ISSN 1022-7954, Russian Journal of Genetics, 2018, Vol. 54, No. 6, pp. 593–603. © Pleiades Publishing, Inc., 2018.
Original Russian Text © A.E. Gareeva, E.K. Khusnutdinova, 2018, published in Genetika, 2018, Vol. 54, No. 6, pp. 585–596.

REVIEWS
AND THEORETICAL ARTICLES

Schizophrenia Genetics

A. E. Gareeva[a], * and E. K. Khusnutdinova[a]

[a] *Institute of Biochemistry and Genetics, Ufa Scientific Center, Russian Academy of Sciences, Ufa, 450054 Russia*

**e-mail: annagareeva@yandex.ru*

Received June 16, 2017; in final form, August 3, 2017

Abstract—Schizophrenia is a complex multifactorial disease, in most cases manifested as a result of the interaction of genetic and psychological factors, as well as certain environmental conditions. However, genetic factors certainly play a determining role in the predisposition to schizophrenia. The coefficient of heritability of schizophrenia is about 80%, which is typical of the most highly inherited multifactorial diseases. This review presents the results of the latest world studies of genetic factors in the development of schizophrenia, including epigenetic, genome-wide association studies, and next generation sequencing.

Keywords: schizophrenia, genetics

DOI: 10.1134/S1022795418050046

INTRODUCTION

Schizophrenia is the most severe mental illness affecting about 0.8–1% of the world's population. The disease manifests at a young age and leads to disability and social disadaptation. Its etiology is not fully understood. A number of etiological and environmental factors are known that play a role in pathogenesis and the results of therapy. Numerous studies demonstrate a high degree of heritability of schizophrenia, varying in the range of 65–80% [1], which is characteristic of the most highly inherited multifactorial diseases.

Schizophrenia is also considered to be a complex genetic disease characterized by the dysfunction of several neurotransmitter systems such as dopaminergic, serotonergic, and glutamatergic.

GENETIC FACTORS OF SCHIZOPHRENIA

Family Studies

The published data demonstrate the fact of the aggregation of schizophrenia in families. It is known that the risk of development of schizophrenia for siblings of the patient is about 9%; for their children, the risk is 13%; and for their parents, it is only 6%. A lower risk of development of schizophrenia in parents is probably due to a decrease in reproductive capacity in patients with this disease. The genetic contribution to the development of schizophrenia in relatives of the second generation varies from 2 to 6%, while in the general population it is 1% [2].

According to a number of studies, the risk of development of schizophrenia can be increased in relatives of female patients and patients with early onset of the disease. In addition, relatives of schizophrenic patients have a higher risk of development of other mental illnesses, such as bipolar psychosis and unipolar depression [2]. It is believed that the age of onset and course of the disease, type of onset, and premorbid state are symptoms of familial accumulation of the disease [2].

Twin Studies

Several studies found that for monozygotic twins the total concordance rate is 40–65%, and for dizygotic twins it is 0–28% [3]. According to meta-analysis, the heritability of predisposition to schizophrenia is 81%. The ability of event-related potentials (ERPs) of the brain is known to reflect the synchronized neuronal activity during the thought processes. In the study of cognitive impairment in schizophrenia and other severe neurodegenerative diseases, various ERP endophenotypes are used. Lack of ERPs accumulates in families of patients with mental illness [4]. Twin studies have demonstrated the inheritance of ERP endophenotypes [5, 6] and a correlation with the genetic predisposition to schizophrenia [7]. Taking these data into consideration, one can assume that disturbances in the ERP can be considered as endophenotypes of schizophrenia [8].

Study of Foster Families

It was shown that adopted biological relatives of schizophrenic patients have an increased risk of development of this disease. In foster children who have first-degree schizophrenic relatives, the risk of development of schizophrenia is increased 10-fold compared to a healthy control [9]. The risk of development

Table 1. Genes associated with schizophrenia according to linkage analyses

Gene	Chromosomal region	Function	Reference
DRD2	11q23	Dopaminergic system	[11]
ERBB4	2q33.3-q34	Tyrosine kinase receptor NRG1	[12, 13]
GARBB2	5q34	GABAergic system	[11, 14]
GRIN2B	12p12	Glutamatergic system	[11, 15]
HTR2A	13q14-21	Serotonergic system	[11, 16]
IL1B	2q14	Immune system	[11, 17]
NOTCH4	6p21.3	Neuronal development	[18, 19]
NRXN1	2p16.3	Synapses	[20]
PDE4B	1p31	Synapses	[21, 22]
PRODH	22q11	Glutamate synthesis	[11, 23]
RELN	7q22	Synapses	[24, 25]

of schizophrenia is observed in children whose mothers suffer from schizophrenia only if they are in a foster family with mental illnesses. At the same time adopted children from healthy parents do not have a risk of development of schizophrenia if they get into a family where parents suffer from schizophrenia spectrum disorders [10].

The contribution of the genetic component to schizophrenia is obvious according to family and twin studies and studies of adopted children [2]. Since the 1980s, a huge amount of data on the genetic predisposition to schizophrenia has been collected.

Studies of genetic risk factors for the development of schizophrenia include a number of approaches. Widely used methods of analysis of genetic linkage made it possible to identify a large number of loci and candidate genes the polymorphism of which could be associated with the risk of development of schizophrenia.

The very first approach to study the genetic basis of schizophrenia was the analysis of linkage in the families of schizophrenic patients, which made it possible to detect genomic regions associated with schizophrenia. These analyses began in the late 1980s (Table 1). It is now well known that linkage analyses are not entirely good for the study of mental illness. The main problems to be faced are a small effect of single genes, a small number of patients in families, incomplete penetrance, broad diagnostic boundaries, and, thus, difficulties in determining the phenotype [2].

The first linkage analysis was conducted by Sherrington et al. [26] in 1988 in Icelanders and Britons. They showed the linkage of schizophrenia to a group of markers on the long arm of the chromosome 5. Some data from linkage analyses are well known, which were confirmed later in replicative studies. Thus, the regions associated with schizophrenia are 1q21-q22 [27, 28], 8p21 [29, 30], 13q32 [29, 31], and 6p21-p22 [32, 33].

Using meta-analysis for 18 linkage assays, the linkage to 8p, 13q, and 22q chromosomal regions was confirmed [34]. Another meta-analysis based on 20 linkage analyses confirmed the linkage of schizophrenia to the 2p12-q22.1, 2q22.1-q23.3, 3p25.3-p22.1, 5q23.2-q34, 6pter-p21.1, 8p22-p21.1, 11q22.3-q24.1, 14pter-q13.1, 20p12.3-p11, and 22pter-q12.3 chromosomal regions [35].

A large-scale genome-wide association study of 1004 patients, including 12 neurophysiological and neurocognitive endophenotypes, was conducted by a consortium on the genetics of schizophrenia. An analysis of the linkage with 12 endophenotypes revealed the association of the 3p14 chromosomal region (*SYNPR, ATXN7*, *PRICKLE2*, and *MITF*) with the saccade test and the 1p36 chromosomal region (*PAX7*, *UBR4*, *ALDH4A1*, *NBL1*, *HTR6*, *EPHA8*, and *EPHB2*) with an emotion recognition test that reached the genome-wide significance level with LOD score of 4.0 (3p14) and 3.5 (1p36). The linkage of the 2p25 and 16q23 chromosomal regions with spatial orientation, 2q24 and 2q32 with sensorimotor ability, 5p15 with prepulse inhibition, 8q24 with the California word memorization test, and 10q26 and 12p12 with the ability to memorize faces of people with a fairly high level of genome-wide significance with a LOD score greater than 2.2 was revealed [36].

Epigenetic Studies

Despite the existence of evidence of the involvement of genetic and environmental factors in the pathogenesis of schizophrenia, to date there is no clear idea of their interaction. In the last decade owing to innovative molecular approaches, epigenetic studies have significantly increased the understanding of molecular mechanisms that mediate environmental effects on gene expression and their activity.

MicroRNA is a class of small noncoding RNA that is capable of inhibiting mRNA translation or is involved in the degradation of target mRNA. In one of the postmortem studies of brain samples, an increase

in the expression of miR-106b and a decrease in the expression of miR-24, miR-26b, miR-30e, and miR-92 were found in 16 patients with schizophrenia [37].

There is evidence confirming an increase in the biogenesis of microRNAs in the dorsolateral prefrontal cortex and the upper temporal gyrus in patients with schizophrenia, resulting in an increase in the amount of RNA-binding protein Dgcr8 required for the maturation of primary microRNA [37]. In another study of postmortem brain samples, an increase in the amount of miR-181b, miR-15a, miR-15b, miR-195, and miR-107 was found in patients with schizophrenia. Moreover, the target genes of these microRNAs are the candidate genes of schizophrenia involved in the pathogenesis of the disease; among them, there are genes of receptors of glutamate (*GRM5*, *GRM7*, *GRIK2*, *GRIN1*, and *GRID*), serotonin (*HTR1B*, *HTR2C*, and *HTR4*), gammaaminobutyric acid (*GABR1* and *GABRA1*), dopamine (*DRD1*), and M-cholinergic receptor 1, as well as the genes of brain neurotrophic factor (*BDNF*), neuregulin 1 (*NRG1*), relin (*RELN*), and ataxin 2 (*SCA2*) [37].

Experiments on animal models have shown that schizophrenia-like symptoms induced by prenatal stress in mice are associated with epigenetic modifications of GABAergic interneurons of the *GAD1* and *RELN* genes and metabotropic receptors of glutamate *mGlu2/3* [38]. The offspring of females who had stress showed an increased level of DNA methyltransferases DNMT and therefore increased expression of DNMT in GABAergic neurons associated with reduced expression of *GAD1* and *RELN* in childhood and adulthood. Adult mice showed hyperactivity, decreased social interaction, and prepulse inhibition, representing a real model of schizophrenia [2].

Thus, epigenetic regulatory factors in the pathogenesis of schizophrenia are of great interest; however, replication of already obtained data is required. Despite the fact that the exact nature is largely unknown, epigenetic changes are undoubtedly involved in the pathophysiology of schizophrenia and probably affect individual sensitivity to antipsychotic therapy [2].

The high heterogeneity of the clinical manifestations of such a complex disease as schizophrenia depends on several factors. Genetic individual variability (single nucleotide polymorphisms (SNP) and copy number variation), environmental factors (such as early stress events, drug abuse, nutritional components, and viral effects), and epigenetic changes interact with each other. In particular, the environment has a more direct effect on epigenetic control, which in turn directly affects the expression of genes regardless of the genotype. On one hand, the interaction between genetic and epigenetic factors mediated by environmental factors contributes to the heterogeneity of phenotypes not only observed at the clinical level but also measurable in the form of neuropsychological and neurophysiological patterns. On the other hand, such factors also influence the neurobiological interface directly affected by drugs, for example, receptors for neurotransmitters and synaptic proteins, thus influencing the antipsychotic response. While in the past the clinical efficacy of an antipsychotic drug was a guide to its neurobiological mechanisms, a deeper knowledge of the fundamentals of biomolecules of schizophrenia and discoveries of new promising technologies will allow the creation of new drugs based on the discovered new targets. Animal models play a key role in testing new targets and drugs and can lead to the prediction of the clinical course and to therapy more adapted to the patient [2].

APPROACHES TO THE STUDY OF GENETICS OF SCHIZOPHRENIA

Investigation of Schizophrenia Candidate Genes

The search for candidate genes based on the etiopathogenetic hypothesis is another approach to studying the genetic basis of schizophrenia as a multifactorial disease. These are the genes of components of neurotransmitter systems—dopamine, serotonin, and glutamate receptors, as well as neurotrophins and neurexins. The results of association studies on polymorphic variants of candidate genes of schizophrenia were presented by us earlier [39–44]. The advantage of the search for candidate genes is in its power; however, if the polymorphic variant has a small effect, it cannot be reproduced in replicative studies.

Gatt et al. [45] presented a review of meta-analyses based on the search for candidate genes. Of the 97 polymorphic variants, the most significant association with schizophrenia was shown for the neuronal development genes (*AHI1*, *MTHFR*, *RELN*, and *TRKA*) and the dopaminergic (*COMT*, *DRD2*, *DRD3*, and *DRD4*), glutamatergic (*DAOA*, *GABRB2*, and *NRG1*), serotoninergic (*HTR2A*, *SLC6A4*, and *TPH1*), and immune (*IL1B*) systems [45].

Genome-Wide Association Studies

Since 2006, genome-wide association studies have been conducted in various populations of the world. New genes associated with the development of schizophrenia in Europeans and Asians have been discovered. Replicative and functional studies are performed to confirm the role of the identified polymorphic variants of genes in the development of schizophrenia. Taking into account the results of the studies carried out so far, genes of predisposition to schizophrenia can be subdivided depending on their role in the etiopathogenesis of this disease.

Genome-wide association studies allow simultaneously genotyping several hundred thousand polymorphic gene loci and finding each gene in the genome. Like linkage analysis, GWAS is a method that is free of hypotheses and thus able to identify genes, revealing

yet unknown pathogenic mechanisms, possibly playing an important role in the development of schizophrenia. GWAS is the result of colossal technological advances and is now transforming the way of study of multifactorial diseases. GWAS really demonstrates the main advantages, such as high resolution and high power, to detect small genetic effects. It should be noted that there is a major nuance in interpreting the results of GWAS—statistical significance. Since about one million single nucleotide polymorphisms (SNPs) are tested simultaneously, it is necessary to introduce a correction for multiple comparisons with the significance level p of about 5E-08 to minimize the risk of false positive results. However, such a high statistical threshold value may make it difficult to detect genes that are truly associated with the disease, but give small risks. To increase the sample size and thereby maximize the statistical power, several consortia have been created and now most studies are being carried out in collaboration with many centers around the world.

The first genome-wide association analysis with schizophrenia revealed the association of the polymorphic locus rs752016 of the *PLXNA2* gene [46]. It is known that the *PLXNA2* gene (1q32) is a member of the semaphorin receptor family and plays an active role in the development and functioning of the brain [46]. Proteins of this family are involved in the development of axons and neuronal regenerations [47]. Mice showed a decrease in the *PLXNA2* gene expression in the cerebral cortex after birth, which is associated with its participation in the development of neuronal connections [48]. Need et al. [49] conducted a genome-wide association study on a sample of 871 patients and 863 healthy individuals and a replicative sample of 1460 patients and 12995 healthy Europeans. It was shown that the polymorphic locus rs1289726, located in 1q23.3 region 297 kb from the *PBX1* gene, was associated with schizophrenia with a rather high level of significance of 2E-04 [49].

According to a number of genome-wide association studies conducted later, the association of some polymorphic variants of genes located in the region of the main histocompatibility complex MHC (6p.22.1-p22.3) with a predisposition to schizophrenia in European populations was revealed. The genome-wide study by Stefansson et al. [18] within the international consortia SGENE, ISC, MGS aimed at the investigation of the genetics of schizophrenia (the sample of patients was 12945 and the control was 34591 individuals) demonstrated the association of seven polymorphic variants of genes located in the region of the main histocompatibility complex MHC (6p.22.1-p22.3) with the development of schizophrenia with a genome-wide significance level for Europeans: rs6913660 of the *HIST1H2B* gene (p = 1.1E-09), rs13219354 (p = 1.3E-10); rs6932590 (p = 1.4E-12) of the *PRSS16* gene; rs13211507 of the *PGBD1* gene (p = 8.3E-11); rs3131296 of the *NOTCH4* gene (p = 2.3E-10); rs12807809 of the *NRGN* gene (p = 2.4E-09); rs9960767 of the *TCF4* gene (p = 4.1E-09) [18, 50]. Later, the data obtained by Stefansson et al. were confirmed in the genome-wide association studies of European [50, 51] and Japanese [52] populations. These results indicate that the main histocompatibility complex is an important region in the formation of the organism's response to stress and infection and indicate the importance of considering the influence of the infectious component for understanding the biological mechanisms underlying the development of schizophrenia and other mental illnesses.

Subsequently, an international schizophrenia consortium (ISC) conducted a study involving 3322 patients with schizophrenia and 3587 individuals of a control group of European origin to test the hypothesis of polygenic inheritance of schizophrenia, according to which the interaction of nonallelic genes can cause schizophrenia as a phenotype [51]. This study showed that polygenic variants that increase the risk of development of schizophrenia play the same role for bipolar disorder [51]. Polymorphic loci rs3130375, rs13194053, and rs3130297, localized in the region of the main histocompatibility complex MHC, were associated with the risk of development of schizophrenia [53]. The polymorphic locus rs6904071, localized in the region of the major histocompatibility complex MHC, was associated with cognition impairment in patients with schizophrenia compared with the control, as well as with episodic memory and a decrease in hippocampal volume in patients [53]. The largest association with schizophrenia was shown for the polymorphic locus in the region of the myosin *XVIIIB* gene (*MYO18B*) located on chromosome 22 (22q12.1) [51]. The association of this gene with schizophrenia was not further confirmed in any study. However, a genome-wide study conducted in 2013 revealed the association of the *MYO5B* gene with the risk of bipolar disorder. It is known that this *MYO5B* gene is involved in the pathogenesis of bipolar disorder through the dysfunction of the glutamatergic system [53]. The results of this study were confirmed by replication in the Chinese population [54].

The Psychiatric Genomic Consortium on Genetics of Schizophrenia PGC-SZ is the largest consortium conducting research in biological psychiatry. This consortium has more than 500 researchers from 25 countries and owns data of 170000 DNA samples, providing the central base for genome-wide association studies in the world [55, 56]. A genome-wide analysis and subsequent data replication within the PGC-SZ consortium, involving more than 20000 individuals at each stage, revealed the association of ten SNPs with the risk of development of schizophrenia [55]. Among these SNPs, the association of six polymorphic loci with the risk of schizophrenia was established for the first time: rs1625579 in the *MIR137* gene (1p21.3), known as the neurogenesis and neuronal development regulator; rs17662626 near the

PCGEM1 gene (2q32.3) (prostate-specific transcript 1); rs10503253 in the *CSMD1* gene (8p23.2) (CUB and Sushi multiple domain 1), which is known to be expressed in all tissues, but the highest level of the product is found in the brain, and its role in neurodegenerative and neurological diseases may be related to the fact that proteins involved in regulation of complement can also control synaptic functions; rs7004633 in the region of the *MMP16* gene (8q21.3) (metallopeptidase 16 matrix); rs7914558 in the *CNNM2* gene (10q24.32-q24.3) (cyclin M2); and rs11191580 in the *NT5C2* gene (5'-nucleotidase 2). It is known that the detected association of two SNPs rs2021722 of the *TRIM26* gene (6p21.32-p22.1) (tripartite motif-containing 26) and rs12966547 of the *TCF4* gene (18q21.1) (transcription factor 4) by the PGC-SZ were also found in earlier studies. As a result of this study, it was found that the *TCF4* gene contains the MIR137 mRNA binding site and that microRNA mediated dysregulation can be considered as a new mechanism for the pathogenesis of schizophrenia [55].

In a combined sample of European patients with schizophrenia and bipolar disorder, the association of polymorphic loci of the *ITIH4* (rs2239547) ($p = 2.5E-08$), *ANK3* (rs10994359) ($p = 2.5E-08$), and *CACNA1C* (rs4765905) ($p = 7E-09$) genes was found (9394 patients and 12462 healthy individuals) [55].

The previous genome-wide association analysis and its replication revealed the association of the polymorphic variant rs10761482 of the *ANK3* gene with schizophrenia in Norwegians [57]. The gene of ankyrin 3 encodes a human protein belonging to the ankyrin family (10q21). It was initially found in the nodes of Ranvier and neuromuscular junctions. Alternative splicing generates several forms of the protein; they can be expressed in other types of tissues and cells as well. The *ANK3* gene (10q21.2) plays an integrative role in the regulation of neuronal activity.

The hypothesis of the development of schizophrenia, which is based on the dysfunction of the myelination of nerve fibers, arose as a result of histological studies and neuroimaging. The reduction of myelin or the integrity of the axonal membrane in the temporal lobe in patients with schizophrenia [58], the ultrastructural changes in myelin sheath platelets in the frontal cortex of the brain, and the loss of correlation between neuronal density and the number of axons in the corpus callosum were described [59, 60]. A decrease in the expression of neuronal genes and myelination genes in patients with schizophrenia has been reported [61, 62], in particular, the *ANK3* gene [63].

Roussos and Haroutunian [64] proposed a neuroglytic pathogenesis pathway that plays a huge role in the development of this disease on the basis of the existence of changes in neurotransmitter systems and synaptic cytoarchitectonics that contribute to the etiopathogenesis of schizophrenia, which is based on disturbances in Ranvier nodes as one of the functional units [51, 64].

The ITIH4 glycoprotein (3p21.1) encoded by the heavy chain inhibitor 4 gene of the inter-alpha trypsin is secreted into the blood, where it circulates in plasma and cleaves the kallikrein into smaller fragments. ITIH4 glycoprotein forms complexes with hyaluronic acid SHAP-HA, which are supposed to play an important role in the inflammatory response.

The *CACNA1C* gene (p13.33) encodes the alpha-1 subunit of potential-dependent calcium channels. Calcium channels mediate the influx of calcium ions into the cell during the polarization of the membrane. The alpha-1 subunit consists of 24 transmembrane segments and forms pores through which the ions pass into the cell. The association of the polymorphic locus rs1006737 of the *CACNA1C* gene with an increase in activity of the amygdala in patients with schizophrenia and bipolar disorder [65], as well as memory processes in regions of the hippocampus in healthy individuals, was identified [66]. Huang et al. [67] showed the association of the polymorphic locus rs1006737 of the *CACNA1C* gene with a reduction in the gray matter of the brain in Chinese patients with schizophrenia.

Chen et al. [68] conducted a genome-wide study on a sample of CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and MGS-GAIN (13038 patients with schizophrenia and 16636 healthy individuals) of European origin. Two polymorphic loci rs3828611 and rs10043986 of the *CMYA5* gene, nonsynonymous substitutions, were found. In the combined sample of CATIE and MGS-GAIN, the polymorphic locus rs4704591 of the *CMYA5* gene was also associated with schizophrenia with a high level of significance. It was shown that these polymorphic markers are in linkage disequilibrium with each other (rs3828611–rs10043986, $r^2 = 0.008$; rs10043986–rs4704591, $r^2 = 0.204$). In addition, there is an assumption about the interaction of the candidate genes of schizophrenia *DTNBP1* and *CMYA5* that is based on their participation in common pathogenic processes. These results were confirmed in a meta-analysis of 23 replicative studies (912 families consisting of 4160 individuals, as well as 11380 schizophrenic patients and 15021 healthy individuals) showing the association of polymorphic loci rs10043986 and rs4704591 of the *CMYA5* gene (rs10043986, OR = 1.11, 95% CI = 1.04–1.18, $p = 8.2E-04$ and rs4704591, OR = 1.07, 95% CI = 1.03–1.11, $p = 3.0E-04$) with a risk of development of schizophrenia. On the basis of the data obtained, it can be assumed that the *CMYA5* gene is associated with a risk of development of schizophrenia. Further study of the function of this gene is required to confirm these results [68].

A genome-wide association study [69] of 795 Chinese patients resistant to schizophrenia therapy (RST) and 806 healthy individuals revealed the association of six polymorphic loci with a fairly high level of signifi-

cance: rs10218843 ($p = 3.04E-07$) and rs11265461 ($p = 1.94E-07$) of the gene encoding a family of proteins that transmit the signal for activation of the lymphocyte molecule member 1 (*SLAMF1*, 1q23.3); rs4699030 ($p = 1.94E-06$) and rs230529 ($p = 1.74E-07$) of the gene encoding the nuclear transcription factor 1 subunit kB (*NFKB1*, 4q24); rs13049286 ($p = 3.05E-05$) and rs3827219 ($p = 1.66E-05$) of the serine/threonine kinase gene (*RIPK4*, 21q22.3). The encoded protein can also activate NFkappaB and is required for the differentiation of keratinocytes. SNP rs739617 ($p = 3.87E-05$) of the gene of cytokinesis 4 (*DOCK4*, 7q31.1) was also associated with RST. The association of the polymorphic locus rs28362691, located in the promoter of the *NFKB1* gene, with the RST was shown after the resequencing of this region of the chromosome ($p = 4.85E-06$). It was found that the *NFKB1*-94delATTG* allele (rs28362691) was associated with a decreased promoter activity, compared with the *NFKB1*-94insATTG* allele in SH-SY5Y cells. This study suggests that rs28362691 of the *NFKB1* gene may be involved in the development of the RST [69].

In a genome-wide association study [70] involving 2454 European patients with schizophrenia with positive, negative, and general psychopathologic symptoms, no SNP reached the 1.67E-08 genomic significance level. However, a number of genes and chromosomal regions associated with schizophrenia with a high level of significance were found: with positive symptoms—18q23 (rs7233060 *CTDP1*, $p = 2.53E-07$), 5q12.3 (rs17206232 *ADAMTS6*, $p = 1.45E-06$), 13q21.2 (rs2323266 *PCDH20*, $p = 3.13E-06$), 10q11.21 (rs10900020 *CXCL12*, $p = 3.46E-06$), 5q11.2 (rs10052004, $p = 3.62E-06$), 4p16.3 (rs959770 *ZFYVE28*, $p = 9.40E-06$), and 20q13.31 (rs11699237, $p = 9.96E-06$); with negative symptoms—20q13.31 (rs11699237, $p = 3.13E-06$), 18p11.21 (rs1455244, $p = 3.22E-06$), 15q22.2 (rs7172342 *RORA*, $p = 3.83E-06$), 6p21.32 (rs4530903, $p = 4.83E-06$), and 8q13.2 (rs13278432, $p = 9.65E-06$); with general psychopathologic symptoms—12q24.21 (rs1920592, $p = 1.05E-06$) and 18q23 (rs4798896, $p = 3.81E-06$) [70].

Within the Irish Schizophrenia Genomics Consortium (ISGC) and the Welcome Trust Case Control Consortium2 (WTCCC2) involving 1606 patients with schizophrenia and 1794 healthy individuals, the involvement of polymorphic loci of the 6p21 chromosomal region (rs204999) of the main histocompatibility complex and 2p16 (rs2312147 *VRK2*, $p = 4.94E-03$), 2q32.1 (rs1344706 *ZNF804A*, $p = 5.56E-03$), and 18q21.1 (rs17594526 *TCF4*, $p = 1.05E-03$), previously shown to associate with schizophrenia [18, 51, 71] and confirmed by a replicative study with 13195 patients and 31021 healthy individuals, was shown. SNP rs204999 is in linkage disequilibrium with seven other SNPs covering the 32.26 Mb region including the *PPT*, *PRRT1*, *EGFL8*, *AGPAT1*, and *RNF5* genes. None of these genes was associated with schizophrenia according to previously conducted genome-wide studies. The authors suggest the existence of the functional role of rs204999 in the regulation of these genes.

A genome-wide study in 2012 involving 20000 healthy individuals and 915354 unaffected SNPs found that 23% of the variations responsible for schizophrenia were SNPs, which primarily were frequent [72].

As part of the consortium on the genetics of schizophrenia (PGC-SZ), in 2014, another large-scale genome-wide association study was carried out involving 36989 patients with schizophrenia and 113075 healthy individuals. It is known that, among the 108 genes associated with schizophrenia with a high level of significance, 83 were previously associated with the disease from previous genome-wide projects [73]. Associated genes are widely expressed in the CNS and the immune system, which, by assumption of a number of investigators, is involved in the pathogenesis of schizophrenia. Thus, the association of polymorphic loci of genes of dopaminergic (e.g., *DRD2* gene) and glutamatergic (*GRIN2A*, *GRIA1*, and *GRM3*) neurotransmission with a risk of development of schizophrenia with genome-wide significance level was shown, which is consistent with one of the leading hypotheses for development of schizophrenia—hypofunction of the glutamatergic system [73, 74].

A genome-wide association study by Hall et al. [75] was aimed at finding the association of ERP endophenotypes: deficiency of suppression of the potential P50 (DS P50), sensory processing disorder (SPD), and gamma oscillations (GO). The sample consisted of 271 patients with schizophrenia and 128 healthy individuals of European origin. As a result of the study, the association of SNP at 14q31.3 rs10132223, $p = 1.27E-09$, with SPD was revealed. The association of this SNP with affective psychosis is well known according to the international consortium on genetics of schizophrenia (PGS-GWAS) [75]. In addition, the association of a auditory steady-state response (ASSR) was found with SNP rs181531738, $p = 9.77E-08$; rs146360492, $p = 9.05E-08$; and rs114213960, $p = 8.47E-08$ of the serine peptidase *CORIN* gene, localized in the 4p12 region 512 bp apart from the *ATP10D* gene (ATPase, class V, type 10D) and 167 kb apart from the gene of beta-subunit of gamma-aminobutyric acid *GABRB1*. These SNPs are in strong linkage disequilibrium with one another ($r^2 > 0.8$) [75].

Thus, the advantage of large-scale genome-wide association studies is that the long lists of polymorphic loci obtained provide a key to the solution of the etiology of schizophrenia; however, the precise use of these polymorphic markers for the diagnosis or prognosis of this disease has not yet been determined [76].

Polygenic Risk Score

GWAS studies have provided strong evidence that mental disorders are highly polygenetic; their genetic

architecture consists of many frequent genetic variants. To achieve the genome-wide level of significance p, the values must pass a strict threshold. According to some estimates, when carrying out about one million association tests, the significance threshold after applying the correction for multiple comparisons is 0.05/1000000, or 5E-08 [77]. To fulfill this condition, for alleles with a small effect, samples of very large sizes reaching tens of thousands of patients and healthy individuals are required.

Despite the fact that the total number of loci exceeding the genome-wide level of statistical significance is often small, GWAS usually gives much more random associations with small p values than expected. This pattern is consistent with the polygenic genetic architecture and gives a push to the development of new biostatistical approaches [78]. The polygenic risk score and the estimate of variance explained by all SNPs are two commonly used methods [78].

Copy Number Variation

In general, genomic studies have shown two broad classes of genetic markers for the risk of schizophrenia: multiple SNPs and rare highly penetrant submicroscopic chromosomal deletions and duplications, known as copy number variations (CNV), including *de novo* mutations [79]. The size of the CNV varies from 1000 bp to more than 100 kb. CNVs are pathogenic to a number of mental disorders, such as mental retardation, autism, and schizophrenia [80].

It was found that CNVs at 1q21.1, 15q11.2, 15q13.3, 22q11.2, 16p11.2, and 16p13.1 occur much more often in patients with schizophrenia than in control samples. It is known that CNV can alter the expression of genes encoding proteins or families of proteins and lead to the development of schizophrenia [56]. Since the development of schizophrenia is obviously due to the interaction of many factors, the most resultant at present is the search for a multitude of genes with little effect, each of which would increase the risk of schizophrenia, or the search for very rare mutations with significant effect [56].

One of the main problems in the search for genes associated with schizophrenia is a diagnostic definition, since often the diagnostic criteria have wide boundaries and can vary from study to study. Therefore, the determination of a more specific definition of a trait that would not differ between studies is an important fundamental task.

The search for genetic markers taking into account endophenotypes is most preferable. Endophenotypes are described as genetically inherited internal phenotypes, detectable by biochemical testing or microscopy [2].

Frequent and rare polymorphic variants do not explain all cases of schizophrenia. It was estimated that 10000 frequent polymorphic variants account for about 32% of predisposition to schizophrenia [81]. CNVs occur with a much lower frequency; they are only 2–5% of cases of schizophrenia. A large proportion of unexplained heredity leads to the hypothesis that de novo mutations could explain the portion of lost heredity and as a result has become the subject of intensive study.

Next Generation Sequencing. De novo Mutations and Schizophrenia

Exome-wide and genome-wide sequencing technologies can be used for case-control studies or search for *de novo* mutations by sequencing of the genomes of healthy parents and their sick child (trio). In the study by Xu et al. [82], exomes of 53 trios with a sporadic form of the disease were sequenced, as well as of 20 individuals of the control group. A total of 40 *de novo* mutations were found in 27 schizophrenic patients, including a potentially destructive mutation in the *DGCR2* gene located in the 22q11.2 microdeletion region, which is known to have a significant genetic factor in the development of schizophrenia [82]. The results of the exome sequencing of genomic DNA in 399 individuals, including 105 probands with schizophrenia, 84 healthy siblings, and 210 healthy parents, suggest that a disturbance of neurogenesis in the prefrontal cortex of embryos can play a decisive role in the pathophysiology of schizophrenia [83]. Exome sequencing of 57 trios with sporadic or familial disease showed a 3.5-fold increase in the proportion of *de novo* nonsense mutations in the case of sporadic schizophrenia. Moreover, mutations were found in the genes also involved in autism (*AUTS2*, *CHD8*, and *MECP2*) and mental retardation (*HUWE1* and *TRAPPC9*) and demonstrate the common genetic etiology of these diseases. Functionally the *CHD8*, *MECP2*, and *HUWE1* genes participate in epigenetic regulation of transcription, which presumably can be an important risk mechanism [84]. The most wide-ranging exome-wide studies have confirmed the cross of not only genes, but even mutations with similar functional effects for schizophrenia, autism spectrum disorders, and mental retardation [85, 86]. According to another UK10K multicenter study involving a total of 4264 patients with schizophrenia, 9343 healthy individuals, and 1077 trios, a genome-wide significance level (p = E5.6-09) was achieved with a rare polymorphic variant in the gene encoding the histone-methyltransferase complex *SETD1A* [87]. The same group showed the involvement of this *SETD1A* gene also in the pathogenesis of other mental diseases and established a crossover of schizophrenia with other diseases of neuronal development [87].

Genetic studies over the past decade have contributed to a fundamental understanding of the nature of schizophrenia with the identification of the first undeniable loci and risk genes and the discovery that rare gene variants also contribute to the genetic predisposition to this disease. The results begin to reveal the

main gene networks and biochemical pathways, to work out the design of neurobiological studies of the disease, and to influence the strategy of pharmacotherapeutic studies and (although this was not discussed in this review) are close to the impact on clinical and diagnostic practice. Together with these discoveries, there comes a sobering realization that the genetic basis of schizophrenia was in many ways even more complex than anticipated. Discovering the loci and genes responsible for the development of schizophrenia is a triumph, but this is only the beginning of a long process toward a significant biological understanding, as well as the improvement of therapy for this disease. Genetics complements, but does not replace, other key elements in the development of medicines and also does not remove many other barriers. But at least genetic data provide a solid foundation on which to build the next generation of studies, the integration of genomics with other "omics," the development of new analytical and bioinformatic tools, the discovery of mechanisms for the interaction of genes with each other and with the surrounding environment, and clarifying how genes and their variants are actually involved in the pathophysiology of the disease. It is to be hoped that these opportunities will stimulate further scientific and pharmaceutical investments.

REFERENCES

1. Kaur, H., Jajodia, A., Grover, S., et al., Synergistic association of *PI4KA* and *GRM3* genetic polymorphisms with poor antipsychotic response in south Indian schizophrenia patients with low severity of illness, *Am. J. Med. Genet., Part B*, 2014, vol. 165, no. 8, pp. 635—646. doi 10.1002/ajmg.b.32268
2. Bosia, M., Pigoni, A., and Cavallaro, R., Genomics and epigenomics in novel schizophrenia drug discovery: translating animal models to clinical research and back, *Expert Opin. Drug Disc.*, 2015, vol. 10, no. 2, pp. 125—139. doi 10.1517/17460441.2015.976552
3. Cardno, A.G. and Gottesman, I.I., Twin studies of schizophrenia: from bow–and–arrow concordances to star wars Mx and functional genomics, *Am. J. Med. Genet.*, 2000, vol. 97, no. 1, pp. 12—17.
4. Perez, V.B., Roach, B.J., Woods, S.W., et al., Early auditory gamma-band responses in patients at clinical high risk for schizophrenia, *Clin. Neurophysiol.*, 2013, vol. 62. suppl., p. 147.
5. Hall, M.H., Schulze, K., Rijsdijk, F., et al., Heritability and reliability of P300, P50 and duration mismatch negativity, *Behav. Genet.*, 2006, vol. 36, no. 6, pp. 845—857. doi 10.1007/s10519-006-9091-6
6. Hall, M.H., Taylor, G., Sham, P., et al., The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia, *Schizophr. Bull.*, 2011, vol. 37, pp. 778—787. doi 10.1093/schbul/sbp134
7. Bramon, E., McDonald, C., Croft, R.J., et al., Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study, *Neuroimage*, 2005, vol. 27, no. 4, pp. 960—968. doi 10.1016/j.neuroimage.2005.05.022
8. Turetsky, B.I., Kohler, C.G., Indersmitten, T., et al., Facial emotion recognition in schizophrenia: when and why does it go awry?, *Schizophr. Res.*, 2007, vol. 94, no. 1, pp. 253—263. doi 10.1016/j.schres.2007.05.001
9. Ingraham, L.J. and Kety, S.S., Adoption studies of schizophrenia, *Am. J. Med. Genet.*, 2000, vol. 97, no. 1, pp. 18—22.
10. Thapar, A., Langley, K., Asherson, P., and Gill, M., Gene—environment interplay in attention-deficit hyperactivity disorder and the importance of a developmental perspective, *Br. J. Psychiatry*, 2007, vol. 190, no. 1, pp. 1—3. doi 10.1192/bjp.bp.106.027003
11. Allen, N.C., Bagade, S., McQueen, M.B., et al., Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database, *Nat. Genet.*, 2008, vol. 40, no. 7, pp. 827—834. doi 10.1038/ng.171
12. Chong, V.Z., Thompson, M., Beltaifa, S., et al., Elevated neuregulin-1 and ErbB4 protein in the prefrontal cortex of schizophrenic patients, *Schizophr. Res.*, 2008, vol. 100, no. 1, pp. 270—280. doi 10.1016/j.schres.2007
13. Hahn, C.G., Wang, H.Y., Cho, D.S., et al., Altered neuregulin 1–erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia, *Nat. Med.*, 2006, vol. 12, no. 7, pp. 824—828. doi 10.1038/nm1418
14. Zhao, C., Xu, Z., Chen, J., et al., Two isoforms of GABAA receptor β2 subunit with different electrophysiological properties: differential expression and genotypical correlations in schizophrenia, *Mol. Psychiatry*, 2006, vol. 11, no. 12, pp. 1092—1105. doi 10.1038/sj.mp.4001899
15. Li, D. and He, L., Association study between the NMDA receptor 2B subunit gene (*GRIN2B*) and schizophrenia: a HuGE review and meta-analysis, *Genet. Med.*, 2007, vol. 9, no. 1, pp. 4—8. doi 10.109701.gim.0000250507.96760.4b
16. Martucci, L., Wong, A.H., De Luca, V., et al., N-methyl-D-aspartate receptor *NR2B* subunit gene *GRIN2B* in schizophrenia and bipolar disorder: polymorphisms and mRNA levels, *Schizophr. Res.*, 2006, vol. 84, no. 2, pp. 214—221. doi 10.1016/j.schres.2006.02.001
17. Shi, J., Gershon, E.S., and Liu, C., Genetic associations with schizophrenia: meta-analyses of 12 candidate genes, *Schizophr. Res.*, 2008, vol. 104, no. 1, pp. 96—107. doi 10.1016/j.schres.2008.06.016
18. Stefansson, H., Ophoff, R.A., Steinberg, S., et al., Common variants conferring risk of schizophrenia, *Nature*, 2009, vol. 460, no. 7256, pp. 744—747. doi 10.1038/nature08186
19. Wang, Z., Wei, J., Zhang, X., et al., A review and re-evaluation of an association between the NOTCH4 locus and schizophrenia, *Am. J. Med. Genet., Part B*, 2006, vol. 141, no. 8, pp. 902—906. doi 10.1002/ajmg.b.30383
20. Etherton, M.R., Blaiss, C.A., Powell, C.M., and Südhof, T.C., Mouse neurexin-1α deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments, *Proc. Natl.*

Acad. Sci. U.S.A., 2009, vol. 106, no. 42, pp. 17998—18003. doi 10.1073/pnas.0910297106

21. Fatemi, S.H., King, D.P., Reutiman, T.J., et al., *PDE4B* polymorphisms and decreased PDE4B expression are associated with schizophrenia, *Schizophr. Res.*, 2008, vol. 101, no. 1, pp. 36—49. doi 10.1016/j.schres.2008.01.029
22. Kähler, A.K., Otnaess, M.K., Wirgenes, K.V., et al., Association study of *PDE4B* gene variants in Scandinavian schizophrenia and bipolar disorder multicenter case–control samples, *Am. J. Med. Genet., Part B*, 2010, vol. 153, no. 1, pp. 86—96. doi 10.1002/ajmg.b.30958
23. Gogos, J.A., Santha, M., Takacs, Z., et al., The gene encoding proline dehydrogenase modulates sensorimotor gating in mice, *Nat. Genet.*, 1999, vol. 21, no. 4, pp. 434—439. doi 10.1038/7777
24. Guidotti, A., Auta, J., Davis, J.M., et al., Decrease in reelin and glutamic acid decarboxylase67 (*GAD67*) expression in schizophrenia and bipolar disorder: a postmortem brain study, *Arch. Gen. Psychiatry*, 2000, vol. 57, no. 11, pp. 1061—1069.
25. Lipska, B.K., Peters, T., Hyde, T.M., et al., Expression of DISC1 binding partners is reduced in schizophrenia and associated with *DISC1* SNPs, *Hum. Mol. Genet.*, 2006, vol. 15, no. 8, pp. 1245—1258. doi 10.1093/hmg/ddl040
26. Sherrington, R., Brynjolfsson, J., Petursson, H., et al., Localization of a susceptibility locus for schizophrenia on chromosome 5, *Nature*, 1988, vol. 336, no. 6195, pp. 164—167. doi 10.1038/336164a0
27. Brzustowicz, L.M., Hodgkinson, K.A., Chow, E.W., et al., Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22, *Science*, 2000, vol. 288, no. 5466, pp. 678—682.
28. Zheng, Y., Wang, X., Gu, N., et al., A two-stage linkage analysis of Chinese schizophrenia pedigrees in 10 target chromosomes, *Biochem. Biophys. Res. Commun.*, 2006, vol. 342, no. 4, pp. 1049—1057. doi 10.1016/j.bbrc.2006.02.041
29. Blouin, J.L., Dombroski, B.A., Nath, S.K., et al., Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21, *Nat. Genet.*, 1998, vol. 20, no. 1, pp. 70—73. doi 10.1038/1734
30. Gurling, H.M.D., Kalsi, G., Brynjolfson, J., et al., Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23, *Am. J. Hum. Genet.*, 2001, vol. 68, no. 3, pp. 661—673. doi 10.1086/318788
31. Brzustowicz, L.M., Honer, W.G., Chow, E.W., et al., Linkage of familial schizophrenia to chromosome 13q32, *Am. J. Hum. Genet.*, 1999, vol. 65, no. 4, pp. 1096—1103.
32. Moises, H.W., Yang, L., Kristbjarnarson, H., et al., An international two-stage genome-wide search for schizophrenia susceptibility genes, *Nat Genet.*, 1995, vol. 11, no. 3, pp. 321—324. doi 10.1038/ng1195-321
33. Maziade, M., Roy, M.A., Rouillard, E., et al., A search for specific and common susceptibility loci for schizophrenia and bipolar disorder: a linkage study in 13 target chromosomes, *Mol. Psychiatry*, 2001, vol. 6, no. 6, pp. 684—693. doi 10.1038/sj.mp.4000915
34. Badner, J.A. and Gershon, E.S., Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia, *Mol. Psychiatry*, 2002, vol. 7, no. 4, pp. 405—411. doi 10.1038/sj.mp.4001012
35. Lewis, C.M., Levinson, D.F., Wise, L.H., et al., Genome scan meta-analysis of schizophrenia and bipolar disorder: 2. Schizophrenia, *Am. J. Hum. Genet.*, 2003, vol. 73, no. 1, pp. 34—48. doi 10.1086/376549
36. Greenwood, T.A., Swerdlow, N.R., Gur, R.E., et al., Genome-wide linkage analyses of 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia, *Am. J. Psychiatry*, 2013, vol. 170, no. 5, pp. 521—532. doi 10.1176/appi.ajp.2012.12020186
37. Abdolmaleky, H.M., Yaqubi, S., Papageorgis, P., et al., Epigenetic dysregulation of *HTR2A* in the brain of patients with schizophrenia and bipolar disorder, *Schizophr. Res.*, 2011, vol. 129, no. 2, pp. 183—190. doi 10.1016/j.schres.2011.04.007
38. Matrisciano, F., Tueting, P., Dalal, I., et al., Epigenetic modifications of GABAergic interneurons are associated with the schizophrenia-like phenotype induced by prenatal stress in mice, *Neuropharmacology*, 2013, vol. 68, pp. 184—194. doi 10.1016/j.neuropharm.2012.04.013
39. Gareeva, A.E., Zakirov, D.F., and Khusnutdinova, E.K., Association polymorphic variants of *GRIN2B* gene with paranoid schizophrenia and response to typical neuroleptics in Russians and Tatars from Bashkortostan Republic, *Russ. J. Genet.*, 2013, vol. 49, no. 9, pp. 962—968. https://doi.org/10.1134/S1022795413080024.
40. Gareeva, A.E., Zakirov, D.F., Valinurov, R.G., and Khusnutdinova, E.K., Polymorphism of *RGS2* gene: genetic markers of risk for schizophrenia and pharmacogenetic markers of typical neuroleptics efficiency, *Mol. Biol.* (Moscow), 2013, vol. 47, no. 6, pp. 814—820. doi 10.1134/S0026893313060046
41. Galaktionova, D.Y., Gareeva, A.E., Khusnutdinova, E.K., and Nasedkina, T.V., Association of *SLC18A1, TPH1*, and *RELN* gene polymorphisms with risk of paranoid schizophrenia, *Mol. Biol.* (Moscow), 2014, vol. 48, no. 4, pp. 546—555 doi 10.1134/S0026893314030042
42. Gareeva, A.E. and Khusnutdinova, E.K., Glutamate receptors genes polymorphism and the risk of paranoid schizophrenia in Russians and Tatars from the Republic of Bashkortostan, *Mol. Biol.* (Moscow), 2014, vol. 48, no. 5, pp. 671—680. doi 10.1134/S0026893314050033
43. Gareeva, A.E., Traks, T., Koks, S., and Khusnutdinova, E.K., The role of neurotrophins and neurexins genes in the risk of paranoid schizophrenia in Russians and Tatars, *Russ. J. Genet.*, 2015, vol. 51, no. 7, pp. 683—694. doi 10.1134/S102279541506006X
44. Gareeva, A.E., Kinyasheva, K.O., Galaktionova, D.Y., et al., Polymorphism of brain neurotransmitter system genes: search for pharmacogenetic markers of haloperidol efficiency in Russians and Tatars, *Mol. Biol.* (Moscow), 2015, vol. 49, no. 6, pp. 858—866. doi 10.1134/S0026893315050076
45. Gatt, J.M., Burton, K.L., Williams, L.M., et al., Specific and common genes implicated across major mental disorders: a review of meta-analysis studies, *J. Psy-*

chiatr. Res., 2015, vol. 60, pp. 1—13. doi 10.1016/j.jpsychires.2014.09.014

46. Mah, S., Nelson, M.R., Delisi, L.E., et al., Identification of the semaphorin receptor PLXNA2 as a candidate for susceptibility to schizophrenia, *Mol. Psychiatry*, 2006, vol. 11, no. 5, pp. 471—478.
47. Tamagnone, L., Artigiani, S., Chen, H., et al., Plexins are a large family of receptors for transmembrane, secreted, and GPI–anchored semaphorins in vertebrates, *Cell*, 1999, vol. 99, no. 1, pp. 71—80.
48. Murakami, Y., Suto, F., Shimizu, M., et al., Differential expression of plexin-A subfamily members in the mouse nervous system, *Dev. Dyn.*, 2001, vol. 220, no. 3, pp. 246—258. doi 10.1002/1097-0177(20010301)220:3<246::AID-DVDY1112>3.0.CO;2-2
49. Need, A.C., Ge, D., Weale, M.E., et al., A genome wide investigation of SNPs and CNVs in schizophrenia, *PLoS Genet.*, 2009, vol. 5, no. 2. e1000373. doi 10.1371/journal.pgen.1000373
50. Shi, J., Levinson, D.F., Duan, J., et al., Common variants on chromosome 6p22.1 are associated with schizophrenia, *Nature*, 2009, vol. 460, no. 7256, pp. 753—757. doi 10.1038/nature08192
51. Purcell, S.M., Wray, N.R., Stone, J.L., et al., Common polygenic variation contributes to risk of schizophrenia and bipolar disorder, *Nature*, 2009, vol. 460, no. 7256, pp. 748—752. doi 10.1038/nature08185
52. Ikeda, M., Aleksic, B., Kinoshita, Y., et al., Genome-wide association study of schizophrenia in a Japanese population, *Biol. Psychiatry*, 2011, vol. 69, no. 5, pp. 472—478. doi 10.1016/j.biopsych.2010.07.010
53. Walters, J.T., Rujescu, D., Franke, B., et al., The role of the major histocompatibility complex region in cognition and brain structure: a schizophrenia GWAS follow-up, *Am. J. Psychiatry*, 2013, vol. 170, no. 8, pp. 877—885. doi 10.1176/appi.ajp.2013.12020226
54. Chen, Y., Tian, L., Zhang, F., et al., Myosin Vb gene is associated with schizophrenia in Chinese Han population, *Psychiatry Res.*, 2013, vol. 207, no. 1, pp. 13—18. doi 10.1016/j.psychres.2013.02.026
55. Ripke, S., Sanders, A.R., Kendler, K.S., et al., Genome-wide association study identifies five new schizophrenia loci: Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, *Nat. Genet.*, 2011, vol. 43, no. 10, pp. 969—976. doi 10.1038/ng.940
56. Giusti-Rodríguez, P. and Sullivan, P.F., The genomics of schizophrenia: update and implications, *J. Clin. Invest.*, 2013, vol. 123, no. 11, pp. 4557—4563. doi 10.1172/JCI66031
57. Athanasiu, L., Mattingsdal, M., Kahler, A.K., et al., Gene variants associated with schizophrenia in a Norwegian genome-wide study are replicated in a large European cohort, *J. Psychiatr. Res.*, 2010, vol. 44, no. 12, pp. 748—753. doi 10.1016/j.jpsychires.2010.02.002
58. Foong, J., Symms, M.R., Barker, G.J., et al., Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging, *Brain*, 2001, vol. 124, no. 5, pp. 882—892.
59. Bernstein, H.G., Steiner, J., and Bogerts, B., Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy, *Expert Rev. Neurother.*, 2009, vol. 9, no. 7, pp. 1059—1071. doi 10.1586/ern.09.59
60. Simper, R., Walker, M.A., Black, G., et al., The relationship between callosal axons and cortical neurons in the planum temporale: alterations in schizophrenia, *Neurosci. Res.*, 2011, vol. 71, no. 4, pp. 405—410. doi 10.1016/j.neures.2011.08.007
61. Tkachev, D., Mimmack, M.L., Ryan, M.M., et al., Oligodendrocyte dysfunction in schizophrenia and bipolar disorder, *Lancet*, 2003, vol. 362, no. 9386, pp. 798—805.
62. Cruz, D.A., Weaver, C.L., Lovallo, E.M., et al., Selective alterations in postsynaptic markers of chandelier cell inputs to cortical pyramidal neurons in subjects with schizophrenia, *Neuropsychopharmacology*, 2009, vol. 34, no. 9, pp. 2112—2124. doi 10.1038/npp.2009.36
63. Konrad, A. and Winterer, G., Disturbed structural connectivity in schizophrenia—primary factor in pathology or epiphenomenon?, *Schizophr. Bull.*, 2008, vol. 34, no. 1, pp. 72—92.
64. Roussos, P. and Haroutunian, V., Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities, *Front. Cell Neurosci.*, 2014, vol. 8, p. 5. doi 10.3389/fncel.2014.00005
65. Tesli, M., Koefoed, P., Athanasiu, L., et al., Association analysis of *ANK3* gene variants in Nordic bipolar disorder and schizophrenia case–control samples, *Am. J. Med. Genet., Part B,* 2011, vol. 156, no. 8, pp. 969—974. doi 10.1002/ajmg.b.31244
66. Krug, A., Witt, S.H., Backes, H., et al., A genome-wide supported variant in *CACNA1C* influences hippocampal activation during episodic memory encoding and retrieval, *Eur. Arch. Psychiatry Clin. Neurosci.*, 2013, vol. 264, no. 2, pp. 103—110. doi 10.1007/ s00406-013-0428-x
67. Huang, L., Mo, Y., Sun, X., et al., The impact of *CACNA1C* allelic variation on regional gray matter volume in Chinese population, *Am. J. Med. Genet., Part B*, 2016, vol. 171, no. 3, pp. 396—401. doi 10.1002/ajmg. b.32418
68. Chen, X., Lee, G., Maher, B.S., et al., GWA study data mining and independent replication identify cardiomyopathy-associated 5 (*CMYA5*) as a risk gene for schizophrenia, *Mol. Psychiatry*, 2011, vol. 16, no. 11, pp. 1117—1129. doi 10.1038/mp.2010.96
69. Liou, Y.J., Wang, H.H., Lee, M.T., et al., Genome-wide association study of treatment refractory schizophrenia in Han Chinese, *PLoS One*, 2012, vol. 7, no. 3. e33598. doi 10.1371/journal.pone.0033598
70. Fanous, A.H., Zhou, B., Aggen, S.H., et al., Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms, *Am. J. Psychiatry*, 2012, vol. 169, no. 12, pp. 1309—1317. doi 10.1176/appi.ajp.2012.12020218
71. O'Donovan, M.C., Craddock, N., Norton, N., et al., Identification of loci associated with schizophrenia by genome-wide association and follow-up, *Nat. Genet.*, 2008, vol. 40, no. 9, pp. 1053—1055. doi 10.1038/ng.201
72. Lee, K.W., Woon, P.S., Teo, Y.Y., et al., Genome wide association studies (GWAS) and copy number variation (CNV) studies of the major psychoses: what have we

learnt?, *Neurosci. Biobehav. Rev.*, 2012, vol. 36, no. 1, pp. 556—571. doi 10.1016/j.neubiorev.2011.09.001

73. Ripke, S., Neale, B.M., Corvin, A., et al., Biological insights from 108 schizophrenia-associated genetic loci, *Nature*, 2014, vol. 511, no. 7510, p. 421. doi 10.1038/nature13595
74. Zhang, Y., Fan, M., Wang, Q., et al., Polymorphisms in microRNA genes and genes involving in NMDAR signaling and schizophrenia: a case–control study in Chinese Han population, *Sci. Rep.*, 2015, vol. 5. doi 10.1038/srep12984
75. Hall, J., Trent, S., Thomas, K.L., et al., Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity, *Biol. Psychiatry*, 2015, vol. 77, no. 1, pp. 52—58. doi 10.1016/j.biopsych.2014.07.011
76. Loh, P.R., Bhati, G., Gusev, A., et al., Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis, *Nat. Genet.*, 2015, vol. 47, no. 12, pp. 1385—1392.
77. Chanock, S.J., Manolio, T., Boehnke, M., et al., Replicating genotype—phenotype associations, *Nature*, 2007, vol. 447, no. 7, pp. 655—660. doi 10.1038/447655a
78. Wray, N.R., Lee, S.H., Mehta, D., et al., Research review: polygenic methods and their application to psychiatric traits, *J. Child Psychol. Psychiatry*, 2014, vol. 55, no. 10, pp. 1068—1087. doi 10.1111/jcpp.12295
79. Bassett, A.S., Scherer, S.W., and Brzustowicz, L.M., Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease, *Am. J. Psychiatry*, 2010, vol. 167, no. 8, pp. 899—914. doi 10.1176/appi.ajp.2009.09071016
80. Kirov, G., Grozeva, D., Norton, N., et al., Support for the involvement of large copy number variants in the pathogenesis of schizophrenia, *Hum. Mol. Genet.*, 2009, vol. 18, no. 8, pp. 1497—1503. doi 10.1093/hmg/ddp043
81. Ripke, S., O'Dushlaine, C., Chambert, K., et al., Genome-wide association analysis identifies 13 new risk loci for schizophrenia, *Nat. Genet.*, 2013, vol. 45, no. 10, pp. 1150—1159. doi 10.1038/ng.2742
82. Xu, B., Roos, J.L., Dexheimer, P., et al., Exome sequencing supports a *de novo* mutational paradigm for schizophrenia, *Nat. Genet.*, 2011, vol. 43, no. 9, pp. 864—868. doi 10.1038/ng.902
83. Gulsuner, S., Walsh, T., Watts, A.C., et al., Spatial and temporal mapping of *de novo* mutations in schizophrenia to a fetal prefrontal cortical network, *Cell*, 2013, vol. 154, no. 3, pp. 518—529. doi 10.1016/j.cell.2013.06.049
84. McCarthy, S.E., Gillis, J., Kramer, M., et al., *De novo* mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability, *Mol. Psychiatry*, 2014, vol. 19, no. 6, pp. 652—658. doi 10.1038/mp.2014.29
85. Fromer, M., Pocklington, A.J., Kavanagh, D.H., et al., *De novo* mutations in schizophrenia implicate synaptic networks, *Nature*, 2014, vol. 506, no. 7487, pp. 179—184. doi 10.1038/nature12929
86. Purcell, S.M., Moran, J.L., Fromer, M., et al., A polygenic burden of rare disruptive mutations in schizophrenia, *Nature*, 2014, vol. 506, no. 7487, pp. 185—190. doi 10.1038/nature12975
87. Singh, G., Talwar, I., Sharma, R., et al., Analysis of *ANKKI* (rs1800497) and *DRD2* (rs1079597, rs1800498) variants in five ethnic groups from Punjab, North-West India, *Gene*, 2016, vol. 584, no. 1, pp. 69—74. doi 10.1016/j.gene.2016.03.009

Translated by A. Kashevarova