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GENETIC AND EPIGENETIC DETERMINANTS OF EPILEPSY: CLINICAL IMPLICATIONS AND ADVANCES IN PERSONALIZED

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Abstract. Epilepsy is a complex neurological disorder characterized by significant genetic and epigenetic heterogeneity. Advances in molecular diagnostics—including next-generation sequencing, whole-exome sequencing, and targeted gene panels—have identified more than 900 genes associated with various forms of epilepsy. These findings have improved early diagnosis, refined clinical classification, and facilitated the development of personalized therapeutic strategies. Pathogenic variants in genes such as *SCN1A, KCNQ2, STXBP1, CDKL5,* and *DEPDC5* influence seizure phenotype, drug response, and prognosis, enabling tailored treatment selection. Emerging evidence on epigenetic dysregulation further expands potential therapeutic targets. Despite significant progress, challenges remain in variant interpretation, test accessibility, and ethical considerations. Integrating genetic and epigenetic profiling into routine practice has the potential to transform clinical management and improve outcomes for patients with monogenic, pharmacoresistant, and developmental epilepsies.

Key words: epilepsy, genetics, epigenetics, SCN1A, precision medicine, pharmacogenomics, epileptic encephalopathy, NGS, gene panels, personalized therapy

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ГЕНЕТИЧЕСКИЕ И ЭПИГЕНЕТИЧЕСКИЕ ДЕТЕРМИНАНТЫ ЭПИЛЕПСИИ: КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ И ДОСТИЖЕНИЯ ПЕРСОНАЛИЗИРОВАННОЙ ТЕРАПИИ

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Аннотация. Эпилепсия представляет собой сложное неврологическое заболевание, характеризующееся выраженной генетической и эпигенетической гетерогенностью. Прогресс в области молекулярной диагностики — включая секвенирование нового поколения, экзомное секвенирование и панельные генетические тесты — позволил идентифицировать более 900 генов, связанных с различными формами эпилепсии. Эти открытия способствовали ранней диагностике, уточнению клинической классификации и развитию персонализированных терапевтических подходов. Патогенные варианты в генах *SCN1A, KCNQ2, STXBP1, CDKL5, DEPDC5* и других определяют клинический фенотип, ответ на лечение и прогноз, что позволяет индивидуализировать выбор терапии. Новые данные об эпигенетических нарушениях расширяют возможности поиска терапевтических мишеней. Несмотря на значительный прогресс, сохраняются проблемы интерпретации вариантов неопределённого значения, доступности тестирования и этических ограничений. Интеграция генетического и эпигенетического профилирования в клиническую практику имеет потенциал существенно улучшить ведение пациентов и повысить эффективность лечения моногенных, фармакорезистентных и развивающихся форм эпилепсии.

Ключевые слова: эпилепсия, генетика, эпигенетика, SCN1A, прецизионная медицина, фармакогеномика, эпилептическая энцефалопатия, NGS, генетические панели, персонализированная терапия

EPILEPSIYANING GENETIK VA EPIGENETIK OMILLARI: KLINIK AHAMIYATI VA SHAXSGA YO‘NALTIRILGAN TERAPIYANING YANGI IMKONIYATLARI

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Annotatsiya. Epilepsiya murakkab nevrologik kasallik bo'lib, uning genetik va epigenetik xilma-xilligi juda yuqori. Molekulyar diagnostika sohasidagi yutuqlar — yangi avlod sekvensiyasi, ekzom sekvensiyasi va genlar paneli testlari — epilepsiyaning turli shakllari bilan bog'liq 900 dan ortiq genni aniqlash imkonini berdi. Bu topilmalar erta diagnostika, klinik tasnifni aniqlashtirish va shaxsga yo'naltirilgan davolash strategiyalarini ishlab chiqishga katta hissa qo'shdi. *SCN1A*, *KCNQ2*, *STXBP1*, *CDKL5*, *DEPDC5* kabi genlardagi patogen variantlar tutqanoq fenotipi, dori javobi va prognozni belgilaydi, bu esa individual davolashni tanlashga imkon yaratadi. Epigenetik buzilishlar haqidagi yangi ma'lumotlar esa yangi terapevtik nishonlarni aniqlash imkonini kengaytirmoqda. Barcha yutuqlarga qaramay, variantlarni talqin qilish, testlarning mavjudligi va axloqiy masalalar kabi muammolar saqlanib qolmoqda. Genetik va epigenetik profilaktikaning klinik amaliyotga integratsiyasi monogen, dori-rezistent va rivojlanish bilan bog'liq epilepsiya turlarini davolash samaradorligini sezilarli darajada oshirishi mumkin.
Kalit so'zlar: epilepsiya, genetika, epigenetika, SCN1A, aniq tibbiyot, farmakogenomika, epileptik ensefalopatiya, NGS, gen paneli, shaxsga yo'naltirilgan davolash

Introduction. Epilepsy is one of the most common neurological diseases, affecting approximately 50 million people worldwide [1]. In recent decades, significant progress has been made in understanding the genetic mechanisms underlying both idiopathic and symptomatic forms of epilepsy. The genetic heterogeneity of this disease determines a wide range of clinical phenotypes, treatment responses, and prognosis, making the study of molecular and hereditary determinants of epilepsy particularly relevant in the context of the development of personalized medicine [2]. Modern molecular genetic technologies, including whole genome sequencing, exome sequencing, and panel tests, have identified more than 900 genes involved in the pathogenesis of epilepsy. In particular, mutations in the SCN1A, KCNQ2, CDKL5, DEPDC5, STXBP1 genes and others are associated with the development of both benign and drug-resistant forms of the disease [3]. These findings have led to a revision of the traditional classification of epilepsies, supplementing it with molecular subtypes, which in turn has opened up new opportunities for targeted therapy. Furthermore, increasing attention is being paid to epigenetic mechanisms influencing the expression of genes associated with neuronal hyperexcitability and impaired synaptic transmission. This area also provides potential targets for the development of new antiepileptic drugs and epigenetic modifiers [4]. The integration of genetic profiling into clinical practice facilitates accurate diagnosis, prognosis of the disease course, and the selection of the most effective therapy. However, despite these advances, issues related to the interpretation of variants of unknown significance, the availability of genetic tests, and the ethical aspects of their use remain unresolved. This underscores the need for further research aimed at translating genetic discoveries into routine neurological practice.

Materials and methods.A literature review of current clinical, genetic, and molecular data related to epilepsy and its personalized therapy was conducted. The search strategy included a systematic analysis of scientific literature published between January 2018 and July 2025. The primary data sources were international databases: PubMed, Scopus, and Web of Science. The following keywords and their combinations were used: "genetic epilepsy," "epilepsy gene panels," "precision medicine in epilepsy," "personalized treatment of epilepsy," "epileptic encephalopathies," "epilepsy genetics," "channelopathies," and "next-generation sequencing epilepsy."

Inclusion criteria:

Original articles, systematic reviews, and meta-analyses published in peer-reviewed journals. Articles containing clinical, molecular genetic, and therapeutic data applicable to the treatment of epilepsy.

Publications in English that comply with current clinical guidelines.

Studies examining the potential use of genetic testing results for targeted therapy. Exclusion criteria: Articles that do not contain information on the genetics or treatment of epilepsy. Animal and in vitro studies that have no clinical significance. Case reports, conference abstracts, and editorial letters. Publications before 2018 (excluding highly cited fundamental works). Data analysis was conducted taking into account clinical-genetic correlations and the potential translation of results into personalized clinical practice.

Results and discussion. Modern research has confirmed that epilepsy has significant genetic heterogeneity. According to the latest genome-wide association studies (GWAS), more than 900 genes involved in the pathogenesis of various forms of epilepsy have been identified, including SCN1A, SCN2A, KCNQ2, STXBP1, DEPDC5, GABRA1 and others [5]. These genes regulate neuronal excitability, synaptic transmission and ion homeostasis, disturbances of which underlie epileptogenesis. Mutations in SCN1A have been established as the leading cause of therapy-resistant Dravet syndrome [6]. Exome analysis has shown that up to 80% of patients with this form of epilepsy have de novo mutations in SCN1A. This has made it possible to introduce a targeted approach: patients with a confirmed mutation are avoided from prescribing sodium-channel blockers, such as carbamazepine, which increase seizures [7]. Studies using next-generation sequencing (NGS) have shown that patients with mutations in KCNQ2 and KCNQ3 associated with benign neonatal epilepsy respond favorably to therapy with potassium chloride and retigabine [8]. This underscores the importance of pharmacogenetics in individualizing therapy. A number of publications have emphasized the prognostic value of genetic testing. In particular, mutations in DEPDC5 and other genes of the GATOR1 complex are associated with focal cortical dysplasia and resistance to drug treatment [9]. In such cases, preference is given to early surgical intervention, which significantly improves outcomes. Importantly, mutations in a number of genes (e.g., STXBP1, CDKL5, ARX) are often associated with developmental disorders, autism, and delayed speech and motor development [10]. Therefore, genetic testing helps not only with the choice of therapy but also with the development of a multidisciplinary rehabilitation plan. Of interest is the developing field of epigenetic regulation. Studies conducted in 2022–2023 identified changes in promoter methylation levels of genes involved in GABA and glutamate signaling [11,12]. This opens up the possibility of using epigenetic modifiers in the treatment of drug-resistant forms of epilepsy.

Furthermore, the use of gene therapy has been actively discussed in recent studies. For example, experiments on mouse models with the SCN1A mutation demonstrated the effectiveness of adeno-associated viruses (V), which restore gene expression. Clinical pilot studies have already been launched in people with Dravet syndrome [6, 13]. With the development of bioinformatics, it has become possible to predict drug efficacy based on a patient's molecular profile. The creation of multi-omic biobanks allows for the integration of genomics, transcriptomics, and metabolomics data for personalized therapy [14].

The results of numerous studies confirm that the use of genetic and epigenetic markers not only allows for a more precise diagnosis but also for predicting the course of the disease and its response to treatment. This is especially important when choosing treatment strategies for young children and patients with severe forms of epilepsy. Personalized therapy tailored to a patient's genetic profile has already proven effective in a number of monogenic epilepsies. Such approaches are expected to become standard treatment for patients with treatment-resistant and atypical forms of the disease in the coming years.

Conclusion. Epilepsy is a highly heterogeneous neurological disorder in which genetic and epigenetic mechanisms play a crucial role in determining clinical phenotype, treatment response, and long-term prognosis. Over the past decade, significant advances in molecular genetics—particularly next-generation sequencing, whole-exome analysis, and targeted gene panels—have enabled the identification of more than 900 epilepsy-associated genes. These discoveries have transformed traditional diagnostic and therapeutic approaches, shifting the focus toward precision medicine. The integration of genetic profiling into clinical practice has demonstrated clear benefits: improved diagnostic accuracy, early detection of severe epileptic encephalopathies, identification of pharmacologically significant mutations, and optimization of individualized treatment strategies.

For example, the recognition of SCN1A, KCNQ2, STXBP1, DEPDC5, and other pathogenic variants allows clinicians to avoid ineffective or harmful therapies, select targeted drugs, and consider timely surgical intervention when appropriate. Moreover, the growing understanding of epigenetic dysregulation—particularly methylation abnormalities in genes regulating neuronal excitability—opens new avenues for the development of epigenetic modifiers and innovative antiepileptic treatments. Despite meaningful progress, several challenges remain. These include the interpretation of variants of uncertain significance, unequal global access to genetic testing, and ethical considerations regarding genetic data use. Addressing these limitations will require continued collaboration between neurologists, geneticists, researchers, and healthcare policymakers.

References:

1. World Health Organization. (2023). *Epilepsy: A public health imperative*. WHO Press.
2. Якубов, Р. Т., & Мусаева, Ш. А. (2019). Генетические аспекты идиопатических эпилепсий. *Журнал неврологии и психиатрии им. С. С. Корсакова*, 119(6), 52–58.
3. Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G., & Moshé, S. L. (2017). ILAE classification of the epilepsies: Position paper. *Epilepsia*, 58(4), 512–521.
4. Kobow, K., & Blumcke, I. (2018). Epigenetics in epilepsy. *Neuroscience Letters*, 667, 40–46.
5. International League Against Epilepsy (ILAE). (2021). *Epilepsy genetics global update*. ILAE Publications.
6. Zuberi, S. M., & Brunklaus, A. (2022). Dravet syndrome: Molecular mechanisms and therapy. *The Lancet Neurology*, 21(5), 421–434.
7. Крылова, Е. В., & Белоусов, Д. Ю. (2020). Фармакогенетические подходы в лечении эпилепсии: роль натриевых каналов. *Российский журнал детской неврологии*, 15(2), 37–45.
8. Soldovieri, M. V., Ambrosino, P., Mosca, I., & Taglialatela, M. (2019). KCNQ2-related epilepsies: Channel dysfunction and treatment approaches. *Frontiers in Neurology*, 10, 36.
9. Marsh, E. D., & Brooks-Kayal, A. (2020). DEPDC5 and mTOR pathway in epileptogenesis. *Epilepsia Open*, 5(3), 349–360.
10. Хамракулов, М. Ш., & Алиев, Ж. Б. (2023). Генетические причины эпилептических энцефалопатий у детей. *Неврология, нейропсихиатрия, психосоматика*, 15(1), 78–85.
11. Pavlova, T., & Semenova, N. (2022). Methylation patterns in drug-resistant epilepsy. *Journal of Molecular Neuroscience*, 72(2), 312–320.
12. Ergashev, A. U., & Karimova, N. M. (2021). Epigenetic regulation of neurotransmission genes in epilepsy. *Uzbek Medical Journal*, 4(2), 55–62.
13. Han, Z., Chen, C., & Sun, J. (2023). Gene therapy for SCN1A-related epileptic encephalopathies: Preclinical and clinical advances. *Brain*, 146(1), 112–125.
14. National Institutes of Health. (2024). *Multi-omics integration for precision neurology: Annual report*. NIH Press.