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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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GENETIC PREDICTORS OF SCHIZOPHRENIA AND THEIR FEATURES IN INDIVIDUAL ETHNIC POPULATIONS (REVIEW ARTICLE)

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Abstract.

The paper presents a review of current literature data on ongoing international studies to identify genetic predictors of schizophrenia, since heredity and family predisposition to schizophrenia have been known for several decades. New data on the interaction between genetic variants, epigenetic marks, including cross interaction between the processes of DNA methylation and histone modification, affecting the regulation of gene expression under the influence of the environment, are reflected. Particular attention is paid to studies devoted to identifying the features of genetic predictors of schizophrenia in certain ethnic populations, in particular in relation to persons of the Kazakh ethnic group in the Republic of Kazakhstan.

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Key words. Schizophrenia, genetics, epigenome, ethno-cultural features, Kazakh population.

Schizophrenia is a severe mental illness associated with significant social and economic losses [1]. Schizophrenia affects about 1% of the world's population [2,3]. The initial manifestations of the disease often occur in childhood and in adolescence and can lead to early disability, causing significant family and social problems, as well as increasing health care costs [4,5].

Heredity and familial predisposition to schizophrenia have been known for several decades [6]. Although schizophrenia has a fairly strong genetic component with a heritability of about 80%, there is also a significant range of environmental and stressors that may be involved in the development of the disease, such as maternal infections during pregnancy, obstetric complications, childhood trauma, and exposure to cannabis [7].

Epigenetics was originally used to develop mitotic and meiotic changes in gene transcription that could not be attributed to genetic mutations. Later, this referred to changes in the epigenome not transmitted through the germline. Thus, epigenetics refers to a wide range of molecular mechanisms, including DNA methylation of cytosine residues in CpG dinucleotides and post-translational modifications of histones [8]. These mechanisms alter the way transcription factors bind to DNA by modulating its expression. Prenatal and postnatal environmental factors may influence these epigenetic factors responsible for long-term DNA transcription [9]. It is assumed that epigenetic factors, as well as regulatory non-coding RNAs, mediate the action of these environmental factors and play a role in the genesis of this disease [10].

Ongoing genetic research in the field of schizophrenia shows that, despite clear evidence of the presence of a genetic component, it is very difficult to pinpoint the specific genes that cause the disease [11]. Studies have addressed topics that reveal the involvement of nervous system development, glutamate regulation, and differential activation of the immune system in the causes of hereditary predisposition to schizophrenia [12]. Modern epigenetic research aimed at identifying the biological mechanisms underlying family dependence in schizophrenia (SZ) has provided an opportunity to obtain additional information about the interaction of genes and the environment [13].

New data have been obtained on the interaction between genetic variants, epigenetic labels, including cross-interaction between DNA methylation processes and histone modification, affecting the regulation of gene expression under the influence of the environment [14]. A combination of genetic and/or environmental factors during critical periods of brain development is thought to increase the risk of developing schizophrenia [15]. Epigenetic regulations, such as DNA methylation, can mediate gene-environment interactions at the genome level and may serve as a potential substrate to explain the variability in symptom severity and the effect of family heritability [16].

A review of the PubMed database summarized the evidence for two major epigenetic mechanisms in the genesis of schizophrenia: DNA methylation and post-translational modifications of histones. According to the current literature from an epidemiological perspective, the theoretical model of epigenetics is applicable to schizophrenia. It has been found that most environmental factors that have proven to be associated with this disease can generate epigenetic mechanisms. Mutations have been found in regions involved in the epigenetic mechanism among populations with schizophrenia. Some epigenetic changes in sections of DNA have previously been associated with abnormalities in the development of the nervous system. In psychosis, some authors have found differences in the methylation of the COMT gene, the reelin gene, and some genes involved in the dopaminergic, serotonergic, GABAergic, and glutamatergic pathways. Histone modifications have been described, in particular the methylation of histone H3L4.

A review of epigenetic studies of patients with schizophrenia using the postmortem brain or peripheral tissues focused on DNA methylation [17]. This review investigated the most well-known epigenetic labels, including DNA methylation and histone modification, as well as emerging epigenomic RNA mediators, including miRNAs and dnRNAs, and concluded about their potential involvement in the pathophysiology of schizophrenia, based on postmortem analysis of brain tissue in schizophrenia patients.

Given that peripheral tissues such as blood, saliva, and the olfactory epithelium have the same genetic makeup and are exposed to the same environmental influences, studies supporting the use of peripheral tissues to detect epigenomic biomarkers in schizophrenia are of interest, which also describe how these biomarkers can be used to capture the signature of past events that will inform future treatment [18].

DNA methylation (DNA m) is important for brain development and potentially important in schizophrenia. There is evidence in the literature of DNAm in the prefrontal cortex of 335 non-psychiatric control groups throughout life and 191 patients with schizophrenia, which revealed widespread changes in the transition from prenatal to postnatal life. These are changes in DNAm are manifested in the transcriptome, strongly correlate with the shift in the cellular landscape and overlap the areas of genetic risk of schizophrenia [19]. A quarter of published genome-wide associative studies (GWAS) – suggesting loci (4208 out of 15,930, P <10 (-100)) appear as significant quantitative methylation feature (meQTL) loci, including 59.6% of GWAS-positive loci of schizophrenia [20].

The studies focus on 104 CpG, which differ between patients with schizophrenia and the control group, they were enriched with genes associated with development and neurodifferentiation. Schizophrenia-related CpG is strongly correlated with changes associated with prenatal-postnatal transition and show little enrichment of GWAS risk loci, but do not correspond to CpG that distinguish adolescence from later adulthood. These findings point to an epigenetic component of the origin of this mental disorder [21].

The result of most studies suggested a negative relationship of the polymorphism of D2-like receptors with the etiology of schizophrenia, but at the same time, the fact of their influence on the clinic and severity of the symptoms of this disease is not denied. Fragments of genes D2-like receptors were amplified by polymerase chain reaction; polymorphisms were identified by methods of polymorphism of the length of restriction fragments and single-strand conformational polymorphism. There were no statistically significant differences in polymorphisms and their combinations between patients with schizophrenia and the control group.

Patients with schizophrenia with D4E1 (A1/A2), which contains 2 and 1 tandem repetitions of a sequence of 12 base pairs in exon 1, had a lower overall score of positive symptoms before treatment than patients with schizophrenia with D4E1 (A1/A1). No association was found between polymorphism and negative symptoms [22].

Of great interest are genetic studies in the field of schizophrenia in individual ethnic populations. For example, the literature presents the first results of a study of variants UCP2 -866G / A / and CFH Y402H on the risk of developing schizophrenia in the Turkish population. In this study, the authors sought to assess whether variants of the Uncoupling protein 2 gene and complement factor H play any role in the risk of developing schizophrenia [23]. This study was conducted on 200 people (100 patients with schizophrenia and 100 healthy people). Genomic DNA was isolated from blood samples. UCP variants 2-866G/A (rs659366) and CFHY402H were analyzed using PCR-PDRF. In this study, the G/G genotype of UCP2-866G/A variants and the G allele were significantly associated with an increased risk of schizophrenia. (p = 0.001, p = 0.001, respectively).

Subjects carrying the UCP2-866G/A G variant genotype had a 4,377-fold increased risk of developing schizophrenia. There was no significant difference between the groups in genotype frequencies and alleles of the CFH Y402H variant (p> 0.05). The observed number of genotypes deviated significantly from that expected in patients with schizophrenia according to HWE. for the UCP2-866G/A variant (p = 0.001). The study concluded that the UCP2-866G/A variant, but not the CFH Y402H variant, may play an important role in the development of schizophrenia.

In China, studies have been conducted to determine the association between the Ser9Gly polymorphism of the dopamine D3 receptor gene and tardive dyskinesia in patients with schizophrenia in the Chinese population [24]. It has been suggested that the dopamine receptor D3(DRD3) may be important for tardive dyskinesia (TD) caused by antipsychotics. Previous studies have demonstrated an association between serine and glycine polymorphism in the first exon of the DRD3 and TD gene; however, the results were inconsistent. Therefore, the authors reproduced these studies on a sample from China. A total of 115 patients with schizophrenia were assessed for TD severity using the Abnormal Involuntary Movement Scale (AIMS) and were subsequently genotyped for polymorphism DRD3. The average SCORE on the AIMS scale in patients carrying heterozygote (DRD3 (ser-gly)) was significantly higher than in patients with homozygotes (DRD3 (ser-ser) and DRD3 (gly-gly)). Thus, the results obtained in this study confirmed the conclusions of previous studies.

Genetic studies in the field of schizophrenia have been conducted on the South Indian population [25]. The aim of this study was to study the genetic variations of DNA methyltransferase genes that predispose to the risk of developing schizophrenia. The authors tested the polymorphism of DNA methyltransferases, DNMT1, DNMT3A, DNMT3B and DNMT3L in 330 patients with schizophrenia and 302 healthy people from the control group for association with schizophrenia in the South Indian population. These polymorphisms were also tested for subgroup analysis considering the patient's sex, age of onset of the disease and family history. DNMT1 rs2114724 (genotype P = 0.004, allele P = 0.022) and rs2228611 (genotype P = 0.004, allele P = 0.022) were found to be largely related at the genotypic and allelic level to schizophrenia in the South Indian population.

Genotype DNMT3B rs2424932 (P = 0.023) and allele (P = 0.0063) increased the risk of schizophrenia in men but not in women. DNMT3B rs1569686 (genotype P = 0.027, allele P = 0.033) was found to be associated with early onset schizophrenia, as well as with family history and early onset (genotype P = 0.009). DNMT 3L rs2070565 (genotype P = 0.007, allele P = 0.0026) poses an increased risk of developing schizophrenia at an early age in individuals with a family history. In-silico prognosis has shown the functional significance of these SNPs in gene regulation. The results of this study may have significant implications for considering and understanding the genetic control of differences in methylation levels from an ethnic perspective.

In large-scale genetic studies of schizophrenia, samples of European origin have been reported primarily, which potentially did not take into account important biological discoveries [26]. A large-scale genetic study has now been conducted, involving representatives from East Asia (22,778 cases of schizophrenia and 35,362 people in the control group). In this study, 21 genome-wide significant associations were identified in 19 genetic loci. The common genetic variants that create the risk of schizophrenia have very similar effects between East Asian and European ancestors (genetic correlation = 0.98 ± 0.03), indicating that the genetic basis of schizophrenia and its biology are widespread among populations in different regions of the world. A fixed-effect meta-analysis involving people from East Asia and Europe identified 208 significant associations in 176 genetic loci (53 new).

Accurate mapping of trans ancestors reduced the set of possible causal variants in 44 loci. Polygenic risk scores have reduced efficacy in inter-pedigree transfer, highlighting the importance of including sufficient samples of major ancestral groups to ensure their generalizability among populations.

The study of genetic predictors of schizophrenia, which begins in childhood, was also carried out in the Republic of Kazakhstan in relation to persons of the Kazakh ethnic group [27-29]. In particular, in one of the previously conducted studies [27], the sample of patients consisted of 112 people of Kazakh nationality aged 4 to 30 years. The average age in the group of patients at the time of the examination was 16.8 years (the study included adults in whom the onset of schizophrenia was recorded in childhood). The control group consisted of 190 individuals of Kazakh ethnicity aged 19 to 76 years, who had no history of psychoneurological diseases. The average age in the control group was 31.6 years.

A replicative analysis of the associations of 15 SNPs in the region of 14 genes previously identified in wide-genome studies (GWAS) with early-onset schizophrenia in Kazakhs was carried out. An association of early schizophrenia with markers of three genes (VRK2, KCNB2 and CPVL) was found. Using multivariate data dimensionality reduction methods, two groups of four and six genes were found to exhibit intergenic epistatic interactions. The gene ontologies of the 14 genes studied were reduced to variants of one molecular function (peptidase activity) and one biological process (positive regulation of biosynthesis processes). Bioinformatic analysis of the protein interactions of the products of the studied genes showed that the products of six of the 14 genes can be involved in a single interconnected network, the main link of which is the ubiquitinylation of them by the UBC protein.

For replicative association analysis, this study selected 15 single-nucleotide genetic markers for which a highly reliable association with schizophrenia and cognitive traits that are endophenotypes of this disease in GWAS [30-36] was identified. Of the 30 genotype distributions studied, two deviations from the distribution expected in PCV were observed for the single-nucleotide polymorphism rs8020441 of the ZFP64 P gene. 1 in the group of patients with schizophrenia and for rs2252521 of the C PVL gene in the control sample. In general, the allele frequencies in patients and in the control were close and within the variations observed in world populations according to the HapMap and "1000 genomes" projects [37,38].

Minor allele rs2252521 of the CPVL gene (OR = 1.46, p = 0.037) and major alleles rs2312147 of the VRK2 gene (OR = 1.72, p = 0.008) and rs2247572 of the KCNB2 gene (OR = 1.54, p = 0.030) were significantly more common among patients with early schizophrenia Kazakhs compared with the control group. For two of the three associated markers (SNP genes VRK2 and KCNB2), the association was confirmed by significant differences in the distribution of genotypes, estimated according to the criterion of maximum chi-squared likelihood. For rs2252521 of the CPVL gene, the differences in the distribution of genotypes were close to statistically significant (p = 0.092).

All three SNPs associated with early schizophrenia in Kazakhs have been found to be non-coding nucleotide substitutions localized in introns. The first set of consistent cross validations consisted of four interacting genes: SLCO6A1, VRK2, ZFP64P1, and CSMD1, with only one of them (VRK 2) demonstrated a statistically significant association with schizophrenia in Kazakhs at the level of individual SNPs. The second set included six single-nucleotide cumulatively active polymorphism variants and in addition to the four SNPs described above, it included two more polymorphic variants: rs17594526 of the TCF4 gene and rs2229741 of the NRIP1 gene.

The balance accuracy of the training and test samples for this set of markers was 90.55% (sensitivity 98.95%, specificity 82.14%) and 53.64% (sensitivity 44.02%, specificity 65.09%; P = 0.377). For this combination of markers, despite the high balance accuracy (>90%) of the training sample, there was a weaker classification ability on 10 test samples. The authors note that it is likely that the problems of small sample size that arise during multiple testing with an increase in the number of subgroups with an increase in the number of interacting genes in the training sample could lead to a decrease in sensitivity and a loss of statistical significance of the model.

According to the results of this study, the association of schizophrenia with early onset in Kazakhs of the Republic of Kazakhstan with markers of three genes (VRK2, KCNB2 and CPVL), who had previously found a highly reliable connection with the disease or its endophenotypes in wide-genomic associative studies, was revealed. The VRK2 gene encodes a protein serine/threonine protein kinase that belongs to the casein kinase group I. These protein kinases phosphorylate the hydroxyl group in serine or threonine residues. They are involved in the control of cytoplasmic and nuclear processes, including DNA replication and repair, and are also involved in the control of apoptosis. The possible role of VRK2 in the predisposition to schizophrenia, in our opinion, may be due to the fact that serine / threonine protein kinase binds the protein JIP1, which in neuronal cells serves as an anti-apoptosis factor in response to stress and plays a role in the development of the axon [34]. The association of VRK2 gene markers with schizophrenia was identified in one of the first GWAS [22] on Caucasoids. Later, the association rs2312147 of this gene with the disease

was replicated in the Chinese [35]. The authors believe that the independent replication of the association of this gene in Asian Mongoloids (Chinese and Kazakhs) possibly demonstrates the race-specific nature of the association, probably associated with the features of the structure of the gene pool or patterns of linkage disequilibrium in this locus in Mongoloids.

With regard to the markers of the other two genes (KCNB2 and CPVL), the association with which was replicated in Kazakhs, the mechanisms of their possible involvement in susceptibility to the disease are even less clear. Markers of these genes have been identified in recent GWAS [26,27] as associated with cognitive abilities, which are endophenotypes of schizophrenia. The KCNB2 gene encodes a protein that is a member of the potential-dependent potassium channel. The gene is expressed in the smooth muscle cells of the gastrointestinal tract. The protein encoded by the CPVL gene is carboxypeptidase and has a strong sequence similarity to serine-type carboxypeptidases. The authors suggest that the association with the disease of markers in the locus of CPVL may not be associated with this gene, but with the nearby locus LOC100506497, which encodes miscRNA.

According to the results of the study of allelic polymorphism of the serotonin receptor 5HTR2A gene in children and adolescents with schizophrenia of the Kazakh population, it was suggested that there are significant differences in the distribution of genotype and allele frequencies both between patients with schizophrenia and mentally healthy individuals, and between different variants of schizophrenia itself [29].

Thus, modern genetic studies have identified several risk candidate genes or genome regions for schizophrenia, and epidemiological studies have identified several environmental risk factors [39]. However, the etiology of schizophrenia is still largely unknown [40]. Epigenetic mechanisms, such as DNA methylation and histone modifications, may explain the interaction between genetic and environmental factors at the molecular level, and accumulated evidence suggests that such epigenetic changes are involved in the pathophysiology of schizophrenia. [41] However, replication studies are needed to confirm previous findings and to investigate the causal relationship of epigenetic changes in schizophrenia [42], which determines the relevance of further research.

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რეზიუმე: ნაშრომში წარმოდგენილია დღესდღეობით ჩატარებული შიზოფრენიის გენეტიკური ფაქტორების გამოვლენის საერთაშორისო კვლევების თანამედროვე ლიტერატურული მონაცემების მიმოხილვა, ვინაიდან მემკვიდრეობა და შიზოფრენიისადმი ოჯახური მიდრეკილება ცნობილია უკვე რამდენიმე ათწლეულობის განმავლობაში. ასახულია გენეტიკური ვარიანტების, ეპიგენეტიკური ნიშნების შორის ურთიერთქმედების ახალი მონაცემები, მათ შორის დნმ-ის მეთილაციისა და ჰისტონების მოდიფიკაციის პროცესების ჯვარედინი ურთიერთქმედება, რომლებიც გავლენას ახდენენ გენების ექსპრესიის რეგულაციას გარემოს გავლენის ქვეშ. განსაკუთრებული ყურადღება ექცევა კვლევებს, რომელიც მიძღვნილია შიზოფრენიის გენეტიკური ფაქტორების მახასიათებლების გამოვლენას ცალკეულ ეთნიკურ პოპულაციებში, კერძოდ ყაზახური ეთნოსის პირებთან მიმართებაში ყაზახეთის რესპუბლიკაში

კვლევა შესრულებულია პროექტის ფარგლებში: „პერსონალიზებული და პრევენციული მედიცინის დანერგვის ნაციონალური პროგრამა ყაზახეთის რესპუბლიკაში“ IRN OR12165486.

საკვანძო სიტყვები: შიზოფრენია, გენეტიკა, ეპიგენომი, ეთნოკულტურული თავისებურებანი, ყაზახური პოპულაცია

ГЕНЕТИЧЕСКИЕ ПРЕДИКТОРЫ ШИЗОФРЕНИИ И ИХ ОСОБЕННОСТИ В ОТДЕЛЬНЫХ ЭТНИЧЕСКИХ ПОПУЛЯЦИЯХ (обзорная статья)

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Резюме: В работе представлен обзор современных литературных данных о проводимых в настоящее время международных исследованиях по выявлению генетических предикторов шизофрении, так как

наследственность и семейная предрасположенность к шизофрении известны уже в течении нескольких десятилетий. Отражены новые данные о взаимодействии между генетическими вариантами, эпигенетическими метками, включая перекрестное взаимодействие между процессами метилирования ДНК и модификации гистонов, влияющих на регуляцию экспрессии генов под влиянием окружающей среды. Особое внимание уделено исследованиям, посвященным выявлению особенностей генетических предикторов шизофрении в отдельных этнических популяциях, в частности в отношении лиц казахского этноса в Республике Казахстан.

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Ключевые слова: шизофрения, генетика, эпигеном, этнокультуральные особенности, казахская популяция.