



Genetic Markers in Psychiatry

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Abstract

Psychiatric disorders such as addiction (substance use and addictive disorders), depression, eating disorders, schizophrenia, and post-traumatic 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 \times gene and gene \times 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

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disorders, novel subtypes of the diseases and tailored, personalized approach to therapy.

Keywords

Addiction • Depression • Eating disorders • Schizophrenia • Genetics • Markers • PTSD

Introduction

Psychiatric disorders are among the leading causes of 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 twenty-first 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 to 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 and 1.2. Risk loci are located in both coding and noncoding 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, and 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 the 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]. A 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 neglect 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 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, 25]. 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-CHRNA4 gene cluster encoding for $\alpha 5$, $\alpha 3$, and $\beta 4$ 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 size (<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 prespecified 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 the USA that were of either 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 (*ANKKI*) [40]. For both variants an association with opioid dependence in European [41] as well as in Han Chinese [42] subjects was found. 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 G 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 abovementioned 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 was 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 \times gene interactions that could have additive or masking effect. After all, it is evident that the search for 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). A 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 and 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-arachidonylethanolamine (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 an 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]. 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 and 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, genome-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 the 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-acyltransferase (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),

Table 1 Genes and polymorphisms associated with anorexia nervosa

Gene	Gene description	Polymorphism	References
<i>Anorexia nervosa</i>			
<i>ORPD1</i>	Delta-opioid receptor type 1	rs569356; rs521809; rs4654327	[72, 73]
<i>5-HTR1D</i>	Serotonin receptor type 1D	rs674386; rs856510	[72, 73]
<i>5-HT2A</i>	Serotonin receptor type 2A	rs6311	[67, 68, 84]
<i>5-HTT</i>	Serotonin transporter	<i>5-HTTLPR</i>	[76, 77]
<i>TPH2</i>	Tryptophan hydroxylase	rs1473473	[78]
<i>DRD2</i>	Dopaminergic receptor type 2	rs1799732; rs6275; rs1800497; rs6278	[72]
<i>DRD4</i>	<i>Dopamine receptor type 4</i>	rs1800955; DRD4 haplotypes	[83, 84]
<i>COMT</i>	Catechol- <i>O</i> -methyltransferase	rs4680	[80, 95]
<i>GHRL</i>	Ghrelin	rs696217	[85]
<i>GOAT</i>	Ghrelin O-acyl-transferase	rs10096097	[87]
<i>AgRP</i>	Agouti-related protein	rs5030980	[96]
<i>BDNF</i>	Brain-derived neurotrophic factor	rs6265	[91]
<i>SK3</i>	Calcium-activated potassium channel	CAG repeat	[93]

Table 2 Genes and polymorphisms associated with bulimia nervosa

Gene	Gene description	Polymorphism	References
<i>Bulimia nervosa</i>			
<i>5-HT2A</i>	Serotonin receptor type 2A	rs6311	[97, 98]
<i>GHSR</i>	Growth hormone secretagogue receptor	rs495225	[95]
<i>ERβ</i>	Estrogen receptor beta gene	rs4986938; rs928554	[99]
<i>CB1R</i>	Cannabinoid receptor type 1	rs1049353	[90]
<i>FAAH</i>	Fatty acid amide hydrolase	rs324420	[90]
<i>FTO</i>	Fat mass and obesity	rs9939609	[92]
<i>BDNF</i>	Brain-derived neurotrophic factor	rs6265; rs56164415	[91]

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 reexperience, 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 [106–108], however, several negative results have also been reported [109, 110]. A study by Voisey et al. [111] did not confirm the association of the rs1800497 but showed a 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 seven and eight repeats were associated with more severe PTSD symptoms, especially avoidance [115].

Table 3 SNPs and VNTRs significantly associated with PTSD in candidate gene and GWA studies

Nearest gene	Gene description	SNP	References
<i>Candidate gene association</i>			
DRD2	Dopamine receptor 2DRD2/ ANKK1-Taq1A	rs1800497 rs6277	[106–108, 111]
DAT1	The dopamine active transporter 1 gene	VNTR (3' UTR)	[112–114, 153]
DRD4	D4 dopamine receptor	VNTR (exon 3)	[115]
SLC6A4	Sodium-dependent serotonin transporter	rs4795541 rs25531	[121–125]
GABRA2	GABA _A receptor subunit alpha 2	rs279836 rs279826 rs279871	[126]
COMT	Catechol-O-methyltransferase	rs4680	[127–129]
BDNF	Brain-derived neurotrophic factor	rs6265	[132, 133]
CNR1	Cannabinoid receptor 1	rs1049353	[136, 137]
ADCYAP1R1	Pituitary adenylate cyclase-activat- ing polypeptide receptor	rs2267735	[138, 139]
FKBP5	FK506 binding Protein 51	rs3800373 rs9296158 rs1360780 rs9470080	[140–142]
<i>GWAS</i>			
RORA	RAR-related orphan receptor A	rs8042149	[145]
TLL1	Tolloid-like 1	rs6812849	[146]
LINC01090	Long noncoding RNA	rs10170218	[154]
ADCY8	ADCY8 adenylate cyclase 8	rs263232	[147]
PRTFDC1	Phosphoribosyl transferase domain containing 1	rs6482463	[148]
BC036345	Long noncoding RNA	rs717947	[155]
TBC1D2	TBC1 domain family member 2	rs7866350	[149]
ANKRD55 ZNF626	Ankyrin repeat domain 55 Zinc finger protein 626	rs159572 rs11085374	[150]
NLGN1 ZNRD1 AS1	Neuregulin 1 Long noncoding RNA	N/A N/A	[151]
OR11L1	Olfactory receptor family 11 subfamily L Member 1	rs6681483 rs6667389 rs10888255 rs10888257	[152]
KLHL1	Kelch-like protein 1	rs139558732	[144]

Serotonergic activity and concentration are 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 \times environment (G \times E) 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 GABAergic 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 an 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, and rs9470080 in steroid receptor chaperone FK506 Binding Protein 51 gene (*FKBP5*), all in high linkage disequilibrium, showed association with PTSD in gene \times 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 cofactor in predicting the diagnosis and severity of PTSD, with some of them even mechanistically well supported (for example, *FKBP5*), main limitation is that this type of studies cannot easily escape bias. Moreover, the proposed genes did not show a 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 of 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 ($p\text{-value} < 5 \times 10^8$) to achieve appropriate power. Currently, the largest GWAS was done by Psychiatric Genomics Consortium (PGC)—PTSD which comprised of 5000 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.

Other findings in previous less powered GWAS highlighted SNPs in close vicinity of *RORA*, retinoid-related orphan receptor gene [145], zinc-dependent metalloprotease toll-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], and olfactory receptor family 11 subfamily L Member 1—*OR11L1* [152] as potential markers of PTSD (Table 3).

There is no straightforward 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. Neuroligin 1 has an important role in synaptic formation, maturation, and maintenance, and is 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 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* (primarily 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 genes was proven significant in an independent replication cohort. This could be due to the very strict statistical corrections, or complex gene \times 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 postmortem 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 the 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, which is 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 the 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 confirm 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 the 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 the 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 disequilibrium 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 a connection between the first two exons of *NRG1* gene with schizophrenia risk; however, these findings mostly reflect an association between schizophrenia risk and this gene in Caucasians. Therefore, ethnicity should be taken into 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 considered 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 11th chromosome, codes for homonymous protein, and it is regulated by several promoters [191–193]. Multiple studies have been shown an 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 premature 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 a 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 a potential protective effect, while the G allele, which is mostly inherited from heterozygotic 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 the 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 a 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*), protein 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/*DTNBI*), 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/*PPP3CC1*), 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 a highly prevalent neuropsychiatric disorder characterized by many heterogeneous symptoms with varying 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 into 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 background 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 to 45% for general population [198–200]. 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]. Similar to many other neuropsychiatric diseases, a large number of genes expressed in the brain has been involved in the etiology 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 approximately 80% of depression cases reported stressful 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 the identification of novel candidates in depression.

Gene Candidate Studies in Depression

More than 100 candidate gene studies have been conducted in order to investigate potential associations with the 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 interleukins—*IL1B* and *IL6*) and functioning of circadian system (brain and muscle Arnt-like protein-1/*BMAL1*, circadian locomotor output cycles kaput/*CLOCK*, neuronal PAS domain-containing protein 2/*NPAS2*, period circadian regulator 3/*PER3*, cryptochrome 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. Nevertheless, 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 polymorphisms 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 replicate 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 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*), regulating synaptic membrane exocytosis 1 (*RIMS1*), catenin beta 1 (*CTNNB1*), Dmx like 2 (*DMXL2*), synapsin I (*SYN1*), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta (*YWHAB*) and tyrosine 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 × Gene (G×G) and Gene × Environment (G×E) Interaction Studies

Different studies investigated the effects of various gene–gene (G×G) interactions on depression. Neff et al. [252] suggested possible interaction of 5HTTLPR polymorphism with an unknown gene on chromosome 4, whereas the 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 the interaction of polymorphisms in matrix metalloproteinase (*MMP*) genes and TIMP metalloproteinase 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 variations [259]. On the other hand, GWAS demonstrated no significant findings for pairwise G×G interactions, although several nominally significant interactions were found [260].

Considering research on gene and environment (G×E) 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], although other studies observed no significant effects [269]. In addition, significant gene × 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 × 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 × environment effect for polymorphism rs4652467 near centrosomal protein 350 (*CEP350*) gene, which could not be replicated. In Japanese subjects, marginally significant gene × environment effect between stress and rs10510057 polymorphism near the regulator of G protein signaling 10 (*RGS10*) gene was found [283].

Three-way gene × gene × environment interactions in depression were demonstrated for *BDNF* rs6265 and 5HTTLPR polymorphisms with childhood abuse [284] and family environment [285], suggesting the 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 \times environment \times gene interactions were also observed in depression, such as interaction of 5HTTLPR polymorphism with both recent life event and childhood abuse exposure [288]. The example of even higher order interactions is five-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 heterogeneity 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 the involvement of epigenetic regulating mechanisms. Therefore, investigation of gene \times gene and gene \times environment interactions, as well as epigenetic influences, seem most promising 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, modern technology was expected to unravel their genetic background. In the 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 straightforward 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 undisputable 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 \times gene \times environment interactions or environment \times environment \times 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.

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