

GENETIC MECHANISMS OF COMORBIDITY IN SCHIZOPHRENIA AND MAJOR DEPRESSIVE DISORDER: CURRENT STATE OF THE PROBLEM

Valentina Akhmad Ibragim¹, Leyla Eduardovna Fakhrutdinova¹, Zukhra Etibarovna Alekperova¹, Svetlana Ekhtiram Kzy Alekperova¹, Salikhat Shamilevna Yarmetova², Aishat Timurovna Karnailova³, Saida Magomedovna Alisheikhova², Maysarat Rabazanovna Alieva²

¹ Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation

² Dagestan State Medical University, Makhachkala, Russian Federation

³ Pirogov Russian National Research Medical University, Moscow, Russian Federation

ABSTRACT

The comorbid course of schizophrenia and major depressive disorder has been associated with marked clinical heterogeneity, complicating the identification of the mechanisms underlying their co-occurrence. This study aimed to analyze current concepts regarding the genetic mechanisms of comorbidity between schizophrenia and major depressive disorder and to systematize data on shared genetic factors, polygenic predisposition, and molecular pathways. The study was conducted as a systematic critical review of contemporary domestic and international literature. The analysis revealed that the genetic overlap between the two disorders manifests at multiple levels—ranging from common and rare variants and copy number variations to shared loci, genes, biological pathways, and polygenic effects. Research into pleiotropy, genetic correlation, functional genomics, and polygenic risk scores was identified as particularly significant. However, the observed genetic similarity did not constitute evidence of a single, specific mechanism of comorbidity. Interpretation of the results was limited by the heterogeneity of clinical phenotypes, variations in diagnostic criteria and sample ethnic composition, and the underrepresentation of patients with the co-occurrence of schizophrenia and major depressive disorder in large-scale genetic studies. It was concluded that comorbidity should be viewed as the result of an interplay between shared polygenic vulnerability, disorder-specific genetic factors, and additional clinical and environmental modifiers. To validate this model, the study highlights the need for direct investigation of the comorbid phenotype and the integration of GWAS, rare variant and CNV analysis, polygenic risk scores, and functional genomics.

KEYWORDS: *schizophrenia; major depressive disorder; comorbidity; genetic predisposition; polygenic architecture; genetic correlation; polygenic risk scores.*

INTRODUCTION

Schizophrenia and major depressive disorder are common mental illnesses, but they differ in clinical manifestations and have a partially common biological basis. According to the World Health Organization, in 2023, about 27 million people suffered from schizophrenia, and about 322 million suffered from depression [1, 2]. In the Russian Federation, the overall incidence of schizophrenia in 2021 was 309.0 cases per 100,000 population, and the rate of first—time diagnosis was 9.4 cases per 100,000. [3]. In the study of V.V. According to a study conducted by Gafarov and co-authors among Novosibirsk residents aged 25–44, depression was detected in 12.8% of the surveyed, and another 24.5% had an average level of depressive symptoms [4]. These data justify the need for a separate study of cases in which depressive symptoms are combined with schizophrenia.

Diagnostic evaluation of such a combination requires distinguishing between several conditions. Depressive manifestations can occur at different stages of the schizophrenic process and be associated with negative symptoms, side effects of antipsychotic therapy, or an independent depressive disorder [3]. N.A. Schneider, M.A. Novitsky, N.G. Neznanov and co-authors analyzed 459 publications, of which 45 were included in the thematic review; the data obtained indicated possible overlap of genetic and pathophysiological factors [5]. Among the potentially common genes, the authors identified GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2, and BCL9 [5]. However, their role in the formation of the comorbid phenotype requires confirmation. The genetic basis of both disorders is polygenic. In a review by A.A. Shmakova and co-authors in 2023, the heritability of schizophrenia was estimated at 80–85%; GWAS and studies of rare variants revealed numerous risk loci [6]. In 2024, A.E. Gareeva obtained data on genetic markers of paranoid schizophrenia in Russian samples of Russians from the Republic of Bashkortostan and Tatars [7, 8]. For depression, E.D. Kasyanov and co-authors point to another methodological problem: an increase in the number of GWAS participants increases the requirements for the quality of phenotyping, since diagnostic heterogeneity affects the identified genetic associations [9]. In a Russian sample of 4,520 people, D.V. Pinakhina and co-authors found an association in the 7q21 region and considered MAGI2 as a potential candidate, indicating the need for subsequent replication [10]. In a study by V.V. Gafarov and co-authors, SLC6A4 polymorphisms were associated with depression in the Russian population [4]. A.O. Kibitov and D.S. Shumskaya in a review of 2024 Immune and inflammatory mechanisms

have been identified as one of the areas of interpretation of the genomic data of mental disorders [11]. Large-scale transdiagnostic studies also reveal common genetic components of schizophrenia and depression, but the degree of such overlap depends on the characteristics of the studied phenotype [12, 13].

The problem lies not in the absence of common genetic signals, but in the lack of certainty of their relationship to comorbidity. It is not yet possible to determine unequivocally which options are associated with a combination of two diagnoses, which reflect a general predisposition to mental disorders. The comparability of the results is influenced by differences in diagnostic criteria, phenotyping methods, ethnic composition of samples, and genetic approaches.

The aim of the work is to summarize data on the genetic mechanisms of comorbidity in schizophrenia and major depressive disorder, identify common, specific risk factors, characterize the proposed molecular pathways, and determine the limitations of the existing evidence base. The results of studies of polygenic architecture, pleiotropy, rare variants, CNV, and functional genomics are being compared. The possibilities of applying PRS to the comorbid phenotype are considered.

Materials and methods. The research materials were PubMed/MEDLINE and eLibrary databases.RU, CyberLeninka; additionally, article-by-article citation lists and catalogs of scientific publishers were viewed.

The core sample consists of works from 2022-2026. Older sources were involved when the problem under discussion was not fully disclosed. The search strings were formed using Russian and English based on a set of keywords: "schizophrenia", "major depressive disorder", "comorbidity", "genetic predisposition", "genetic correlation", GWAS, PRS, CNV, rare variants, pleiotropy. Combinations were set using the AND, OR operators.

We selected original genetic articles, GWAS, studies of rare variants and CNVs, as well as works with polygenic risk indicators, functional genomics and cross-diagnostic genetics, plus systematic reviews. Priority was given to publications analyzing common variants, loci, biological pathways, or comorbid pathology proper. Special attention was paid to the works on the diagnostic heterogeneity of affective states in patients with schizophrenia.

Here, independent BDD, post-schizophrenic depression, and depressive manifestations in the structure of psychosis are fundamentally distinguished. Meta-analysis of our own data was not performed: this was hindered by pronounced differences between studies in design and diagnostic criteria, in sample characteristics, ethnic composition of participants, and ways to quantify genetic risk.

The selected articles were analyzed according to several parameters: design, size and features of the samples, thoroughness of phenotypic diagnosis, the nature of genotyping, the stability of the detected associations, the presence of independent replicas. Additionally, data on genetic correlation and functional interpretation of signals were studied. The key condition for a critical assessment is the ability to show the connection of genetic factors with a combined pathology, rather than with a predisposition to each disease individually.

Polygenic architecture of schizophrenia and major depressive disorder

Schizophrenia and BDD have a complex polygenic architecture [18,19]. The heritability of schizophrenia is estimated to reach 80-85%, but this figure does not mean the existence of several major genes. A significant proportion of the risk variance is created by thousands of changes, each of which makes a weak or moderate contribution [6, 15]. The development of the GWAS methodology has shifted scientists' attention from candidate genes to panels of loci, as well as rare variants and CNVs [20,21]. As a result, the architecture consists of two layers – frequent alleles with minimal effects and rare mutations that act more strongly [6, 15, 22].

Polygenicity is no less pronounced in depression [23, 24]. The review by J. Flint (2023) names 178 predisposition loci and over two hundred probable candidate genes [16]. In the work of T.D. Als and colleagues, the sample exceeded 1.3 million people, 371,184 of them with depressive disorder. 243 risk loci were identified; 64 of them turned out to be new, and approximately 11,700 variants explained up to 90% of SNP heritability [12,25]. The authors link genetic vulnerability to depression to glutamate and GABA-mediated neurotransmission, as well as to specific brain cell populations [12].

The polygenic organization of both disorders in itself encourages the search for common links of hereditary predisposition – however, the coincidence of individual loci or variants does not yet serve as evidence of their specific contribution to the development of comorbidity. Such a conclusion requires demonstrating the connection of the inherited signal with the combined course of schizophrenia and BDD, and not with each disease individually.

Table 1 – Main research directions of the genetic architecture of schizophrenia and major depressive disorder

Direction	Main results	Representatives of the research	Significance for the study of comorbidity
GWAS of schizophrenia	Identification of multiple risk loci, including common variants with little effect	of A.A. Shmakova, E.V. Semina, E.A. Neufeld, B.D. Tsygankov, M.N. Karagyaur; P.F. Sullivan, S. Yao, J. Hjerling-Leffler	Forms the basis for the search for common genetic signals of the two disorders.
Rare variants and CNVs	Identification of rare genetic changes and copy number variations with a potentially more pronounced effect	A.A. Shmakova et al.; P.F. Sullivan et al.	Allows you to study the mechanisms that may not be detected when analyzing common SNPs.

GWAS BDR	Identification of a large number of loci and confirmation of high polygenicity of depression	J. Flint; T.D. Als et al.	It shows a significant amount of general genetic variability between mental disorders
Russian GWAS BDR	In a Russian sample of 4,520 people, genetic associations were studied, including the MAGI2 region.	D. Pinakhina, D. Yermakovich, E. Vergasova, E.D. Kasyanov et al.	and expands the evidence base, taking into account population specifics.
Candidate-Gene Research	Data on associations of individual genes with depressive symptoms have been obtained.	V.V. Gafarov, E.A. Gromova, M.A. Gubina et al.	Provides data on individual molecular pathways, but requires confirmation in large samples.
Cross-diagnostic analysis	The genetic similarity between various mental disorders is revealed.	V.-R. Bourque et al.; E. Friligkou et al.	It allows you to move from the analysis of individual diseases to the study of a common genetic predisposition.

The maximum information content is provided by combining several analytical levels. GWAS of specific disorders outline the basic architecture of hereditary factors; the study of rare variants complements the list of potential risk determinants, and, finally, a cross-diagnostic approach checks how these sets overlap [26]. Taken separately, no method reveals such a mechanism of comorbidity.

Common genetic factors of schizophrenia and major depressive disorder

The question of the hereditary nature of the joint development of these two diseases is most clearly formulated in the study of N.A. Schneider and his group.

After analyzing 459 publications, the team selected 45 articles, which were included in the review [5]. The authors named GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2, and BCL9 as candidate genes; however, they emphasized that until additional GWAS aimed specifically at the comorbid phenotype are performed, any conclusions are preliminary [5].

V.-R. Bourque et al. had an even more extensive sample: a systematic review covered 28 studies comparing genetic, transcriptomic, and neuroimaging data in patients with schizophrenia, BDD, bipolar disorder, autism, and ADHD. Of all the comparisons performed, 88.6% demonstrated positive sign correlations [13, 27]. Nevertheless, the biological proximity of diagnostic categories does not explain the entire clinical picture of their joint occurrence.

A cross-diagnostic meta-analysis performed by E. Friligkou and colleagues (2025) aimed to find pleiotropic loci and intersecting biological pathways in patients with schizophrenia, BDD, and bipolar affective disorder [17,28]. The data obtained are consistent with the hypothesis of a partial overlap of hereditary risks [29]. A specific gene responsible for comorbidity has not yet been detected.

Molecular and neurobiological mechanisms of genetic overlap

A candidate for the role of a common link is a malfunction of neuronal transmission and synapse plasticity [21,30]. The product of the GRIN1 gene is an NMDA receptor subunit involved in glutamatergic signaling, and N.A. Schneider and co-authors discussed the involvement of this gene in comorbid conditions [5]. The contribution of the serotonergic system is equally likely. V.V. Gafarov and his team investigated polymorphic variants of SLC6A4 in a sample of 403 men and 531 women aged 25-44 (Novosibirsk) and recorded an association with depression [4]. Although such findings describe the serotonin component as a whole, a direct contribution of this pathway to the combination of schizophrenia with BDD is not deduced from them. Extensive work by T.D. Als and co-authors correlates hereditary predisposition to depression with glutamatergic and GABAergic neurotransmission [12]. A.O. Kibitov and D.S. Shumskaya consider inflammatory immune processes to be another line of interpretation of the genetic results [11]. As the publications of P.F. Sullivan and colleagues demonstrate, the path from a locus to a specific cellular or molecular mechanism remains methodologically difficult [15].

Apparently, the genetic intersection unfolds at several levels of the nervous system organization at once [27,31] – the work of synapses, mediator systems, regulation of gene expression and intracellular processes [11,12,15,17,32].

The identification of the association of the same gene with both nosologies does not indicate the identical nature of its action. With regard to the comorbid phenotype, the key question is whether the accumulation of such factors increases the likelihood of a combined course, or whether this is just a marker of the general vulnerability of the nervous system.

Rare variants, copy number variations, and polygenic predisposition

The genetic risk spectrum is not limited to common SNPs alone [18,20,33]. In schizophrenia studies, rare variants, CNVs, as well as whole-exome sequencing materials are added to them [6, 15]. The individual effect of such changes often exceeds the effect of most common polymorphisms [22,34]. As a result, the genetic risk of schizophrenia consists of two components – a mass of common variants with a weak effect and a few rare changes with a stronger effect [6,15,19,20,22].

Rare genetic factors in MDR have so far been studied noticeably weaker than frequent ones. However, large-scale GWAS analyses convincingly demonstrate the pronounced polygenic architecture of the disease: in total, about 11,700 loci accounted for up to 90% of the SNP heritability of depressive disorder [12,35]. The practical consequence is obvious – an adequate assessment of comorbidity requires simultaneous consideration of data on both frequent and rare variants.

Table 2 – Levels of genetic overlap between schizophrenia and major depressive disorder

The level of analysis	What is being studied	Basic data	Limitations of interpretation
Individual SNPs	Associations of specific variants with the disease	Numerous risk variants have been identified for both disorders.	Most of the options have little effect.
Genetic loci	A set of related variants in a specific region of the genome	GWAS make it possible to identify risk-related loci	The associated locus does not always contain a causal variant
Candidate genes	Functionally significant genes	Comorbidity is characterized by GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2, and BCL9	. The results of individual candidate gene studies require replication
CNV and rare variants	Structural changes and rare genetic variants	Additional components of schizophrenia risk are identified	It is difficult to assess the specificity for the comorbid phenotype
The genetic correlation	Average overlap of polygenic effects	Overlap between several mental disorders has been confirmed	Correlation does not prove causation and does not explain the individual clinical phenotype.
Pleiotropy	The effect of one genetic signal on several phenotypes	Modern cross-disorder GWAS identify common loci and biological pathways	The same option can have multidirectional effects.
Functional genomics	Gene expression, tissues, cell types, and biological pathways	Neuronal, glial, GABA, and glutamatergic processes are distinguished.	A functional relationship does not always mean a direct causal role.

A comparison of the analytical levels leads to a simple conclusion: interpretation is most reliable when several methodological approaches come together.

GWAS approaches capture common variants and related loci, rare structural and point changes complete the picture, and correlation analysis, along with functional genomics, makes it possible to judge the likely biological intersection of pathologies. However, the specificity of the combined phenotype is a matter of independent empirical verification.

Polygenic risk indicators and the ability to predict comorbidity

The polygenic risk index (PRS) aggregates the contribution of multiple variants into a single quantitative measure of predisposition [36]. In relation to MDR, the potential of the method is growing in parallel with the enlargement of GWAS samples [25,37].

T.D. Als and co-authors used genetic information in two ways – both to describe depression itself and to analyze its links with other mental disorders. As it turned out, a significant proportion of risk variants affect several diagnoses at once, and the effects are sometimes multidirectional [12].

So far, there have been few attempts to apply PRS to the comorbid picture of schizophrenia + BDD. A methodological trap arises: the schizophrenic risk index predicts schizophrenia, and the depressive PRS predicts depression, while the probability of their joint course is not reflected by either [34,37,38]. There is only one way out – the allocation of a separate phenotype with the formation of a specialized sample for it [26,39].

The crucial condition remains the quality of phenotyping [9,16,40]. According to E.D. Kasyanov and colleagues, diagnostic heterogeneity significantly distorts the results of GWAS depression [9]. For a comorbid condition, the distinction is especially important: independent BDD, post-schizophrenic depression, and depressive symptoms within schizophrenia may be based on various genetic bases.

Limitations of the modern evidence base and research prospects

The imbalance here is obvious: genomic studies of schizophrenia and BDD have reached an impressive scale, but there are relatively few papers where the comorbid phenotype would be studied on its own. [5, 12, 15, 16]. N.A. Schneider and colleagues explicitly say that without new genome-wide and associative data on this combination the picture will remain incomplete [5].

The comparison of the results is also hampered by methodological diversity: the criteria for selecting participants vary, the diagnostic tools are not the same, the depth of phenotypic study is the same, and the ethnic composition of the groups does not match. Since megaprojects are built around separate diagnoses, patients who are diagnosed

with both disorders are included in them in a small number [28,29]. Hence, the purely indirect nature of the extrapolation: the findings of GWAS of schizophrenia and BDD on the comorbid group are transferred only conditionally, before verification on target samples.

Depression has another added difficulty – the heterogeneity of the clinical phenotype itself [16, 24, 40]. As emphasized by E.D. Kasyanov and co-authors, the reliability of modern GWAS ultimately depends on the quality of phenotyping [9].

What should the future design look like? Multilevel: it is rational to combine classical genome-wide search, the study of rare variations and CNVs, polygenic scoring models, transcriptomic profiles and functional genomics approaches [12, 15, 17]. A cross-diagnostic strategy in such a design will make it possible to separate the general background of psychiatric vulnerability and the genetic variants associated primarily with a specific diagnostic combination [13, 17].

According to V.E. Golimbet and T.P. Klyushnik, the separation of hereditary factors between disorders does not negate the existence of special pathophysiological mechanisms in each comorbid condition: the effect of the same variant can change its sign and strength depending on the phenotype [14].

A working interpretation follows from the above – the combination of schizophrenia and BDD occurs where polygenic vulnerability of a general type, specific genetic influences of each disorder and modifiers of clinical or environmental origin intersect. Modern data do not allow us to correlate the contribution of these terms [41]. Verification of such a model requires samples that are genetically and clinically homogeneous, with a verified double diagnosis.

CONCLUSION

A comparison of the accumulated molecular and genetic information indicates that the hereditary predisposition to schizophrenia and BDD partially overlaps, but no complete coincidence has been found. The comorbid phenotype was most directly studied in the work of N.A. Schneider and colleagues, who identified the genes GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2, and BCL9. Cross-diagnostic work expands the list to include common loci and biological pathways. At the same time, a single genetic architecture of mental pathology does not cover the whole picture of comorbidity.

Each analytical layer provides its own unique piece of information. Common variants are recorded by GWAS; rare changes and CNV clarify the structure of hereditary risk, functional genomics correlates genetic signals with synaptic transmission, neuronal and cellular activity. A quantitative measure of the polygenic load is achievable through PRS, however, polygenic scores do not yet provide a specific prediction of the schizophrenic-bipolar combination.

Terminological difficulties have not been eliminated – there are still no clear boundaries between schizoaffective disorder proper, depression that manifested itself after a schizophrenic episode, and affective symptoms that are genetically inherent in the process itself.

Among the explanatory schemes, the three-component one has received the most recognition. According to her, a common phenotype occurs where a polygenic predisposition of a general nature, factors specific to each of the diseases, and modifying environmental or clinical influences intersect. However, the generalization remains speculative – it is not known what the ratio of the contribution of the listed terms is. Only specially planned studies will provide an answer, where comorbidity is verified, diagnostic criteria are unified, and groups are clinically aligned. The greatest prognostic potential lies in combining genome-wide associative studies, data on rare variants and CNVs, polygenic scores, and functional genomic methods, followed by mapping those genetic configurations that increase the chance of simultaneous development of both nosologies.

REFERENCES:

1. The World Health Organization. Schizophrenia [Electronic resource]. 09/11/2026. URL: <https://www.who.int/ru/news-room/fact-sheets/detail/schizophrenia> (date of request: 05.10.2026). <https://www.who.int/ru/news-room/fact-sheets/detail/schizophrenia>
2. The World Health Organization. Depressive disorder (depression) [Electronic resource]. 09/11/2026. URL: <https://www.who.int/ru/news-room/fact-sheets/detail/depression> (date of request: 05.10.2026). <https://www.who.int/ru/news-room/fact-sheets/detail/depression>
3. Schizophrenia: clinical recommendations / Ministry of Health of the Russian Federation. 2024. 217 p. [electronic resource]. URL: <https://base.garant.ru/410585282/> (date of request: 05.10.2026). Clinical guidelines for Schizophrenia
4. Gafarov V. V., Gromova E. A., Gubina M. A., Gagulin I. V., Maksimov V. N., Gafarova A.V. The relationship of polymorphisms of the SLC6A4 serotonin transporter gene with depression // Journal of Neurology and Psychiatry named after S. S. Korsakov. 2024. Vol. 124, No. 2. pp. 135-139. DOI: 10.17116/jnevro2024124021135. <https://doi.org/10.17116/jnevro2024124021135>
5. Shnayder N. A., Novitsky M. A., Neznakov N. G., Limankin O. V., Asadullin A. R., Petrov A. V., Dmitrenko D. V., Narodova E. A., Popenko N. V., Nasyrova R. F. Genetic Predisposition to Schizophrenia and Depressive Disorder Comorbidity // Genes. 2022. Vol. 13, No. 3. Art. 457. DOI: 10.3390/genes13030457. <https://doi.org/10.3390/genes13030457>

6. Shmakova A. A., Semina E. V., Neufeld E. A., Tsygankov B. D., Karagyaur M. N. Analysis of the relationship of genetic factors with the risk of developing schizophrenia // *Journal of Neurology and Psychiatry named after S. S. Korsakov*. 2023. Vol. 123, No. 2. pp. 26-36. DOI: 10.17116/jnevro202312302126. <https://doi.org/10.17116/jnevro202312302126>
7. Gareeva A. E. Genome-wide analysis of the risk association for paranoid schizophrenia in Russians: a search for genetic markers in the chromosomal region 1q43 // *Genetics*. 2024. Vol. 60, No. 1. pp. 101-106. DOI: 10.31857/S0016675824010085. <https://doi.org/10.31857/S0016675824010085>
8. Gareeva A. E. A new genetic marker of paranoid schizophrenia risk in chromosomal region 9q21.13 in Tatars: genome-wide association analysis // *Genetics*. 2024. Vol. 60, No. 1. pp. 106-111. DOI: 10.31857/S0016675824010093. <https://doi.org/10.31857/S0016675824010093>
9. Kasyanov E. D., Rakitko A. S., Rukavishnikov G. V., Golimbet V. E., Shmukler A. B., Ilyinsky V. V., Neznanov N. G., Kibitov A. O., Mazo G. E. Modern research on genome-wide association search in depression: the critical role of phenotyping // *S. S. Korsakov Journal of Neurology and Psychiatry*. 2022. Vol. 122, No. 1. pp. 50-61. DOI: 10.17116/jnevro202212201150. <https://doi.org/10.17116/jnevro202212201150>
10. Pinakhina D., Yermakovich D., Vergasova E., Kasyanov E., Rukavishnikov G., Rezapova V., Kolosov N., Sergushichev A., Popov I., Kovalenko E., Ilinskaya A., Kim A., Plotnikov N., Ilinsky V., Neznanov N., Mazo G., Kibitov A., Rakitko A., Artomov M. GWAS of depression in 4,520 individuals from the Russian population highlights the role of MAGI2 (S-SCAM) in the gut-brain axis // *Frontiers in Genetics*. 2023. Vol. 13. Art. 972196. DOI: 10.3389/fgene.2022.972196. <https://doi.org/10.3389/fgene.2022.972196>
11. Kibitov A. O., Shumskaya D. S. Modern genome-wide associative studies of mental disorders: focus on mechanisms of inflammation // *Siberian Bulletin of Psychiatry and Narcology*. 2024. No. 4 (125). pp. 56-65. DOI: 10.26617/1810-3111-2024-4(125)-56-65. [https://doi.org/10.26617/1810-3111-2024-4\(125\)-56-65](https://doi.org/10.26617/1810-3111-2024-4(125)-56-65)
12. Als T. D., Kurki M. I., Grove J., Voloudakis G., Therrien K., Tasanko E., Nielsen T. T., Naamanka J. K., Veerapen K., Levey D., Bendl J., Bybjerg-Grauholm J., Zeng B., Demontis D., Rosengren A., Athanasiadis G., Bækved-Hansen M., Qvist P., Walters B., Thorgeirsson T., Stefansson H., Musliner K., Rajagopal V., Farajzadeh L., Thirstrup J., Vilhjálmsson B. J., McGrath J., Mattheisen M., Meier S., Agerbo E., Stefansson K., Nordentoft M., Werge T., Hougaard D., Mortensen P., Stein M. B., Gelernter J., Hovatta I., Roussos P., Daly M. J., Mors O., Palotie A., Børglum A. D. Depression pathophysiology, risk prediction of recurrence and comorbid psychiatric disorders using genome-wide analyses // *Nature Medicine*. 2023. Vol. 29, No. 7. P. 1832–1844. DOI: 10.1038/s41591-023-02352-1. <https://doi.org/10.1038/s41591-023-02352-1>
13. Bourque V.-R., Poulain C., Proulx C., Moreau C. A., Joobor R., Forgeot d'Arc B., Huguet G., Jacquemont S. Genetic and phenotypic similarity across major psychiatric disorders: a systematic review and quantitative assessment // *Translational Psychiatry*. 2024. Vol. 14. Art. 171. DOI: 10.1038/s41398-024-02866-3. <https://doi.org/10.1038/s41398-024-02866-3>
14. Golimbet V. E., Klyushnik T. P. Genome-wide studies of comorbidity of somatic and mental diseases // *Journal of Neurology and Psychiatry named after S. S. Korsakov. Special editions*. 2023. Vol. 123, No. 4-2. pp. 60-64. DOI: 10.17116/jnevro202312304260. <https://doi.org/10.17116/jnevro202312304260>
15. Sullivan P. F., Yao S., Hjerling-Leffler J. Schizophrenia genomics: genetic complexity and functional insights // *Nature Reviews Neuroscience*. 2024. Vol. 25, No. 9. P. 611–624. DOI: 10.1038/s41583-024-00837-7. <https://doi.org/10.1038/s41583-024-00837-7>
16. Flint J. The genetic basis of major depressive disorder // *Molecular Psychiatry*. 2023. Vol. 28, No. 6. P. 2254–2265. DOI: 10.1038/s41380-023-01957-9. <https://doi.org/10.1038/s41380-023-01957-9>
17. Friligkou E., Pathak G. A., Tylee D. S., De Lillo A., Koller D., Cabrera-Mendoza B., Polimanti R. Characterizing pleiotropy among bipolar disorder, schizophrenia, and major depression: a genome-wide cross-disorder meta-analysis // *Psychological Medicine*. 2025. Vol. 55. Art. e145. DOI: 10.1017/S0033291725001217. <https://doi.org/10.1017/S0033291725001217>
18. Kato H., Kimura H., Kushima I. et al. The genetic architecture of schizophrenia: review of large-scale genetic studies // *Journal of Human Genetics*. 2023. Vol. 68, No. 3. P. 175–182. DOI: 10.1038/s10038-022-01059-4.
19. Owen M. J., Legge S. E., Rees E. et al. Genomic findings in schizophrenia and their implications // *Molecular Psychiatry*. 2023. Vol. 28, No. 9. P. 3638–3647. DOI: 10.1038/s41380-023-02293-8.
20. Akingbuwa W. A., Hammerschlag A. R., Bartels M. et al. Ultra-rare and common genetic variant analysis converge to implicate negative selection and neuronal processes in the aetiology of schizophrenia // *Molecular Psychiatry*. 2022. Vol. 27. P. 3699–3707. DOI: 10.1038/s41380-022-01621-8.
21. Trubetskoy V., Pardiñas A. F., Qi T. et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia // *Nature*. 2022. Vol. 604, No. 7906. P. 502–508. DOI: 10.1038/s41586-022-04434-5.
22. Liu D., Meyer D., Fennessy B. et al. Schizophrenia risk conferred by rare protein-truncating variants is conserved across diverse human populations // *Nature Genetics*. 2023. Vol. 55, No. 3. P. 369–376. DOI: 10.1038/s41588-023-01305-1.
23. Cui L., Li S., Wang S. et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment // *Signal Transduction and Targeted Therapy*. 2024. Vol. 9, No. 1. Art. 30. DOI: 10.1038/s41392-024-01738-y.
24. Franklin C. E., Achtyes E., Altinay M. et al. The genetics of severe depression // *Molecular Psychiatry*. 2025. Vol. 30, No. 3. P. 1117–1126. DOI: 10.1038/s41380-024-02731-1.

25. Li Y., Dang X., Chen R. et al. Cross-ancestry genome-wide association study and systems-level integrative analyses implicate new risk genes and therapeutic targets for depression // *Nature Human Behaviour*. 2025. Vol. 9. P. 806–823. DOI: 10.1038/s41562-024-02073-6.
26. Harris L., McDonagh E. M., Zhang X. et al. Genome-wide association testing beyond SNPs // *Nature Reviews Genetics*. 2025. Vol. 26, No. 3. P. 156–170. DOI: 10.1038/s41576-024-00778-y.
27. Grotzinger A. D., Mallard T. T., Akingbuwa W. A. et al. Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis // *Nature Genetics*. 2022. Vol. 54, No. 5. P. 548–559. DOI: 10.1038/s41588-022-01057-4.
28. Romero C., Werme J., Jansen P. R. et al. Exploring the genetic overlap between twelve psychiatric disorders // *Nature Genetics*. 2022. Vol. 54, No. 12. P. 1795–1802. DOI: 10.1038/s41588-022-01245-2.
29. Woodward D. J., Thorp J. G., Middeldorp C. M. et al. Leveraging pleiotropy for the improved treatment of psychiatric disorders // *Molecular Psychiatry*. 2025. Vol. 30, No. 2. P. 705–721. DOI: 10.1038/s41380-024-02771-7.
30. Nakamura T., Takata A. The molecular pathology of schizophrenia: an overview of existing knowledge and new directions for future research // *Molecular Psychiatry*. 2023. Vol. 28, No. 5. P. 1868–1889. DOI: 10.1038/s41380-023-02005-2.
31. Roelfs D., van der Meer D., Alnæs D. et al. Genetic overlap between multivariate measures of human functional brain connectivity and psychiatric disorders // *Nature Mental Health*. 2024. Vol. 2, No. 2. P. 189–199. DOI: 10.1038/s44220-023-00190-1.
32. Warren T. L., Tubbs J. D., Lesh T. A. et al. Association of neurotransmitter pathway polygenic risk with specific symptom profiles in psychosis // *Molecular Psychiatry*. 2024. Vol. 29, No. 8. P. 2389–2398. DOI: 10.1038/s41380-024-02457-0.
33. Marshall C. R., Howrigan D. P., Merico D. et al. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects // *Nature Genetics*. 2017. Vol. 49, No. 1. P. 27–35. DOI: 10.1038/ng.3725.
34. Singh T., Poterba T., Curtis D. et al. Rare coding variants in ten genes confer substantial risk for schizophrenia // *Nature*. 2022. Vol. 604, No. 7906. P. 509–516. DOI: 10.1038/s41586-022-04556-w.
35. Tian R., Ge T., Kweon H. et al. Whole-exome sequencing in UK Biobank reveals rare genetic architecture for depression // *Nature Communications*. 2024. Vol. 15, No. 1. Art. 1755. DOI: 10.1038/s41467-024-45774-2.
36. Andreoli L., Peeters H., Van Steen K., Dierickx K. Polygenic risk scores in the clinic: a systematic review of stakeholders' perspectives, attitudes, and experiences // *European Journal of Human Genetics*. 2025. Vol. 33, No. 3. P. 266–280. DOI: 10.1038/s41431-024-01747-z.
37. Kanjira S. C., Adams M. J., Jiang Y. et al. Polygenic prediction of major depressive disorder and related traits in African ancestries UK Biobank participants // *Molecular Psychiatry*. 2025. Vol. 30. P. 151–157. DOI: 10.1038/s41380-024-02662-x.
38. Rodriguez V., Alameda L., Quattrone D. et al. Use of multiple polygenic risk scores for distinguishing schizophrenia-spectrum disorder and affective psychosis categories in a first-episode sample; the EU-GEI study // *Psychological Medicine*. 2023. Vol. 53, No. 8. P. 3396–3405. DOI: 10.1017/S0033291721005456.
39. Jiang W., Chen L., Girgenti M. J., Zhao H. Tuning parameters for polygenic risk score methods using GWAS summary statistics from training data // *Nature Communications*. 2024. Vol. 15, No. 1. Art. 24. DOI: 10.1038/s41467-023-44009-0.
40. Dahl A., Thompson M., An U. et al. Phenotype integration improves power and preserves specificity in biobank-based genetic studies of major depressive disorder // *Nature Genetics*. 2023. Vol. 55, No. 12. P. 2082–2093. DOI: 10.1038/s41588-023-01559-9.
41. Cai N., Dahl A., Border R. et al. The predicament of heritable confounders // *Nature Genetics*. 2026. Vol. 58, No. 2. P. 264–270. DOI: 10.1038/s41588-025-02465-y.
42. Huider F., Milaneschi Y., Pool R. et al. Genetics of major depressive disorder in a homogeneous population with uniform phenotyping // *Molecular Psychiatry*. 2026. Vol. 31, No. 10. P. 5889–5899. DOI: 10.1038/s41380-026-03666-5.

Information about the authors

Valentina Akhmad Ibragim – student, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation, e-mail: ibrahim.vala@yandex.ru, <https://orcid.org/0009-0006-0427-2291>

Leyla Eduardovna Fakhrutdinova – student, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation, e-mail: laylaregina25@gmail.com, <https://orcid.org/0009-0003-3762-3869>

Zukhra Etibarovna Alekperova – student, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation, e-mail: mzolanskaa@gmail.com, <https://orcid.org/0009-0006-3828-3554>

Svetlana Ekhtiram Kyzy Alekperova – student, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation, e-mail: svetaalekperova29@gmail.com, <https://orcid.org/0009-0000-5638-1234>

Salikhat Shamilevna Yarmetova – student, Dagestan State Medical University, Makhachkala, Russian Federation, e-mail: salya.yarmetova@mail.ru

Aishat Timurovna Karnailova – student, Pirogov Russian National Research Medical University, Moscow, Russian Federation, e-mail: karnailova.aishat@gmail.com, <https://orcid.org/0009-0008-7711-116X>

Saida Magomedovna Alisheikhova – student, Dagestan State Medical University, Makhachkala, Russian Federation, e-mail: Alisheikhovas@gmail.com, <https://orcid.org/0009-0008-1830-9803>

Maysarat Rabazanovna Alieva – student, Dagestan State Medical University, Makhachkala, Russian Federation, e-mail: musia.karimova@mail.ru, <https://orcid.org/0009-0008-1254-196X>