence PTSD development and severity [101]. However, twin studies

demonstrated substantial role of genetic inheritance in PTSD etiology, especially in women. It is estimated that PTSD heritability varies from 42% for general population and 72% in all-female subset of patients [103, 104] and is shared with other mental disorders, such as schizophrenia and major depression [104].

Candidate gene studies in PTSD

Previous strategies seeking to identify potential genetic markers of PTSD vulnerability/resilience have been mostly relying on understanding the neurobiological background of PTSD symptomatology and hence offering the genes potentially involved in those processes. This approach was mainly focused on genes involved in dopaminergic, serotonergic and opioid neurotransmitters systems, neurotrophins and the HPA axis. Positive findings from candidate genes, as well as genome wide studies are presented in Table 3. Dopamine and serotonin are catecholamines involved in regulation of mood, memory processes, emotional reactivity, arousal and attention [105] so commonly studied genes were ones encoding for their receptors and transporters.

The T allele of the SNP rs1800497 located in *DRD2* gene was more prevalent in PTSD subjects than in controls and was associated with higher alcohol intake [106, 107, 108], however, several negative results have also been reported [109, 110]. A study by Voisey et al. [111] did not confirm association of the rs1800497, but showed significant excess of the C allele of the SNP rs6277 in PTSD subjects, which is also located in the *DRD2* gene. The 3' untranslated region (3' UTR) of the dopamine active transporter 1 gene (*DAT1*) contains 40 bp variable tandem repeat (VNTR,) where lower number of repeats (9) showed higher risk of PTSD in contrast to higher number (10) of repeats [112-114]. However, a non- replication also exists [109]. The VNTR in dopamine receptor 4 gene (*DRD4*) did not predict the PTSD diagnosis, but 7- and 8-repeats were associated with more severe PTSD symptoms, especially avoidance [115].

Serotonergic activity and concentration is regulated by 5-HT transporter, encoded by the *5HTT* or *SLC6A4* gene. The 5-HTTLPR polymorphism is a functional one, where the shorter variant (the S allele) leads to reduced 5-HTT expression and consequently lower serotonin reuptake. However, another polymorphism rs25531 (A>G substitution), in the same region, also strongly affects 5-HTT expression [116]. Therefore, this polymorphism (5HTTLPR) is considered triallelic. Studies have shown that reduced 5-HTT expression, or the presence of the S allele (or long (L) allele carriers with G substitution) is associated with a potential risk for PTSD [117,118]. Although some studies did not show any association of this polymorphism with PTSD [119,120], its interaction with the environmental factors, such as number and severity of trauma, was reported to be related to PTSD symptoms [121-125]. These gene x environment (GxE) studies demonstrated potential effect of stress and external factors on genetic susceptibility to PTSD, possibly mediated via (de)methylation of DNA regions, as a way of epigenetic control of gene expression [122]. However, these results need to be replicated in larger cohorts.

The inhibitory GABA-ergic system, in addition to dopaminergic and serotonergic systems, is also involved in pathophysiology of anxiety and depression, which are common comorbidities in individuals with PTSD. The rs279836 T allele, rs279826 A allele and rs279871 A allele in the $GABA_A$ receptor subunit alpha 2 (*GABRA2*) were found to significantly interact with severity of childhood abuse to predict PTSD [126].

Another widely studied gene in psychiatric disorders is *COMT* which encodes for COMT enzyme included in degradation of catecholamines. Its functional G>A polymorphism (rs4680) leads to significantly diminished COMT activity in the brain and likely an excess of catecholamines (dopamine, noradrenaline) in the brain of A allele carriers, thereby affecting the neurocircuits of fear inhibition [105]. This SNP, rs4680

was reported to be significant predictor of PTSD in interaction with traumatic load [127-129] and also had effect on cognitive functioning in PTSD patients [130].

Neurotrophin BDNF has numerous roles in central nervous system [131], such as regulation of the stress and fear response, neurogenesis and synaptic plasticity. Since the fear response and lack of fear extinction are hallmark symptoms in PTSD, *BDNF* gene was studied as a candidate gene in PTSD. Functional G>A SNP at codon 66 (rs6265) results in G (valine) to A (methionine) substitution, leading to lower activity-dependent release of the BDNF in hippocampus and potentially inadequate stress response and memory consolidation. Zhang et al. [132] reported higher prevalence of the risk A allele of the rs6265 in veterans with PTSD, successfully integrating the environmental factors in the study. The presence of one or two A allele of the rs6265 was more frequently found in veterans with PTSD with psychotic features than in veterans without psychotic symptoms, or in veterans without PTSD [133].

The HPA axis activates noradrenergic system as a response to stress-induced release of corticotrophin-releasing hormone (CRH) and forms a complex feedback loop between glucocorticoid (GR) and endocannabinoid receptors (CNR1), along with regulating genes [134]. Dysregulation in any part of this system could mediate development and severity of PTSD symptoms. Besides its role in maintaining homeostasis of the HPA axis, endocannabinoid system has a role in memory processing, in particular, in the extinction of the fear memory [135]. The A allele of SNP rs1049353 of *CNR1* gene has been associated with risk for PTSD, and it was also found to interact with childhood physical maltreatment to increase severity of fear experience [136,137].

A polymorphism (rs2267735) in *ADCYAP1R1* (gene that encodes for the receptor for pituitary adenylate cyclase-activating polypeptide - PACAP) was associated with PTSD only in women, but not in men [138], thereby suggesting potential role of estrogen in mechanism of regulation of this gene. Later, Mercer et al. [139] showed the allele-specific binding of estrogen within ADCYAP1R1, in which the risk (C) allele diminished binding of estrogen on estrogen response element in this gene, leading to the lower expression of *ADCYAP1R1* and increased risk for PTSD.

Various SNPs: rs9296158, rs3800373, 1360780, rs9470080 in steroid receptor chaperone FK506 Binding Protein 51 gene (*FKBP5*), all in high linkage disequilibrium, showed association with PTSD in gene x environment fashion, and in particular, interaction with the childhood abuse [140,141]. Klengel et al. [142] proposed selective demethylation of DNA in enhancer region of this gene as a response to glucocorticoids release induced by childhood trauma. Decreased methylation leads to the increased gene expression of FKBP5, a protein also involved in other pathologies such as violent behavior, depression and suicide risk [143]. Although there are several successful candidate gene studies, especially ones which included environment as an important co-factor in predicting the diagnosis and severity of PTSD, with some of them even mechanistically well supported (for example *FKBP*5), main limitation is that this type of studies cannot easily escape bias. Moreover, proposed genes did not show significant effect on PTSD in GWAS.

Genome-wide association studies in PTSD

By the early 2000s, scientific and technological development of GWAS and next-generation sequencing (NGS) made analysis or very large number of SNPs and variable number tandem repeats (VNTRs) possible. These no-hypothesis driven approaches, due to the numerous of analyzed genetic variations (minimum half a million per test), require large sample sizes (>10 000) and very stern statistical correction (p value < $5*10^{8}$) to achieve appropriate power. Currently, the largest GWAS was done by Psychiatric Genomics

Consortium (PGC)-PTSD which comprised 5 000 PTSD subjects and 15 000 controls (mostly trauma-exposed). This study did not provide any SNP in GWAS significant p-value, except for the rs139558732 in African American subgroup [144] located close to Kelch-like protein 1 (*KLHL1*) gene, although this SNP failed to reach statistical significance in transethnic meta-analysis. This study also confirmed SNP-based heritability of PTSD, shared with other psychiatric disorders, primarily schizophrenia, but also bipolar disorder and major depression, and its higher impact on women.

Another findings in previous, less powered GWAS, highlighted SNPs in close vicinity of *RORA*, retinoid-related orphan receptor gene [145], zinc dependent metalloprotease Tolloid-Like 1 or *TLL-1* [146], adenylate cyclase 8 - *ADCY8* [147], a phosphoribosyl transferase domain containing 1 - *PRTFDC1* [148], TBC1 domain family member 2 - *TBC1D2* [149], ankyrin repeat domain 55 – *ANKRD55* [150], neuroligin 1 - *NLGN1* [151], olfactory receptor family 11 subfamily L Member 1 - *OR11L1* [152] as potential markers of PTSD (Table 3).

There is no straight-forward connection of the mentioned genes determined with GWAS with systems explored in candidate gene studies. However, some of them are implicated in basic neurological processes. For example, changes in RORA levels could affect neuron response to oxidative stress and inflammation and was reported to interact with childhood trauma to predict PTSD [156] in addition to original GWAS study. Neurolignin 1 has an important role in synaptic formation, maturation and maintenance and was previously associated with autism and Alzheimer's disease. Its depletion in mouse models resulted in impaired fear memory [157]. The OR11L1 is a G-protein-coupled receptor that initiates and transduces the sense of a smell upon binding odorant molecules [158]. Other positive hits mostly had more systemic roles, for example, *ANKRD55* is a protein involved in autoimmune and inflammatory disorders [150] while *PRTFDC1* could act as a possible tumor-suppressor gene, although its role is not completely determined [159]. The TLL1 and KLHL1 (primarly expressed in brain tissue) have important roles in remodeling of the extracellular matrix [160] and actin fibers [161], respectively, while TBC1D2 affects cell-cell adhesion [162].

The main limitation of GWAS is that none of the mentioned gene was proven significant in an independent replication cohort. This could be due to the very strict statistical corrections, or complex gene x environment network with still undefined effect on PTSD diagnosis. In order to successfully identify genetic and therapeutic targets, the next step relies on founding the large datasets with detailed genetic and environmental information and later their confirmation in mechanistic animal models in addition to neuroimaging genetics in humans. Next iteration by PGC-PTSD will include even more subjects than previous one [144], with total number of participants reaching over 130 000, which could have necessary power to elucidate key genes involved in pathophysiology of PTSD [163].

Analysis of epigenetic mechanisms of gene regulation and focusing on gene expression could point to the molecular mechanisms underlying the PTSD symptomatology, whether analyzed in post-mortem brain tissue, or more systemic, immunological response in peripheral blood. The latter could be easily available to reveal differential signature of PTSD but could also provide an insight into systemic changes reflecting or promoting brain changes [164] that follow the experience of the traumatic event.

Genetic markers of PTSD

Genetic studies in PTSD revealed that genetic background of PTSD is shared with other psychiatric disorders, such as schizophrenia, bipolar disorder and major depression, and the importance of gender.

These studies did not confirm any of the genes in the independent replication cohorts, presumably due to the complexity of the PTSD's underlying neurobiology, lack of statistical power and inadequate sample sizes. Therefore, future studies should include large datasets of both genders and different ethnicities to find significant genetic markers of PTSD.

Genetics of schizophrenia

Schizophrenia

Schizophrenia is a chronic, severe, debilitating psychiatric disorder with prevalence of 1% in the world population [8,165]. Characteristic symptoms of schizophrenia can be divided into positive and negative clusters, which are characterized by delusions, hallucinations, cognitive impairment, lack of interest and behavioral alterations [166]. Etiology, molecular mechanisms and development of schizophrenia are still unclear, however family and twin studies have shown that heritability is more than 80% compared with general population [165]. Schizophrenia is a complex, multifactorial disorder whereas interaction between many suspected genes with the small size effect and environmental triggers are involved in its development [165,167]. GWAS in schizophrenia discovered some potential genes that may represent the increased risk for schizophrenia. These genes are involved in many processes associated with neurogenesis, neurotransmission and other intracellular processes [8], while some risk alleles are shared between schizophrenia and other neuropsychiatric disorders, like depression, bipolar disorder and autism spectrum disorder [168].

Candidate genes in schizophrenia

Candidate genes in schizophrenia are the genes coding proteins involved in neurotransmission, differentiation, proliferation, motility of neurons and cell-cell adhesion. Among them, the first genes were the genes associated with dopaminergic system. COMT is an enzyme involved in catalysis of dopamine; therefore, it directly affects the dopamine level in the brain [169], especially in prefrontal cortex. It is encoded by the *COMT* gene, expressed in neural system. Due to the role of dopaminergic system in development of schizophrenia, *COMT* gene and its polymorphisms have been studied among patients with schizophrenia [169]. The SNP Val158Met (rs4680) in the *COMT* gene is a functional polymorphism that results in G (valine) to A (methionine) substitution at codon 108 for soluble COMT or at codon 158 for membrane-bound COMT [170,171]. The A allele is associated with decreased catalysis of dopamine, better cognitive performance but also increased aggression and better response to antipsychotic drugs [169,172], while the G allele, due to high dopamine metabolism in prefrontal cortex, is associated with reduced cognitive performance and represents higher risk for schizophrenia [169-171]. However, some studies did not find any association between *COMT* rs4680 and the risk for schizophrenia [171,173,174], and such conflicting data can be the result of different ethnic groups and different allele distribution among them [167,175]. Another polymorphism in the *COMT* gene is rs4818 polymorphism, that has been studied among schizophrenia subjects [176] and it is often inherited together with rs4680 polymorphism in a haplotype block. This polymorphism results in leucine to leucine substitution and has a greater influence on dopamine metabolism in the brain than rs4680 polymorphism. Both *COMT* SNPs, rs4680 and rs4818, were associated with treatment resistance, since female, but not male patients with schizophrenia, carriers of the G alleles of the COMT rs4680 and rs4818, and G-G/G-G haplotype, had lower risk of treatment resistance [176].

Genes for dopamine receptors were also studied as risk genes for schizophrenia. There are five subtypes of dopamine receptors encoded with different genes (*DRD1-DRD5*). The D1 dopamine receptor encoded with D1-like receptor gene (*DRD1*) has a major role in cognitive processes and it is assumed to be associated with negative symptoms in schizophrenia [177]. The dopamine receptor gene *DRD2*, coding ther D2 dopamine receptors, targets all antipsychotics acting as antagonists of DRD2 receptors [178]. The C allele of the C957T polymorphism (rs6277) in *DRD2* has been determined as a risk factor for schizophrenia [179]. Although the T allele of the rs6277 polymorphism is associated with poor mRNA stability, it is also linked with better cognitive performance [180]. In addition to polymorphisms in exon region, also polymorphisms in the intronic region can affect receptor function due to alternative splicing of exons. For example, rs1076560 polymorphism in intronic region of *DRD2* gene is associated with deficits in cognitive processes due to altered expression of DRD2. The TT genotype showed great association with schizophrenia risk in family studies, while carriers of the T allele had greater risk for schizophrenia compared with the T allele non-carriers [181]. Lack of association was reported for schizophrenia risk and rs1799732 and rs1800497 polymorphisms, while the rs1801028 polymorphism in *DRD2* gene represents a risk factor for schizophrenia [182]. Nonetheless, besides these polymorphisms, there are some synergistic effects with environmental factors, such as stress, that might affect *DRD2* expression [183]. In addition to *DRD1* and *DRD2* genes, it is assumed that rs6280 polymorphism in the *DRD3* gene that results in serine-glycine substitution is also associated with schizophrenia risk. However, for *DRD3* and *DRD4* genes, there were some associations and some studies failed to comfirm association with schizophrenia risk [184]. Furthermore, downstream genes in dopaminergic signaling are also associated with schizophrenia risk due to changes that can affect signal transmission [183].

Another neurotransmitter system affected in schizophrenia is glutamatergic neurotransmission. Metabotropic glutamate receptor (GRM3 or mGluR3) is encoded with *GRM3* gene and it is expressed in presynaptic neurons. Thus it is assumed that association between GRM3 gene and schizophrenia risk lays in the alterations of glutamatergic neurotransmission and excitatory amino acid transporter 2 (EAAT2) located in hippocampus and prefrontal cortex [185,186]. Variation in this gene increases schizophrenia risk, while the A allele of the polymorphism 4 in intronic region was associated with much worse cognitive performance due to alterations in receptor's activity and impairments in protein synthesis. Therefore, the G allele is considered as a protective factor, though molecular mechanisms are still unknown [185]. In addition, multiple studies showed lack of association between alterations in this gene and risk of schizophrenia [186], due to the impact of this gene on cognitive performance even in healthy controls and different distribution of alleles among different ethnic groups [185].

Disrupted in schizophrenia 1 is a protein encoded with the conversed gene *DISC1*. DISC1 protein interacts with other cytoskeletal, centrosomal and membrane proteins, therefore mediates various functions such as signal transmission, cell transport and gene expression [187,188]. Alterations in *DISC1* are associated with different psychiatric diseases. Various haplotypes in *DISC1* gene can be linked to different diseases, including schizophrenia and schizoaffective disorder. It is assumed that certain haplotypes on 5' end of *DISC1* gene represent schizophrenia risk. Moreover, haplotype block 3 is associated with the risk of the disease. It contains allele that codes for Phe607 and mediates interaction between DISC1 and other proteins. Furthermore, the T allele of rs6675281 polymorphism is associated with schizoaffective disorder, but also with bipolar disorder. Thus, different mechanisms are involved in DISC1 function i.e. different mechanisms associated with *DISC1* gene and interaction between its product and other proteins can represent risk factors for schizophrenia development [187]. The Ser allele of the Ser704Cys polymorphism

together with other SNPs that are in linkage disqulibrium in *DISC1* gene could represent risk factors for schizophrenia, due to alterations in hippocampus and cytoarchitectural impairments [188].

Neuregulin 1 (NRG1) is a member of family neuregulins that plays an important role in neuronal differentiation, proliferation and plasticity, through activation of kinases or coding for epidermal growth factor domain. Its association with schizophrenia is still unclear. However, in more than 80% of studies it is assumed that chromosome 8p is associated with schizophrenia risk. *NRG1* expression is altered among schizophrenia patients, confirming the assumption that this gene is involved in schizophrenia development. Several studies found connection between first two exons of *NRG1* gene with schizophrenia risk, however, these findings mostly reflect association between schizophrenia risk and this gene in Caucasians. Therefore, ethnicity should be taken in account due to the different allelic distribution in various populations. Since schizophrenia is a complex disorder, the association between the *NRG1* gene with schizophrenia should be consider together with other potential gene candidates [189].

BDNF is the most abundant neurotrophin in adult human brain. It is one of the most important factors in neuron growth differentiation, proliferation, plasticity and survival, but also in dopaminergic and serotonergic neurotransmission [190]. *BDNF* gene, which is located on 11^{th} chromosome, codes for homonymous protein and it is regulated by several promoters [191-193]. Multiple studies have been shown association between schizophrenia risk and *BDNF* gene, due to the developmental theory of schizophrenia, pointing to alterations during brain development and alterations in dopaminergic system [191]. The functional polymorphism in *BDNF* gene is Val66Met (rs6265), characterized by G/A substitution resulting in alterations in transport and secretion of pre-mature and mature BDNF [192]. Although there are differences in the allele distribution among various ethnic populations [13], the A allele is assumed to represent a risk factor for schizophrenia, due to its association with reduced hippocampal volume and alterations in its functioning [192]. In addition, the A allele is often associated with positive symptoms that occur in schizophrenia. However, many studies reported conflicting results [193]. Several studies found lack of association between rs6265 polymorphism and schizophrenia, while some studies suggested a potential role of the G allele as a risk factor. These studies assume that the A allele can have potential protective effect, while the G allele, which is mostly inherited from heterozigotic parents, represent a risk factor for schizophrenia. Namely, the GG homozygotes usually have more severe symptoms and more expressed negative symptoms compared to the A allele carriers. Therefore, further investigations are necessary to clarify potential role of rs6265 polymorphism in *BDNF* gene as a risk factor in schizophrenia [193].

Genes and schizophrenia risk

Schizophrenia is a complex, multifactorial psychiatric disease in which development, environmental factors and interactions with multiple genes have synergistic effect. Therefore, various genes are involved in various processes associated with schizophrenia development, progress and treatment response. Genes involved in schizophrenia risk encode for many proteins that play an important role in dopaminergic, serotonergic (*COMT,* activator of D-amino acid oxidase */DAOA/, p*rotein Phosphatase 1 Regulatory Inhibitor Subunit 1B */PPP1R1B/, DRD2, DRD4*) or glutamatergic neurotransmission (*GRM3, GRIA1, GRIN2A*), synaptic transmission (cholinergic receptor nicotinic alpha 7 subunit */CHRNA7/*), differentiation, proliferation and motility of neurons (*DISC1, DISC2, ANK1*), cell-cell adhesion (*DISC1, NRG1*), organelle biogenesis (dystrobrevin beta */DTNB1/*), processing of amino acids (methylenetetrahydrofolate reductase */MTHFR/*), G-protein signaling (regulator of G protein signaling 4

/*RGS4/*), calcium transfer and signaling (calcium voltage-gated channel subunit alpha 1I /*CACNA1I/,* calcium voltage-gated channel auxiliary subunit beta 2 /*CACNB2/,* calcium voltage-gated channel subunit alpha 1 C /*CACNA1C/,* protein phosphatase 3 catalytic subunit gamma */PPP3CC/*), regulation of transcription (transcription factor 4 /*TCF4/,* zinc finger protein 804A */ZNF804A/*), immune system (major histocompatibility complex */MHC/* gene family) metabolism of xenobiotics (cytochrome P450 family 2 subfamily D member 6 /*CYP2D6/*) and many other intracellular and intercellular processes [8,168,194,195]. Besides these gene variants, rare alleles represent also a schizophrenia risk [168].

Genetic markers of schizophrenia

The risk for development of schizophrenia mainly depends on the small size effect of the multiple genes involved in different systemic processes, together with environmental triggers and epigenetic regulation [8,168,194,195].

Genetics of depression

Depression

Depression is higly prevalent neuropsychiatric disorder characterized by many heterogenous symptoms with various severity. In spite of the extensive research, the complex underlying biological determinants of depression are still not clear, resulting in non-adequate treatment. In order to bring new insights in the genetic architecture of depression and offer novel potential targets for therapy, both candidate gene studies and GWAS were applied [196].

Family and twin research has provided strong evidence for the genetic backgrund of depression. A meta-analysis of twin studies demonstrated that the heritability rate for depression is 37% [197], whereas other reports estimated that the depression heritability ranges from 25-45% for general population [198,199,200]. However, higher genetic influence has been suggested in certain depression subtypes, for instance 48-72% in hospitalized depressed patients and even 72% for patients with severe, recurrent depression [201,202]. Similarly to many other neuropsychiatric diseases, a large number of genes expressed in the brain has been involved in the ethiology of depression, with high population occurrence of common gene variants, as well as small contribution of each gene [203,204]. Considering the polygenic features of depression, the investigation of various gene-gene interactions genes might represent a promising approach in depression research.

In addition to genetic factors, diverse environmental influences play an important role in the etiology of depression [196]. A study of Kendler et al. [205] demonstrated that genetic factors and life experiences contribute equally to depression risk. Moreover, it has been shown that stressors were 2.5 times more likely in depressed subjects in comparison to control individuals and that approximatelly 80% of depression cases reported stressfull life events [206,207]. However, as depression develops in only about 20% of subjects exposed to acute stress [208], vulnerability to stress and environmental factors may be dependent on the individual genetic background [209]. Therefore, the investigations of interaction between genes and environment might represent an important tool for identification of novel candidates in depression.

Gene candidate studies in depression

More than 100 candidate gene studies have been conducted in order of investigate potential associations with development of depression [210], and a significant amount of evidence for the genetic influences in depression has been gathered from different sources [211-215]. Various genetic studies investigated polymorphisms in genes associated with serotonergic, adrenergic and dopaminergic neurotransmission, including genes for dopamine receptors - *DRD3, DRD4* and serotonin receptors - *HTR1A, HTR2A, HTR1B, HTR2C*; genes for serotonin, noradrenaline and dopamine transporter - solute carrier family 6 member 4 (*SLC6A4)*, solute carrier family 6 member 2 (*SLC6A2),* solute carrier family 6 member 3 (*SLC6A3)*; genes for the enzymes monoamine oxidase A - *MAOA*, tyrosine hydroxylase - *TH*, tryptophan hydroxylase 1 - *TPH1*, catechol-o-methyl transferase - *COMT*, and the piccolo presynaptic cytomatrix protein - *PCLO* [210]. In addition, polymorphisms in genes involved in regulation of the HPA axis, such as genes coding for glucocorticoid and mineralocorticoid receptors (*NR3C1 and NR3C2*), and CRH receptors (*CRHR1* and *CRHR2*); genes important for neurogenesis and neuroplasticity (*BDNF)*, as well as genes involved in the inflammatory processes (including genes for interleukines - *IL1B* and *IL6*) and functioning of circadian system (Brain and muscle Arnt-like protein-1 /*BMAL1/,* circadian locomotor output cycles kaput */CLOCK/, n*euronal PAS domain-containing protein 2 /*NPAS2/, p*eriod circadian regulator 3 /*PER3/, c*ryptochrome circadian regulator 1 /*CRY1/,* and timeless circadian regulator */TIMELESS/*) have been studied [210]. The research also included various other genes, which are not linked with the general hypotheses of depression etiopathogenesis, with focus on genes for angiotensin-converting enzyme (*ACE*), apolipoprotein E (*APOE*), and methylenetetrahydrofolate reductase (*MTHFR*) [210].

However, a meta-analysis of the findings from 183 studies investigating depression, supported involvement of only several genetic polymorphisms, such as *APOE,* G Protein Subunit Beta 3 */GNB3/* (C825T), *MTHFR* (C677T*),* solute carrier family 6 member 15 or sodium-dependent neutral amino acid transporter B(0)AT2 */SLC6A4/* (40 bp VNTR, *5HTTLPR*), and *SLC6A3* (44 bp Ins/Del) [216]. Subsequent meta-analyses demonstrated associations between depression and *5HTTLPR* [217,218] and *MTHFR* C677T [219], while no associations were reported with *SLC6A2* T-182C and G1287A [220,221], *HTR2A* rs6311 [222], *BDNF* rs6265 [223], and *CLOCK* [224] polymorphisms. Nevethelles, only *GNB3* and *APOE3* associations seem to be depression-specific [225]. As most of these candidate gene studies had low sample sizes and replication issues, analyses involving larger cohorts have been conducted; however, they have not confirmed observed associations [203,226,227]. Therefore, the research focus was shifted to the GWAS.

Genome-wide association studies (GWAS)

GWAS have been increasingly applied during the past decade in order to investigate genetic loci associated with various complex traits. In an unconventional meta-analysis of GWAS data performed by the Psychiatric Genomics Consortium (PGC), none of the investigated polymophisms reached a genome-wide significance level, demonstrating no consistent association with depression [228]. According to the review of Dunn et al. [229], the only genome-wide significant association with depression from 15 reported studies was the one with rs1545843 *SLC6A15* polymorphism, which was replicated at a nominally significant level in four studies [230]. The study conducted in 2015, within the CONVERGE Project including >9000 Chinese females found two loci significantly associated with depression: rs12415800 *SIRT1* polymorphism and rs35936514 of the Phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP)* polymorphism [231].

Since then, more GWAS findings on depression have been published [231-239]; however only three replicated between different studies. The *PCLO* gene originally proposed as a risk gene for depression [240], was found to be significant in the study of Mbarek et al. [236] and replication study by Wray et al. [227]. The associations of rs12552 of the olfactomedin 4 (*OLFM4)* gene polymorphism, as well as different *NEGR1* gene polymorphisms, with depression have been demonstrated in two separate GWAS [234, 238]. The meta-analysis of GWAS performed by Wray et al. [238] identified 44 statistically significant independent loci, of which 30 were new and 14 were significant in a prior studies of depression.

Regarding epigenetic modifications, the genome-wide analysis of DNA methylation profiles in depression demonstrated significant differences in methylation status in the number of frontal cortex regions between healthy subjects and depressed patients [241].

Moreover, in the GWAS of Wong et al. [242], 11 rare variants were associated with depression. Rare variants analyses revealed variations and mutations in different genes including lipase G, endothelial type (*LIPG)* gene [243], phospholysine phosphohistidine inorganic pyrophosphate phosphatase *(LHPP)* and carboxypeptidase X, M14 family member 2 (*CPXM2)* genes [244], syntaxin binding protein 5 (*STXBP5), r*egulating synaptic membrane exocytosis 1 (*RIMS1), c*atenin beta 1 (*CTNNB1),* Dmx like 2 (*DMXL2), s*ynapsin I *(SYN1), t*yrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta (*YWHAB)* and *t*yrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein eta *(YWHAH)* genes [245], slit guidance ligand 3 (*SLIT3)* gene [246-249], *SLC6A2* and *HTR1A* genes [250], and Huntingtin *(HTT)* gene [251] associated with depression and depressive symptoms.

Gene x gene (GxG) and gene x environment (GxE) interaction studies

Different studies investigated the effects of various gene-gene (GxG) interactions on depression. Neff et al. [252] suggested possible interaction of 5HTTLPR polymorphism with an unknown gene on chromosome 4, whereas study of Gabriela Nielsen et al. [253] demonstrated interaction of *MTHFR* A1298C and *COMT* rs4680 polymorphisms. Interactions of polymorphisms within the *CRHR1* and arginine vasopressin receptor 1B (*AVPR1b)* genes may also affect depression [254], although some studies have not confirmed these findings [255]. Interactions between *CRHR1* gene polymorphisms and *BDNF* rs6265 polymorphism have been also reported [256]. In another study, depression was influenced by interaction of polymorphisms in matrix metalloproteinase *(MMP)* genes and TIMP metallopeptidase inhibitor 2 (*TIMP-2)* gene [257]. The significant effect on depression was also observed for interaction between rs41423247 of the CCND1 -Cyclin D1 (*BCL1)* gene and rs1044396 of the cholinergic receptor nicotinic alpha 4 subunit *(CHRNA4)* gene polymorphisms [258], as well as between trace amine associated receptor 6 (*TAAR6)* and heat shock protein 70 (*HSP-70)* gene variantions [259]. On the other hand, GWAS demonstrated no significant findings for pairwise GxG interactions, altough several nominally significant interactions were found [260].

Considering research on gene and enviroment (GxE) interaction in depression, most studies investigated the interaction of specific genes with a variety of stress factors. A significant interaction between *SLC6A* gene polymorphism 5HTTLPR and stressful life events including childhood maltreatment has been demonstrated in depression [261]. This finding has been confirmed in several [262-264], but not in other meta-analyses [265-267]. The differences in the obtained results might be attributed to the various types of stress interacting with 5HTTLPR polymorphism in depressed subjects [268]. Similarly, the interaction of *MAOA* gene polymorphisms and childhood maltreatment, as well as difficulties during maternity, affected depression [202,269,270], altough other studies observed no significant effects [269]. In addition,

significant gene x environment effect on depression has been demonstrated between various stressful life events and polymorphisms in *BDNF* [271,272], *COMT, SLC6A2, FKBP5* and *CRHR1* genes [269], gamma-aminobutyric acid type A receptor alpha 6 subunit (*GABRA6)* gene [273], *IL1B* and *IL-6* genes [274-277], galanin receptor 1 (*GALR1)* and galanin receptor 3 (*GALR3)* genes [278], *CNR1* gene [269,279] and fatty acid amide hydrolase (*FAAH)* gene [280]. Studies have also assessed gene x environment effect on depression in a genome-wide scale. The study enrolling European subjects observed no significant effects of interaction between genes and childhood trauma [281]. The other GWAS in the Mexican American sample revealed 44 gene variants in interaction with stress and affecting depression [242]; however, only the association with PHD finger protein 21B (*PHF21B)* gene has been replicated in a European cohort. Dunn et al. [282] found in African Americans one GWAS significant gene x environment effect for polymorphism rs4652467 near centrosomal protein 350 (*CEP350)* gene, which could not be replicated. In Japanese subjects marginally significant gene x environment effect between stress and rs10510057 polymorphism near regulator of G protein signaling 10 (*RGS10)* gene was found [283].

Three-way gene x gene x environment interactions in depression were demonstrated for *BDNF* rs6265 and 5HTTLPR polymorphisms with childhood abuse [284] and family environment [285], suggesting involvement of epigenetic regulating mechanisms triggered by stress [286]. *BDNF* rs6265 polymorphism also showed positive interaction with glycogen synthase kinase 3 beta (*GSK3B)* gene and recent life events in depression [287]. However, three-way environment x environment x gene interactions were also observed in depression, such as interaction of 5HTTLPR polymorpihism with both recent life event and childhood abuse exposure [288]. The example of even higher order interactions are 5-way interactions of *BDNF* rs6265 polymorphism with four different neurotrophic receptor tyrosine kinase 2 (*NTRK2)* gene polymorphisms [289].

Genetic markers of depression

A large number of candidate gene studies reported associations between various genes and depression; however, most of them have not been confirmed in replication studies and GWAS. The few significant genetic targets found in GWAS are related to mechanisms nonspecific for depression, such as neurogenesis, neuronal synapse, cell contact and DNA transcription [196]. A possible reason for the observed contradictory results might be clinical and biological heterogenity of depression, and identification of additional subgroups with more homogeneous phenotypes may help to better understand the genetic background of depression. In addition, the inconsistency between findings of various genetic studies might be due to the polygenic characteristics of depression with weak effect of individual genes and polymorphisms, but also to a prominent role of environmental factors such as stress, suggesting involvement of epigenetic regulating mechanisms. Therefore, investigation of gene x gene and gene x enviroment interactions, as well as epigenetic influences, seem most promissing approach for determination of additional candidates in depression pathophysiology and development of more efficient pharmacotherapy.

Conclusion

Given the moderate to high heritability of virtually all psychiatric disorders, the modern technology was expected to unravel their genetic background. In previous two decades there was an explosion of genetic studies in psychiatry. In spite of faster-than-ever increasing amount of genomic data, crucial genes which moderate vulnerability were not identified in any psychiatric disorder, except for Alzheimer's dementia. During this intensive search, scientists used either candidate gene or GWAS. The candidate gene approach

appears justified, given that polymorphisms in certain genes affect, among many others, the expression of receptors for neurotransmitters, catalytic efficiency of enzymes, or activity of transporters which are involved in the etiology of the disease. However, those studies frequently, and disappointedly, yielded opposite findings, even in the same disorder. After that, the research focus shifted to the GWAS. However, GWAS revealed no straight-forward connection with candidate genes explored in association studies. Actually, majority of GWAS identified only one or two, out of tens of thousands of SNPs, to be significantly associated with the presence of particular disorder, and some of these genes have yet unknown biological function. Other GWAS did not reach genome-wide significance at all. The main reason for such a lack of robust findings, in any psychiatric disorder, is attributed to genetic complexity of psychiatric disorders and very strict statistical corrections. Accurate diagnosis, sufficient sample size (>10 000), careful consideration of comorbidity and reduction of cross-country heterogeneity are challenges for future GWAS.

The pathway to overcome sample heterogeneity might be to focus on narrowly defined group within a single diagnosis, and especially on endophenotype. In addition to genetic factors, diverse environmental influences contribute to the development of the disease. In spite of undisputible heritability of psychiatric disorders, the way that genetic material predisposes an individual to development of psychopathology is largely unknown. While genetic consortiums are established worldwide, other avenues of investigation hold promise. Those include studies of polygenic risk scores, epigenetic studies, studies of gene-gene and gene-environment interactions, gene x gene x environment interactions or environment x environment x gene interactions in a genome-wide scale, studies of cross-disorder genetics and imaging genetics.

From the clinical point of view, genetics in psychiatry is currently far away from its use in practice. While waiting for new data, psychiatrists rely on their own skills and knowledge: preventive measures in high-risk groups, early recognition and treatment of symptoms, destigmatization and individualized approach to each patient, as much as possible.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Association; 2013.

[2] World Health Organization. (1992). The ICD-10 classification of mental and behavioral disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.

[3] Duncan LE, Cooper BN, Shen H. Robust findings from 25 years of PSTD genetics research. Curr Psychiatry Rep. 2018;20(12):115.

[4] McMahon FJ. Population-based estimates of heritability shed new light on clinical features of major depression. Am J Psychiatry. 2018;175(11):1058-60.

[5] Docherty AR, Moscati AA, Fanous AH. Cross-disorder psychiatric genomics. Curr Behav Neurosci Rep. 2016; 3(3):256-63.

[6] Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet. 2003;123C(1):48-58.

[7] Barnett JH, Smoller JW. The genetics of bipolar disorder. Neuroscience. 2009;164(1):331-43.

[8] Gejman PV, Sanders AR, Duan J. The role of genetics in the etiology of schizophrenia. Psychiatr Clin North Am. 2010;33(1):35-66.

[9] Guffanti G, Gameroff MJ, Warner V, Talati A, Glatt CE, Wickramaratne P, Weissman MM. Heritability of major depressive and comorbid anxiety disorders in multi-generational families at high risk for depression. Am J Med Genet B Neuropsychiatr Genet. 2016;171(8):1072-9.
[10]Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry. 2001;158(10):1568-78.
[11]Browne HA, Gair SL, Scharf JM, Grice DE. Genetics of obsessive-compulsive disorder and related disorders. Psychiatr Clin North Am. 2014;37(3):319-35.
[12]Thornton LM, Mazzeo SE, Bulik CM. The heritability of eating disorders: methods and current findings. Curr Top Behav Neurosci. 2011;6:141-56.
[13]Pivac N, Kim B, Nedic G, Joo YH, Kozaric-Kovacic D, Hong JP, et al. Ethnic Differences in Brain-derived Neurotrophic Factor Val66Met Polymorphism in Croatian and Korean Healthy Participants. Croat Med J. 2009;50(1):43-8.
[14]Noskova T, Pivac N, Nedic G, Kazantseva A, Gaysina D, Faskhutdinova G, et al. Ethnic differences in the serotonin transporter polymorphism (5-HTTLPR) in several European populations. Progr Neuro-Psychopharmacol Biol Psychiatry. 2008;32(7):1735-9.
[15]Sivakumaran S, Agakov F, Theodoratou E, Prendergast JG, Zgaga L, Manolio T, et al. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet. 2011;89(5):607-18.
[16]Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address: douglas.ruderfer@vanderbilt.edu; Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell. 2018;173(7):1705-15.e16.
[17]Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction. 2006;101 Suppl 1:23-30.
[18]Merikangas KR, Avenevoli S. Implications of genetic epidemiology for the prevention of substance use disorders. Addict Behav. 2000;25(6):807-20.
[19]Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. Am J Med Genet. 1996;67(5):473-7.
[20]Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med. 1997;27(6):1381-96.
[21]Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, Nurnberger JI, Jr., et al. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. Arch Gen Psychiatry. 1998;55(11):982-8.
[22]Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. Arch Gen Psychiatry. 2000;57(3):261-9.
[23]Li MD, Cheng R, Ma JZ, Swan GE. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. Addiction. 2003;98(1):23-31.
[24]Nielsen DA, Ji F, Yuferov V, Ho A, Chen A, Levran O, et al. Genotype patterns that contribute to increased risk for or protection from developing heroin addiction. Mol Psychiatry. 2008;13(4):417-28.
[25]Nielsen DA, Ji F, Yuferov V, Ho A, He C, Ott J, et al. Genome-wide association study identifies genes that may contribute to risk for developing heroin addiction. Psychiatr Genet. 2010;20(5):207-14.

[26]Gelernter J, Kranzler HR, Sherva R, Koesterer R, Almasy L, Zhao H, et al. Genome-wide association study of opioid dependence: multiple associations mapped to calcium and potassium pathways. Biol Psychiatry. 2014;76(1):66-74.
[27]Cheng Z, Zhou H, Sherva R, Farrer LA, Kranzler HR, Gelernter J. Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated With Opioid Dependence in European Americans. Biol Psychiatry. 2018;84(10):762-70.
[28]Bierut LJ, Madden PA, Breslau N, Johnson EO, Hatsukami D, Pomerleau OF, et al. Novel genes identified in a high-density genome wide association study for nicotine dependence. Hum Mol Genet. 2007;16(1):24-35.
[29]Bierut LJ, Agrawal A, Bucholz KK, Doheny KF, Laurie C, Pugh E, et al. A genome-wide association study of alcohol dependence. Proc Natl Acad Sci U S A. 2010;107(11):5082-7.
[30]Schumann G, Coin LJ, Lourdusamy A, Charoen P, Berger KH, Stacey D, et al. Genome-wide association and genetic functional studies identify autism susceptibility candidate 2 gene (AUTS2) in the regulation of alcohol consumption. Proc Natl Acad Sci U S A. 2011;108(17):7119-24.
[31]Kroslak T, Laforge KS, Gianotti RJ, Ho A, Nielsen DA, Kreek MJ. The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. J Neurochem. 2007;103(1):77-87.
[32]Oertel BG, Kettner M, Scholich K, Renne C, Roskam B, Geisslinger G, et al. A common human micro-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. J Biol Chem. 2009;284(10):6530-5.
[33]Kumar D, Chakraborty J, Das S. Epistatic effects between variants of kappa-opioid receptor gene and A118G of mu-opioid receptor gene increase susceptibility to addiction in Indian population. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36(2):225-30.
[34]Nikolov MA, Beltcheva O, Galabova A, Ljubenova A, Jankova E, Gergov G, et al. No evidence of association between 118A>G OPRM1 polymorphism and heroin dependence in a large Bulgarian case-control sample. Drug Alcohol Depend. 2011;117(1):62-5.
[35]Hancock DB, Levy JL, Gaddis NC, Glasheen C, Saccone NL, Page GP, et al. Cis-Expression Quantitative Trait Loci Mapping Reveals Replicable Associations with Heroin Addiction in OPRM1. Biol Psychiatry. 2015;78(7):474-84.
[36]Levran O, Londono D, O'Hara K, Nielsen DA, Peles E, Rotrosen J, et al. Genetic susceptibility to heroin addiction: a candidate gene association study. Genes Brain Behav. 2008;7(7):720-9.
[37]Beer B, Erb R, Pavlic M, Ulmer H, Giacomuzzi S, Riemer Y, et al. Association of polymorphisms in pharmacogenetic candidate genes (OPRD1, GAL, ABCB1, OPRM1) with opioid dependence in European population: a case-control study. PLoS One. 2013;8(9):e75359.
[38]Nelson EC, Lynskey MT, Heath AC, Wray N, Agrawal A, Shand FL, et al. Association of OPRD1 polymorphisms with heroin dependence in a large case-control series. Addict Biol. 2014;19(1):111-21.
[39]Randesi M, van den Brink W, Levran O, Blanken P, Butelman ER, Yuferov V, et al. Variants of opioid system genes are associated with non-dependent opioid use and heroin dependence. Drug Alcohol Depend. 2016;168:164-9.
[40]Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68-74.
[41]Vereczkei A, Demetrovics Z, Szekely A, Sarkozy P, Antal P, Szilagyi A, et al. Multivariate analysis of dopaminergic gene variants as risk factors of heroin dependence. PLoS One. 2013;8(6):e66592.
[42]Tsou CC, Chou HW, Ho PS, Kuo SC, Chen CY, Huang CC, et al. DRD2 and ANKK1 genes associate with late-onset heroin dependence in men. World J Biol Psychiatry. 2017:1-11.
[43]Jia W, Shi JG, Wu B, Ao L, Zhang R, Zhu YS. Polymorphisms of brain-derived neurotrophic factor associated with heroin dependence. Neurosci Lett. 2011;495(3):221-4.

[44]Cheng CY, Hong CJ, Yu YW, Chen TJ, Wu HC, Tsai SJ. Brain-derived neurotrophic factor (Val66Met) genetic polymorphism is associated with substance abuse in males. Brain Res Mol Brain Res. 2005;140(1-2):86-90.
[45]Nedic G, Perkovic MN, Sviglin KN, Muck-Seler D, Borovecki F, Pivac N. Brain-derived neurotrophic factor Val66Met polymorphism and alcohol-related phenotypes. Prog Neuropsychopharmacol Biol Psychiatry. 2013;40:193-8.
[46]Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007;30(1):5-13.
[47]Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li TK, et al. Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet. 1999;65(3):795-807.
[48]Bierut LJ, Goate AM, Breslau N, Johnson EO, Bertelsen S, Fox L, et al. ADH1B is associated with alcohol dependence and alcohol consumption in populations of European and African ancestry. Mol Psychiatry. 2012;17(4):445-50.
[49]Tammimaki AE, Mannisto PT. Are genetic variants of COMT associated with addiction? Pharmacogenet Genomics. 2010;20(12):717-41.
[50]Vandenbergh DJ, Rodriguez LA, Miller IT, Uhl GR, Lachman HM. High-activity catechol-O-methyltransferase allele is more prevalent in polysubstance abusers. Am J Med Genet. 1997;74(4):439-42.
[51]Jugurnauth SK, Chen CK, Barnes MR, Li T, Lin SK, Liu HC, et al. A COMT gene haplotype associated with methamphetamine abuse. Pharmacogenet Genomics. 2011;21(11):731-40.
[52]Nedic G, Nikolac M, Sviglin KN, Muck-Seler D, Borovecki F, Pivac N. Association study of a functional catechol-O-methyltransferase (COMT) Val108/158Met polymorphism and suicide attempts in patients with alcohol dependence. Int J Neuropsychopharmacol. 2011;14(3):377-88.
[53]Nedic Erjavec G, Nenadic Sviglin K, Nikolac Perkovic M, Muck-Seler D, Jovanovic T, Pivac N. Association of gene polymorphisms encoding dopaminergic system components and platelet MAO-B activity with alcohol dependence and alcohol dependence-related phenotypes. Prog Neuropsychopharmacol Biol Psychiatry. 2014;54:321-7.
[54]Tiihonen J, Hallikainen T, Lachman H, Saito T, Volavka J, Kauhanen J, et al. Association between the functional variant of the catechol-O-methyltransferase (COMT) gene and type 1 alcoholism. Mol Psychiatry. 1999;4(3):286-9.
[55]Cuesto G, Everaerts C, León LG, Acebes A. Molecular bases of anorexia nervosa, bulimia nervosa and binge eating disorder: shedding light on the darkness. J Neurogenet. 31(4):266-87.
[56]Lindvall Dahlgren C, Wisting l, Rø Ø. Feeding and eating disorders in the DSM-5 era: a systematic review of prevalence rates in non-clinical male and female samples. J Eat Disord. 2017;5:56.
[57]Breithaupt L, Hübel C, Bulik CM. Updates on Genome-Wide Association Findings in Eating Disorders and Future Application to Precision Medicine. Curr Neuropharmacol. 2018;16(8):1102-10.
[58]Trace SE, Baker JH, Penas-Lledo E, Bulik CM. The Genetics of Eating Disorders. Annu Rev Clin Psychol. 2013;9:589-620.
[59]Yilmaz Z, Hardaway JA, Bulik CM. Genetics and epigenetics of eating disorders. Adv Genomics Genet 2015;5:131-50.
[60]Svob Strac D, Nikolac Perkovic M, Nedic Erjavec G, Uzun S, Sagud M, Zivkovic M, et al. The Role of Brain-Derived Neurotrophic Factor (BDNF) in Cognition and Treatment Response. In: Brain-Derived Neurotrophic Factor (BDNF): Therapeutic Approaches, Role in Neuronal Development and Effects on Cognitive Health. Bennet C (ed), New York: Nova Sci Publ., 2015 (Chapter 3): 67-146.

[61]Nakabayashi K, Komaki G, Tajima A, Ando T, Ishikawa M, Nomoto J, et al. Identification of novel candidate loci for anorexia nervosa at 1q41 and 11q22 in Japanese by a genome-wide association analysis with microsatellite markers. J Hum Genet. 2009; 54(9):531-7.
[62]Wang K, Zhang H, Bloss CS, Duvvuri V, Kaye W, Schork NJ, et a. A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. Mol Psychiatry. 2011;16(9):949-59.
[63]Boraska V, Franklin CS, Floyd JA, Thornton LM, Huckins LM, Southam L, et al. A genome-wide association study of anorexia nervosa. Mol Psychiatry. 2014; 19(19):1085-94.
[64] Wade TD, Gordon S, Medland S, Bulik CM, Heath AC, Montgomery GW, et al. Genetic variants associated with disordered eating. Int J Eat Disord. 2013;46(6):594-608.
[65]Bulik CM, Kleiman SC, Yilmaz Z. Genetic epidemiology of eating disorders. Curr Opin Psychiatry. 2016; 29(6):383-8.
[66]Root TL, Szatkiewicz JP, Jonassaint CR, Thornton LM, Pinheiro AP, Strober M, et al. Association of candidate genes with phenotypic traits relevant to anorexia nervosa. Eur Eat Disord Rev. 2011;19(6):487-93.
[67]Martaskova D, Slachtova L, Kemlink D, Zahorakova D, Papezova H. Polymorphisms in serotonin-related genes in anorexia nervosa. The first study in Czech population and meta analyses with previously performed studies. Folia Biol. (Praha) 2009;55(5):192-7.
[68]Kipman A, Bruins-Slot L, Boni C, Hanoun N, Ades J, BlotP, et al. 5-HT2A gene promoter polymorphism as a modifying rather than a vulnerability factor in anorexia nervosa. Eur Psychiatry. 2002;17(4):227-29.
[69]Gorwood P, Kipman A, Foulon C. The human genetics of anorexia nervosa. Eur J Pharmacol. 2003;480(1-3):163-70.
[70]Koren R, Duncan AE, Munn-Chernoff MA, Bucholz KK, Lynskey MT, Heath AC, et al. Preliminary evidence for the role of HTR2A variants in binge eating in young women. Psychiatr Genet. 2014;24(1):28–33.
[71]Munn-Chernoff MA, Baker JH. A primer on the genetics of comorbid eating disorders and substance use disorders. Eur Eat Disord Rev. 2016;24(2):91-100.
[72]Bergen AW, van den Bree MBM, Yeager M, Welch R, Ganjei JK, Haque K, et al. Candidate genes for anorexia nervosa in the 1p33-36 linkage region: Serotonin 1D and delta opioid receptor loci exhibit significant association to anorexia nervosa. Mol Psychiatry. 2003;8(4):397-406.
[73]Brown KMO, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE. Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. Biol Psychiatry. 2007;61(3):367-73.
[74]Kiezebrink K, Mann ET, Bujac SR, Stubbins MJ, Campbell DA, Blundell JE. Evidence of complex involvement of serotonergic genes with restrictive and binge purge subtypes of anorexia nervosa. World J Biol Psychiatry. 2010;11(6):824-33.
[75]Hernández S, Camarena B, González L, Caballero A, Flores G, Aguilar A. A family-based association study of the HTR1B gene in eating disorders. Rev Bras Psiquiatr. 2016;38(3):239-42.
[76]Lee Y, Lin PY. Association between serotonin transporter gene polymorphism and eating disorders: a meta-analytic study. Int J Eat Disord. 2010;43(6):498-504.
[77]Calati R, De Ronchi D, Bellini M, Serretti A. The 5-HTTLPR polymorphism and eating disorders: a meta-analysis. Int J Eat Disord. 2011; 4(3):191-9.
[78]Slof-Op't Landt MC, Meulenbelt I, Bartels M, Suchiman E, Middeldorp CM, Houwing-Duistermaat JJ, et al. Association study in eating disorders: TPH2 associates with anorexia nervosa and self-induced vomiting. Genes Brain Behav. 2011;10(2):236-43.
[79]Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, Treasure JT, et al. Evidence for a susceptibility gene for anorexia nervosa on chromosome 1. Am J Hum Genet. 2002;70(3):787-92.

[80]Frisch A, Laufer N, Danziger Y, Michaelovsky E, Leor S, Carel C, et al. Association of anorexia nervosa with the high activity allele of the COMT gene: a family-based study in Israeli patients. Mol Psychiatry. 2001;6(2):243-5.
[81]Mikolajczyk E, Smiarowska M, Grzywacz A, Samochowiec J. Association of eating disorders with catechol-O-methyltransferase gene functional polymorphism. Neuropsychobiology 2006;54(1):82-6.
[82]Davis C, Levitan RD, Yilmaz Z, Kaplan AS, Carter JC, Kennedy JL. Binge eating disorder and the dopamine D2 receptor: genotypes and sub-phenotypes. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38(2):328-35.
[83]Bachner-Melman R, Lerer E, Zohar AH, Kremer I, Elizur Y, Nemanov L, et al. Anorexia nervosa, perfectionism, and dopamine D4 receptor (DRD4). Am J Med Genet. B Neuropsychiatr Genet. 2007;144B (6):748-56.
[84]Gervasini G, González LM, Gamero-Villarroel C, Mota-Zamorano S, Carrillo JA, Flores I, et al. Effect of dopamine receptor D4 (DRD4) haplotypes on general psychopathology in patients with eating disorders. Gene 2018;654:43-8.
[85]Dardennes RM, Zizzari P, Tolle V, Foulon C, Kipman A, Romo L, et al. Family trios analysis of common polymorphisms in the obestatin/ghrelin, BDNF and AGRP genes in patients with anorexia nervosa: association with subtype, body-mass index, severity and age of onset. Psychoneuroendocrinology. 2007;32(2):106-13.
[86]Monteleone P, Tortorella A, Castaldo E, Di Filippo C, Maj M. The Leu72Met polymorphism of the ghrelin gene is significantly associated with binge eating disorder. Psychiatr Genet. 2007;17(1):13-6.
[87]Muller TD, Tschöp MH, Jarick I, Ehrlich S, Scherag S, Herpertz-Dahlmann B, et al. Genetic variation of the ghrelin activator gene ghrelin O-acyltransferase (GOAT) is associated with anorexia nervosa. J Psychiatr Res. 2011;45(5):706-11.
[88]Boraska V, Davis OS, Cherkas LF, Helder SG, Harris J, Krug I, et al. Genome-wide association analysis of eating disorder-related symptoms, behaviors, and personality traits. Am J Med Genet B Neuropsychtr Genet. 2012;159B(7):803-11.
[89]Versini A, Ramoz N, Le Strat Y, Scherag S, Ehrlich S, Boni C, et al. Estrogen receptor 1 gene (ESR1) is associated with restrictive anorexia nervosa. Neuropsychopharmacology. 35(8):1818-25.
[90]Monteleone P, Bifulco M, Di Filippo C, Gazzerro P, Canestrelli B, Monteleone F, et al. Association of CNR1 and FAAH endocannabinoid gene polymorphisms with anorexia nervosa and bulimia nervosa: evidence for synergistic effects. Genes Brain Behav. 2009;8(7):728-32.
[91]Ribases M, Gratacòs M, Fernández-Aranda F, Bellodi L, Boni C, Anderluh M, et al. Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations. Hum Mol Genet. 2004;13(12):1205-12.
[92]Muller TD, Greene BH, Bellodi L, Cavallini MC, Cellini E, Di Bella D, et al. Fat mass and obesity-associated gene (FTO) in eating disorders: evidence for association of the rs9939609 obesity risk allele with bulimia nervosa and anorexia nervosa. Obes Facts. 2012;5(3):408-19.
[93]Koronyo-Hamaoui M, Frisch A, Stein D, Denziger Y, Leor S, Michaelovsky E, et al. Dual contribution of NR2B subunit of NMDA receptor and Ca2+-activated K+ channel to genetic predisposition to anorexia nervosa. J Psychiatr Res. 2007;41(1-2):160-7.
[94]Liu X, Bipolar Genome Study (BiGS). Kelsoe JR, Greenwood TA. A genome-wide association study of bipolar disorder with comorbid eating disorder replicates the SOX2-OT region. J Affect Disord. 2016;189:141-9.
[95]Miyasaka K, Hosoya H, Sekime A, Ohta M, Amono H, Matsushita S, et al. Association of ghrelin receptor gene polymorphism with bulimia nervosa in a Japanese population. J Neural Transm. 2006;113(9):1279-85.

[96] Vink T, Hinney A, van Elburg AA, van Goozen SH, Sandkuijl LA, Sinke RJ, et al. Association between an agouti-related protein gene polymorphism and anorexia nervosa. Mol. Psychiatry. 2001;6(3):325-8.
[97] Nishiguchi N, Matsushita S, Suzuki K, Masanobu M, Shirakawa O, Higuchi S. Association between 5HT2A receptor gene promoter region polymorphism and eating disorders in Japanese patients. Biol Psychiatry. 2001;50(2):123-8.
[98] Ricca V, Nacmias B, Cellini E, Di Bernardo M, Rotella CM, Sorbi S. 5-HT2A receptor gene polymorphism and eating disorders. Neurosci Lett. 2002;323(2):105-8.
[99] Nilsson M, Naessen S, Dahlman I, Linden Hirschberg A, Gustafsson JA, Dahlman-Wright K. Association of estrogen receptor beta gene polymorphisms with bulimic disease in women. Mol Psychiatry. 2004;9(1):28-34.
[100] Bulik-Sullivan B, Finucane H, Anttila V, Gusev A, Day F, ReproGen Consortium, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015;47(11):1236-41.
[101] Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:15057.
[102] Kessler RC, Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry. 2000;61(Suppl 5):4-12.
[103] Stein MB, Jang KJ, Taylor S, Vernon PA, Livesley WJ (2002): Genetic and environmental influences on trauma exposure and posttraumatic stress disorder: A twin study. Am J Psychiatry. 2002;159(10):1675-81.
[104] Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, et al. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Arch Gen Psychiatry. 2012;69(3):293-9.
[105] Amstadter AB, Nugent NR, Koenen KC. Genetics of PTSD: Fear Conditioning as a Model for Future Research. Psychiatr Ann. 2009;39(6):358-67.
[106] Comings DE, Comings BG, Muhleman D, Dietz G, Shahbahrami B, Tast D, et al. The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. JAMA. 1991;266(13):1793-1800.
[107] Comings DE, Muhleman D, Gysin R. Dopamine D2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: a study and replication. Biol Psychiatry. 1996;40(5):368–72.
[108] Young RM, Lawford BR, Noble EP, Kann B, Wilkie A, Ritchie T, et al. Harmful drinking in military veterans with post-traumatic stress disorder: association with the D2 dopamine receptor A1 allele. Alcohol Alcohol. 2002;37(5):451-6.
[109] Bailey JN, Goenjian AK, Noble EP, Walling DP, Ritchie T, Goenjian HA. PTSD and dopaminergic genes, DRD2 and DAT, in multigenerational families exposed to the Spitak earthquake. Psychiatry Res. 2010;178(3):507-10.
[110] Hemmings SM, Martin LI, Klopper M, van der Merwe L, Aitken L, de Wit E, et al. BDNF Val66Met and DRD2 Taq1A polymorphisms interact to influence PTSD symptom severity: a preliminary investigation in a South African population. Prog Neuropsychopharmacol Biol Psychiatry. 2013;40:273-80.
[111] Voisey J, Swagell CD, Hughes IP, Morris CP, van Daal A, Noble EP, et al. The DRD2 gene 957C > T polymorphism is associated with posttraumatic stress disorder in war veterans. Depress Anxiety. 2009;26(1):28-33.
[112] Drury SS, Theall KP, Keats BJB, Scheeringa M. The Role of the Dopamine Transporter (DAT) in the Development of PTSD in Preschool Children. J Trauma Stress 2009;22(6):534-9.
[113] Valente NLM, Vallada H, Cordeiro Q, Miguita K, Bressan RA, Andreoli SB, et al. Candidate-gene approach in posttraumatic stress disorder after urban violence: association analysis of the genes

encoding serotonin transporter, dopamine transporter, and BDNF. J Mol Neurosci. 2011;44(1):59-67.
[114] Li L, Bao Y, He S, Wang G, Guan Y, Ma D, et al. The Association Between Genetic Variants in the Dopaminergic System and Posttraumatic Stress Disorder: A Meta-Analysis. Medicine. 2016;95(11):e3074.
[115] Dragan WL, Oniszczenko W. The association between dopamine D4 receptor exon III polymorphism and intensity of PTSD symptoms among flood survivors. Anxiety Stress Coping. 2009;22(5):483-95.
[116] Nakamura M, Ueno S, Sano A, Tanabe H. The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol Psychiatry. 2000;5(1):32-8.
[117] Lee HJ, Lee MS, Kang RH, Kim H, Kim SD, Kee BS, et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. Depress Anxiety. 2005;21(3):135-9.
[118] Wang Z, Baker DG, Harrer J, Hamner M, Price M, Amstadter A. The relationship between combat-related posttraumatic stress disorder and the 5-HTTLPR/rs25531 polymorphism. Depress Anxiety. 2011;28(12):1067-73.
[119] Mellman TA, Alim T, Brown DD, Gorodetsky E, Buzas B, Lawson WB, et al. Serotonin polymorphisms and posttraumatic stress disorder in a trauma exposed African American population. Depress Anxiety. 2009;26(11):993-7.
[120] Kovacic Petrovic Z, Nedic Erjavec G, Nikolac Perkovic M, Peraica T, Pivac N. No association between the serotonin transporter linked polymorphic region polymorphism and severity of posttraumatic stress disorder symptoms in combat veterans with or without comorbid depression. Psychiatry Res. 244:376-81.
[121] Kilpatrick DG, Koenen KC, Ruggiero KJ, Acierno R, Galea S, Resnick HS, et al. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. Am J Psychiatry. 2007;164(11):1693-9.
[122] Koenen KC, Aiello AE, Bakshis E, Amstadter AB, Ruggiero KJ, Acierno R, et al. Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. Am J Epidemiol. 2009;169(6):704-11.
[123] Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, et al. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry. 2009;66(11):1201–9.
[124] Gressier F, Calati R, Balestri M, Marsano A, Alberti S, Antypa N, et al. The 5-HTTLPR polymorphism and posttraumatic stress disorder: a meta-analysis. J Trauma Stress. 2013;26(6):645-53.
[125] Liu Y, Garrett ME, Dennis MF, Green KT; VA Mid-Atlantic MIRECC Registry Workgroup, Ashley-Koch AE, et al. An Examination of the Association between 5-HTTLPR, Combat Exposure, and PTSD Diagnosis among U.S. Veterans. PLoS ONE. 2015;10(3):e0119998.
[126] Nelson EC, Agrawal A, Pergadia ML, Lynskey MT, Todorov AA, Wang JC, et al. Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults. Mol Psychiatry. 2009;14(3):234-5.
[127] Kolassa I-T, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJF. The Risk of Posttraumatic Stress Disorder After Trauma Depends on Traumatic Load and the Catechol-O-Methyltransferase Val158Met Polymorphism. Biol Psychiatry. 2010;67(4):304-8.

[128] Valente NLM, Vallada H, Cordeiro Q, Bressan RA, Andreoli SB, Mari JJ, et al. Catechol-O-methyltransferase (COMT) val158met Polymorphism as a Risk Factor for PTSD After Urban Violence. J Mol Neurosci. 2011;43(3):516-23.
[129] Clark R, DeYoung CG, Sponheim SR, Bender TL, Polusny MA, Erbes CR, et al. Predicting post-traumatic stress disorder in veterans: Interaction of traumatic load with COMT gene variation. J Psychiatr Res.2013;47(12):1849–56.
[130] Havelka Mestrovic A, Tudor L, Nikolac Perkovic M, Nedic Erjavec G, Kovacic Petrovic Z, Svob Strac D, et al. Significant association between catechol-O-methyltransferase (COMT) Val158/108Met polymorphism and cognitive function in veterans with PTSD. Neurosci Lett. 2018;666:38-43.
[131] Notaras M, Hill R, van den Buuse M. The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy. Mol Psychiatry. 2015;20(8):916-930.
[132] Zhang L, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, Li XX, et al. PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Mol Psychiatry. 2014;19(1):8-10.
[133] Pivac N, Kozaric-Kovacic D, Grubisic-Ilic M, Nedic G, Rakos I, Nikolac M, et al. The association between brain-derived neurotrophic factor Val66Met variants and psychotic symptoms in posttraumatic stress disorder. World J Biol Psychiatry. 2012;13(4):306-11.
[134] Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry. 2003;160(9):1554-65.
[135] Lutz B. The endocannabinoid system and extinction learning. Mol Neurobiol. 2007; 36(1):92-101.
[136] Lu AT, Ogdie MN, Järvelin MR, Moilanen IK, Loo SK, McCracken JT, et al. Association of the cannabinoid receptor gene (CNR1) with ADHD and post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(8):1488-94.
[137] Mota N, Sumner JA, Lowe SR, Neumeister A, Uddin M, Aiello AE, et al. The rs1049353 Polymorphism in the CNR1 Gene Interacts With Childhood Abuse to Predict Posttraumatic Threat Symptoms. J Clin Psychiatry. 2015;76(12):1622-3.
[138] Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011;470(7335):492-7.
[139] Mercer KB, Dias B, Shafer D, Maddox SA, Muller JG, Hu P, et al. Functional evaluation of a PTSD-associated genetic variant: estradiol regulation and ADCYAP1R1. Transl. Psychiatry. 2016;6(12):e978.
[140] Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299(11):1291-305.
[141] Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Farrer LA, et al. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. Neuropsychopharmacology. 2010;35(8):1684-92.
[142] Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013;16(1):33-41.
[143] Ramikie TS, Ressler KJ. Stress-related disorders, pituitary adenylate cyclase—activating peptide (PACAP)ergic system, and sex differences. Dialogues Clin Neurosci. 2016;18(4):403-13.
[144] Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, et al. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol Psychiatry. 2018;23(3):666-73.

[145] Logue MW, Baldwin C, Guffanti G, Melista E, Wolf EJ, Reardon AF, et al. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Mol Psychiatry. 2013;18(8):937-42.
[146] Xie P, Kranzler HR, Yang C, Zhao H, Farrer LA, Gelernter J. Genome-wide association study identifies new susceptibility loci for posttraumatic stress disorder. Biol Psychiatry. 2013;74(9):656-63.
[147] Wolf EJ, Rasmusson AM, Mitchell KS, Logue MW, Baldwin CT, Miller MW. A genome-wide association study of clinical symptoms of dissociation in a trauma-exposed sample. Depress Anxiety. 2014;31(4):352-60.
[148] Nievergelt CM, Maihofer AX, Mustapic M, Yurgil KA, Schork NJ, Miller MW, et al. Genomic predictors of combat stress vulnerability and resilience in U.S. marines: a genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. Psychoneuroendocrinology. 2015;51:459-71.
[149] Ashley-Koch AE, Garrett ME, Gibson J, Liu Y, Dennis MF, Kimbrel NA. Veterans Affairs Mid-Atlantic Mental Illness Research, Education, and Clinical Center Workgroup, Beckham JC, Hauser MA. Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq-Afghanistan era veterans. J Affect Disord. 2015;184:225–34.
[150] Stein MB, Chen C, Ursano RJ, Cai T, Gelernter J, Heeringa SG, et al. Army Study to Assess Risk and Resilience in Servicemembers (STARRS) Collaborators. Genome-wide association studies of posttraumatic stress disorder in 2 cohorts of us army soldiers. JAMA Psychiatry. 2016;73(7):695-704.
[151] Kilaru V, Iyer SV, Almli LM, Stevens JS, Lori A, Jovanovic T, et al. Genome-wide gene-based analysis suggests an association between Neuroligin 1 (NLGN1) and post-traumatic stress disorder. Transl Psychiatry. 2016;6:e820.
[152] Melroy-Greif WE, Wilhelmsen KC, Yehuda R, Ehlers CL. Genome-wide association study of post-traumatic stress disorder in two high-risk populations. Twin Res Hum Genet. 2017;20(3):197-207.
[153] Segman RH, Cooper-Kazaz R, Macciardi F, Goltser T, Halfon Y, Dobroborski T, et al. Association between the dopamine transporter gene and posttraumatic stress disorder. Mol Psychiatry. 2002;7(8):903-7.
[154] Guffanti G, Galea S, Yan L, Roberts AL, Solovieff N, Aiello AE, et al. Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for posttraumatic stress disorder in women. Psychoneuroendocrinology. 2013;38(12):3029-38.
[155] Almli LM, Stevens JS, Smith AK, Kilaru V, Meng Q, Flory J, et al. A genome-wide identified risk variant for PTSD is a methylation quantitative trait locus and confers decreased cortical activation to fearful faces. Am J Med Genet B Neuropsychiatr Genet. 2015;168B(5):327-36.
[156] Lowe SR, Meyers JL, Galea S, Aiello AE, Uddin M, Wildman DE, et al. RORA and posttraumatic stress trajectories: main effects and interactions with childhood physical abuse history. Brain Behav. 2015;5(4):e00323.
[157] Sindi IA, Dodd PR. New insights into Alzheimer's disease pathogenesis: the involvement of neuroligins in synaptic malfunction. Neurodegener Dis Manag. 2015;5(2):137-45.
[158] Mainland JD, Li YR, Zhou T, Liu WL, Matsunami H. Human olfactory receptor responses to odorants. Sci Data. 2015;2:150002.
[159] Suzuki E, Imoto I, Pimkhaokham A, Nakagawa T, Kamata N, Kozaki KI, et al. PRTFDC1, a possible tumor-suppressor gene, is frequently silenced in oral squamous-cell carcinomas by aberrant promoter hypermethylation Oncogene. 2007;26(57):7921-32.

[160] Apte SS, Parks WC. Metalloproteinases: A parade of functions in matrix biology and an outlook for the future. Matrix Biol. 2015; 44-46:1-6.
[161] Nemes JP, Benzow KA, Moseley ML, Ranum LP, Koob MD. The SCA8 transcript is an antisense RNA to a brain-specific transcript encoding a novel actin-binding protein (KLHL1). Hum Mol Genet. 2000;9(10):1543-51.
[162] Frasa MA, Maximiano FC, Smolarczyk K, Francis RE, Betson ME, Lozano E, et al. Armus is a Rac1 effector that inactivates Rab7 and regulates E-cadherin degradation. Curr Biol. 2010;20(3):198-208.
[163] Nievergelt CM, Ashley-Koch AE, Dalvie S, Hauser HA, Morey RA, Smith AK, et al. Genomic Approaches to Posttraumatic Stress Disorder: the Psychiatric Genomic Consortium Initiative. Biol Psychiatry. 2018;83(10):831-9.
[164] Andrews JA, Neises KD (2012): Cells, biomarkers, and post-traumatic stress disorder: evidence for peripheral involvement in a central disease. J Neurochem. 2012;120(1):26-36.
[165] Williams HJ, Owen MJ, O'Donovan MC. Schizophrenia genetics: new insights from new approaches. Br Med Bull. 2009;91:61-74.
[166] Karayiorgou M, Gogos JA. Schizophrenia genetics: uncovering positional candidate genes. Eur J Hum Genet. 2006;14:512-9.
[167] Gonzalez-Castro TB, Hernandez-Diaz Y, Juarez-Rojop IE, Lopez-Navarez ML, Tovilla-Zarate CA, Fresan A. The role of a catechol-O-methyltransferase (COMT) Val158Met genetic polymorphism in schizophrenia: a systematic review and updated meta-analysis on 32,816 subjects. Neuromol Med. 2016;18(2):216-31.
[168] Rees E, O'Donovan MC, Owen MJ. Genetics of schizophrenia. Current Opinion in Behavioral Sciences. 2015;2:8-14.
[169] Bilder RM, Volavka J, Czbor P, Malhotra AK, Kennedy JL, Ni X et al. Neurocognitive correlates of the COMT Val158Met polymorphism in chronic schizophrenia. Biol Psychiatry. 2002;52:701-7.
[170] Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE et al. Effect of COMT Val108/158met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U.S.A. 2001;98(12):6917-22.
[171] Fan JB, Zhang CS, Gu NF, Li XW, Sun WW, Wang HY et al. Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biol Psychiatry. 2004;57:139-44.
[172] Huang E, Zai CC, Lisoway A, Maciukiewicz M, Felsky D, Tiwari AK et al. Catechol-O-methyltransferase Val158Met polymorphism and clinical response to antipsychotic treatment in schizophrenia and schizo-affective disorder patients: a meta-analysis. Int J Neuropsychopharmacol. 2016;19(5):1-12.
[173] Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. Am J Psychiatry. 2003;160:469-76.
[174] Nikolac M, Sagud M, Nedic G, Nenadic Sviglin K, Mihaljevic Peles A, Uzun S, et al. The lack of association between catechol-O-methyl-transferase Val108/158Met polymorphism and smoking in schizophrenia and alcohol dependence. Letter to the Editor. Psychiatry Res. 2013;205:179-80.
[175] Herken H, Emin Erdal M. Catechol-O-methyltransferase gene polymorphism in schizophrenia: evidence for association between symptomatology and prognosis. Psychiatric Genetics. 2000;11:105-9.

[176] Sagud M, Tudor L, Uzun S, Nikolac Perkovic M, Zivkovic M, Konjevod M et al. Haplotypic and genotypic association of catecol-O-methyktransferase rs4680 and rs4818 polymorphisms and treatment resistance in schizophrenia. Front Pharmacol. 2018;9:1-14.
[177] Huo R, Wei Z, Xiong Y, Jiang J, Liu Y, Yan Y et al. Association of dopamine receptor D1 (DRD1) polymorphisms with risperidone treatment response in Chinese schizophrenia patients. Neurosci Lett. 2014;584:178-83.
[178] Matsumoto J, Nagaoka A, Kunii Y, Miura I, Hino M, Niwa S-I et al. Effects of the −141C insertion/deletion polymorphism in the dopamine D2 receptor gene on the dopamine system in the striatum in patients with schizophrenia. Psychiatry Research. 2018;264:116-8.
[179] Smith CT, Dang LC, Buckholtz JW, Tetreault AM, Cowan RL, Kessler RM et al. The impact of common dopamine D2 receptor gene polymorphisms on D2/3 receptor availability: C957T as a key determinant in putamen and ventral striatum. Transl Psychiatry. 2017;7:e1091.
[180] Persson J, Stenfors C. Superior cognitive goal maintenance in carriers of genetic markers linked to reduced striatal D2 receptor density (C957T and DRD2/ANKK1-TaqIA). PLoS ONE. 2018;13(8):1-12.
[181] Cohen OS, Weickert TW, Hess JL, Paish LM, McCoy SY, Rothmond DA et al. A splicing-regulatory polymorphism in DRD2 disrupts ZRANB2 binding, impairs cognitive functioning and increases risk for schizophrenia in six Han Chinese samples. Mol Psychiatry. 2015;1-8.
[182] Yao J, Pan Y-Q, Ding M, Pang H, Wang B-J. Association between DRD2 (rs1799732 and rs1801028) and ANK1 (rs1800497) polymorphisms and schizophrenia: a meta-analysis. Am J Med Genet Part B. 2014; 168B:1–13.
[183] Howes OD, McCutcheon R, Owen MJ, Murray RM. The role of genes, stress, and dopamine in the development of schizophrenia. Biol Psychiatry. 2017;8:9-20.
[184] Okuyama Y, Ishiguro H, Toru M, Arinami T. A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem Biophys Res Commun. 1999;258:292-5.
[185] Egan MF, Straub RE, Goldberg TE, Yakub I, Callicott JH, Hariri AR et al. Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. Proc Natl Acad Sci U.S.A. 2004;101(34):12604-12609.
[186] Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005;10:40-68.
[187] Hodkinson CA, Goldman D, Jaeger J, Persaud S, Kane JM, Lipsky RH et al. Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. Am J Hum Genet. 2004;75:862-72.
[188] Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. Proc Natl Acad Sci U.S.A. 2005;102(24):8627-32.
[189] Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. Biol Psychiatry. 2006;60:132-40.
[190] Huang E, Hettige NC. Zai G, Tomasi J, Huang J, Zai CC et al. BDNF Val66Met polymorphism and clinical response to antipsychotic treatment in schizophrenia and schizoaffective disorder patients: a meta-analysis. Pharmacogenomics J. 2018; doi: 10.1038/s41397-018-0041-5. [Epub ahead of print].

[191] Hong CJ, Younger WY, Lin CH, Tsai SJ. An association study of a brain-derived neurotrophic factor Val66Met polymorphism and clozapine response of schizophrenic patients. Neurosci Lett. 2003;349:206-8.
[192] Kheirollahi M, Kazemi E, Ashouri S. Brain-derived neurotrophic factor gene Val66Met polymorphism and risk of schizophrenia: a meta-analysis of case–control studies. Cell Mol Neurobiol. 2015;36(1):1-10.
[193] Notaras M, Hill R, van den Buuse M. A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. Neurosci Biobehav Rev. 2015;51:15-30.
[194] Blasi G, Selvaggi P, Fazio L, Antonucci LA, Taurisano P, Masellis R et al. Variation in dopamine D2 and serotonin 5HTt2A receptor genes is associated with working memory processing and response to treatment with antipsychotics. Neuropsychopharmacology. 2015;40(7):1600-8.
[195] Kavanagh DH, Tansey KE, O'Donovan MC, Owen MJ. Schizophrenia genetics: emerging themes for a complex disorder. Mol Psychiatry. 2015;20(1):72-6.
[196] Gonda X, Petschner P, Eszlari N, Baksa D, Edes A, Antal P, et al. Genetic variants in major depressive disorder: From pathophysiology to therapy. Pharmacol Ther. 2018; pii: S0163-7258(18):30156-6.
[197] Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000; 157(10):1552–62.
[198] Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish national twin study of lifetime major depression. Am J Psychiatry. 2006;163(1):109-14.
[199] Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. Nat Genet. 2016;48(9):980-3.
[200] Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. Classification of common human diseases derived from shared genetic and environmental determinants. Nat Genet. 2017;49(9):1319-25.
[201] Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet. 2012;13(8):537-51.
[202] Uher R. Gene-environment interactions in severe mental illness. Front Psychiatry. 2014;5:48.
[203] Flint J, Kendler KS. The genetics of major depression. Neuron. 2014;81(3):484-503.
[204] Mullins N, Lewis CM. Genetics of Depression: Progress at Last. Curr Psychiatry Rep. 2017;19(8):43.
[205] Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Sources of Parent-Offspring Resemblance for Major Depression in a National Swedish Extended Adoption Study. JAMA Psychiatry. 2018;75(2):194-200.
[206] Hammen C. Stress and depression. Annu Rev Clin Psychol. 2005;1:293-319.
[207] Hammen C, Kim EY, Eberhart NK, Brennan PA. Chronic and acute stress and the prediction of major depression in women. Depress Anxiety. 2009;26(8):718-23.
[208] Brown GW, Bifulco A, Harris TO. Life events, vulnerability and onset of depression: some refinements. Br J Psychiatry. 1987;150:30-42.
[209] Kendler KS, Karkowski-Shuman L. Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? Psychol Med. 1997;27(3):539-47.
[210] Shadrina M, Bondarenko EA, Slominsky PA. Genetics Factors in Major Depression Disease. Front Psychiatry. 2018;9:334.

[211] Kautzky A, Baldinger P, Souery D, Montgomery S, Mendlewicz J, Zohar J, et al. The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression. Eur Neuropsychopharmacol. 2015;25(4):441-53.
[212] Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat Neurosci. 2015;18(2):199-209.
[213] Marx P, Antal P, Bolgar B, Bagdy G, Deakin B, Juhasz G. Comorbidities in the diseasome are more apparent than real: What Bayesian filtering reveals about the comorbidities of depression. PLoS Comput Biol. 2017;13(6):e1005487.
[214] Purves KL, Coleman JRI, Rayner C, Hettema JM, DeckertJ, McIntosh AM, et al. The Common Genetic Architecture of Anxiety Disorders. 2017; bioRxiv 203844.
[215] Yu C, Baune BT, Licinio J, Wong ML. A novel strategy for clustering major depression individuals using whole-genome sequencing variant data. Sci Rep. 2017;7:44389.
[216] López-León S, Janssens A, González-Zuloeta Ladd AM, Del-Favero J, Claes SJ, Oostra BA, et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry. 2008;13(8):772-85.
[217] Clarke H, Flint J, Attwood AS, Munafò MR. Association of the 5-HTTLPR genotype and unipolar depression: a meta-analysis. Psychol Med. 2010;40(11):1767-78.
[218] Kiyohara C, Yoshimasu K. Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: a meta-analysis. Psychiatr Genet. 2010;20(2):49-58.
[219] Wu YL, Ding XX, Sun YH, Yang HY, Chen J, Zhao X, et al. Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:78-85.
[220] Zhao X, Huang Y, Ma H, Jin Q, Wang Y, Zhu G. Association between major depressive disorder and the norepinephrine transporter polymorphisms T-182C and G1287A: a meta-analysis. J Affect Disord. 2013;150(1):23-8.
[221] Zhou Y, Su H, Song J, Guo L, Sun Y. Association between norepinephrine transporter T-182C polymorphism and major depressive disorder: a meta-analysis. Neurosci Lett. 2014;561:64-8.
[222] Jin C, Xu W, Yuan J, Wang G, Cheng Z. Meta-analysis of association between the -1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder. Neurol Res. 2013;35(1):7-14.
[223] Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, et al. No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(1):61-70.
[224] Kishi T, Yoshimura R, Fukuo Y, Kitajima T, Okochi T, Matsunaga S, et al. The CLOCK gene and mood disorders: a case-control study and meta-analysis. Chronobiol Int. 2011;28(9):825-33.
[225] Gatt JM, Burton KL, Williams LM, Schofield PR. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. J Psychiatr Res. 2015;60:1-13.
[226] Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol Psychiatry. 2011;16(5):516-32.

[227] Wray NR, Pergadia ML, Blackwood DH, Penninx BW, Gordon SD, Nyholt DR et al. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Mol Psychiatry. 2012;17(1):36-48.
[228] Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, et al. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2013;18(4):497-511.
[229] Dunn EC, Brown RC, Dai Y, Rosand J, Nugent NR, Amstadter AB, et al. Genetic Determinants of Depression: Recent Findings and Future Directions. Harv Rev Psychiatry. 2015;23(1):1-18.
[230] Kohli MA, Lucae S, Saemann PG, Schmidt MV, Demirkan A, Hek K, et al. The Neuronal Transporter Gene SLC6A15 Confers Risk to Major Depression. Neuron. 2011;70(2):252-65.
[231] CONVERGE consortium. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature. 2015;523(7562):588-91.
[232] Ware EB, Mukherjee B, Sun YV, Diez-Roux AV, Kardia SL, Smith JA. Comparative genome-wide association studies of a depressive symptom phenotype in a repeated measures setting by race/ethnicity in the multi-ethnic study of atherosclerosis. BMC Genet. 2015;16:118.
[233] Huo YX, Huang L, Zhang DF, Yao YG, Fang YR, Zhang C, et al. Identification of SLC25A37 as a major depressive disorder risk gene. J Psychiatr Res. 2016;83:168-75.
[234] Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet. 2016;48(9):1031-6.
[235] Okbay ABaselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet. 2016;48(6):624-33.
[236] Mbarek H, Milaneschi Y, Hottenga JJ, Ligthart L, de Geus EJC, Ehli EA, et al. Genome-Wide Significance for PCLO as a Gene for Major Depressive Disorder. Twin Res Hum Genet. 2017;20(4):267-70.
[237] Power RA, Tansey KE, Buttenschøn HN, Cohen-Woods S, Bigdeli T, Hall LS, et al. Genome-wide Association for Major Depression Through Age at Onset Stratification: Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Biol Psychiatry. 2017;81(4):325-35.
[238] Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668-81.
[239] Xiao X, Zheng F, Chang H, Ma Y, Yao YG, Luo XJ, et al. The Gene Encoding Protocadherin 9 (PCDH9), a Novel Risk Factor for Major Depressive Disorder. Neuropsychopharmacology. 2018;43(5):1128-37.
[240] Sullivan PF, de Geus EJ, Willemsen G, James MR, Smit JH, Zandbelt T, et al. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Mol Psychiatry. 2009;14(4):359-75.
[241] Sabunciyan S, Aryee MJ, Irizarry RA, Rongione M, Webster MJ, Kaufman WE, et al. Genome-wide DNA methylation scan in major depressive disorder. PLoS One. 2012;7(4):e34451.
[242] Wong ML, Arcos-Burgos M, Liu S, Vélez JI, Yu C, Baune BT et al. The PHF21B gene is associated with major depression and modulates the stress response. Mol Psychiatry. 2017;22(7):1015-25.

[243] Amin N, Jovanova O, Adams HH, Dehghan A, Kavousi M, Vernooij MW, et al. Exome-sequencing in a large population-based study reveals a rare Asn396Ser variant in the LIPG gene associated with depressive symptoms. Mol Psychiatry. 2017;22(4):537-43.
[244] Knowles EE, Kent JW Jr, McKay DR, Sprooten E, Mathias SR, Curran JE, et al. (2016). Genome-wide linkage on chromosome 10q26 for a dimensional scale of major depression. J Affect Disord. 2016;191:123-31.
[245] Pirooznia M, Wang T, Avramopoulos D, Potash JB, Zandi PP, Goes FS. High-throughput sequencing of the synaptome in major depressive disorder. Mol Psychiatry. 2016;21(5):650-5.
[246] Glessner JT, Wang K, Sleiman PM, Zhang H, Kim CE, Flory JH, et al. Duplication of the SLIT3 locus on 5q35.1 predisposes to major depressive disorder. PLoS One. 2010;5(12):e15463.
[247] Cukier HN, Dueker ND, Slifer SH, Lee JM, Whitehead PL, Lalanne E, et al. Exome sequencing of extended families with autism reveals genes shared across neurodevelopmental and neuropsychiatric disorders. Mol Autism. 2014;5(1):1.
[248] Rucker JJ, Breen G, Pinto D, Pedroso I, Lewis CM, Cohen-Woods S, et al. Genome-wide association analysis of copy number variation in recurrent depressive disorder. Mol Psychiatry. 2013;18(2):183-9.
[249] Rucker JJ, Tansey KE, Rivera M, Pinto D, Cohen-Woods S, Uher R, et al. Phenotypic Association Analyses With Copy Number Variation in Recurrent Depressive Disorder. Biol Psychiatry. 2016;79(4):329-36.
[250] Haenisch B, Linsel K, Brüss M, Gilsbach R, Propping P, Nöthen MM, et al. Association of major depression with rare functional variants in norepinephrine transporter and serotonin1A receptor genes. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(7):1013-6.
[251] Perlis RH, Smoller JW, Mysore J, Sun M, Gillis T, Purcell S, et al. Prevalence of incompletely penetrant Huntington's disease alleles among individuals with major depressive disorder. Am J Psychiatry. 2010;167(5):574-9.
[252] Neff CD, Abkevich V, Potter J, Riley R, Shattuck D, Katz DA. Evidence for epistasis between SLC6A4 and a chromosome 4 gene as risk factors in major depression. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(1):321-2.
[253] Gabriela Nielsen M, Congiu C, Bortolomasi M, Bonvicini C, Bignotti S, Abate M, et al. MTHFR: Genetic variants, expression analysis and COMT interaction in major depressive disorder. J Affect Disord. 2015;183:179-86.
[254] Szczepankiewicz A, Leszczyńska-Rodziewicz A, Pawlak J, Rajewska-Rager A, Wilkosc M, Zaremba D, et al. Epistatic interaction between CRHR1 and AVPR1b variants as a predictor of major depressive disorder. Psychiatr Genet. 2013;23(6):239-46.
[255] Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. Family-based study of AVPR1B association and interaction with stressful life events on depression and anxiety in suicide attempts. Neuropsychopharmacology. 2013;38(8):1504-11.
[256] Xiao Z, Liu W, Gao K, Wan Q, Yang C, Wang H, et al. Interaction between CRHR1 and BDNF genes increases the risk of recurrent major depressive disorder in Chinese population. PLoS One. 2011;6(12):e28733.
[257] Bobińska K, Szemraj J, Czarny P, Gałecki P. Role of MMP-2, MMP-7, MMP-9 and TIMP-2 in the development of recurrent depressive disorder. J Affect Disord. 2016;205:119-29.

[258] Reuter M, Markett S, Melchers M, Montag C. Interaction of the cholinergic system and the hypothalamic-pituitary-adrenal axis as a risk factor for depression: evidence from a genetic association study. Neuroreport. 2012;23(12):717-20.
[259] Pae CU, Drago A, Forlani M, Patkar AA, Serretti A. Investigation of an epistastic effect between a set of TAAR6 and HSP-70 genes variations and major mood disorders. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(2):680-3.
[260] Murk W, DeWan AT. Exhaustive Genome-Wide Search for SNP-SNP Interactions Across 10 Human Diseases. G3 (Bethesda). 2016;6(7):2043-50.
[261] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301(5631):386-9.
[262] Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry. 2011;68(5):444-54.
[263] Sharpley CF, Palanisamy SK, Glyde NS, Dillingham PW, Agnew LL. An update on the interaction between the serotonin transporter promoter variant (5- HTTLPR), stress and depression, plus an exploration of non-confirming findings. Behav Brain Res. 2014;273:89-105.
[264] Bleys D, Luyten P, Soenens B, Claes S. Gene-environment interactions between stress and 5-HTTLPR in depression: A meta-analytic update. J Affect Disord. 2018;226:339-45.
[265] Munafò MR, Durrant C, Lewis G, Flint J. Gene x Environment Interactions at the Serotonin Transporter Locus. Biol Psychiatry. 2009;65(3):211-9.
[266] Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. 2009;301(23):2462-71.
[267] Culverhouse RC, Saccone NL, Horton AC, Ma Y, Anstey KJ, Banaschewski T, 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;23(1):133-42.
[268] Gonda X, Eszlari N, Kovacs D, Anderson IM, Deakin JF, Juhasz G, et al. Financial difficulties but not other types of recent negative life events show strong interactions with 5-HTTLPR genotype in the development of depressive symptoms. Transl Psychiatry. 2016;6:e798.
[269] Mandelli L, Serretti A. Gene environment interaction studies in depression and suicidal behavior: An update. Neurosci Biobehav Rev. 2013;37(10 Pt 1):2375-97.
[270] Naoi M, Maruyama W, Shamoto-Nagai M. Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis. J Neural Transm (Vienna). 2018;125(1):53-66.
[271] Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med. 2014;12:7.
[272] Zhao M, Chen L, Yang J, Han D, Fang D, Qiu X, et al. BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. J Affect Disord. 2018;227:226-35.
[273] Gonda X, Sarginson J, Eszlari N, Petschner P, Toth ZG, Baksa D, et al. A new stress sensor and risk factor for suicide: the T allele of the functional genetic variant in the GABRA6 gene. Sci Rep. 2017;7(1):12887.

[274] Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Mol Psychiatry. 2016;21(5):642-9.
[275] Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P, et al. Effects of IL1B single nucleotide polymorphisms on depressive and anxiety symptoms are determined by severity and type of life stress. Brain Behav Immun. 2016;56:96-104.
[276] Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P, et al. Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. J Neural Transm (Vienna). 2016;123(5):541-8.
[277] Tartter M, Hammen C, Bower JE, Brennan PA, Cole S. Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1beta in youth. Brain Behav Immun. 2015;46:104-11.
[278] Juhasz G, Hullam G, Eszlari N, Gonda X, Antal P, Anderson IM, et al. Brain galanin system genes interact with life stresses in depression-related phenotypes. Proc Natl Acad Sci U.S.A. 2014;111(16):E1666-73.
[279] Juhasz G, Chase D, Pegg E, Downey D, Toth ZG, Stones K, et al. CNR1 Gene is Associated with High Neuroticism and Low Agreeableness and Interacts with Recent Negative Life Events to Predict Current Depressive Symptoms. Neuropsychopharmacology. 2009;34(8):2019-27.
[280] Lazary J, Eszlari N, Juhasz G, Bagdy G. Genetically reduced FAAH activity may be a risk for the development of anxiety and depression in persons with repetitive childhood trauma. Eur Neuropsychopharmacol. 2016;26(6):1020-8.
[281] Van der Auwera S, Peyrot WJ, Milaneschi Y, Hertel J, Baune B, Breen G, et al. Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes: The childhood trauma working-group of PGC-MDD. Am J Med Genet B Neuropsychiatr Genet. 2018;177(1):40-9.
[282] Dunn EC, Wiste A, Radmanesh F, Almli LM, Gogarten SM, Sofer T, et al. Genome-wide association study (GWAS) and genome-wide by enviroment interaction study (GWEIS) of depressive symptoms in African American and Hispanic/latina women. Depress Anxiety. 2016;33(4):265-80.
[283] Otowa T, Kawamura Y, Tsutsumi A, Kawakami N, Kan C, Shimada T, et al. The First Pilot Genome-Wide Gene-Environment Study of Depression in the Japanese Population. PLoS One. 2016;11(8):e0160823.
[284] Grabe HJ, Schwahn C, Mahler J, Appel K, Schulz A, Spitzer C, et al. Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36(2):264-70.
[285] Dalton ED, Hammen CL, Najman JM, Brennan PA. Genetic susceptibility to family environment: BDNF Val66met and 5-HTTLPR influence depressive symptoms. J Fam Psychol. 2014;28(6):947-56.
[286] Ignácio ZM, Réus GZ, Abelaira HM, Quevedo J. Epigenetic and epistatic interactions between serotonin transporter and brain-derived neurotrophic factor genetic polymorphism: insights in depression. Neuroscience. 2014;275:455-68.
[287] Yang C, Xu Y, Sun N, Ren Y, Liu Z, Cao X, et al. The combined effects of the BDNF and GSK3B genes modulate the relationship between negative life events and major depressive disorder. Brain Res. 2010;1355:1-6.

[288] Juhasz G, Gonda X, Hullam G, Eszlari N, Kovacs D, Lazary J, et al. Variability in the effect of 5-HTTLPR on depression in a large European population: the role of age, symptom profile, type and intensity of life stressors. PLoS One. 2015;10(3):e0116316.

[289] Lin E, Hong CJ, Hwang JP, Liou YJ, Yang CH, Cheng D, et al. Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. Rejuvenation Res. 2009;12(6):387-93.