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THE ROLE OF GENETIC DISORDERS IN THE FORMATION OF NEURAL NETWORKS IN AUTISM

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Abstract
Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions with marked clinical and genetic heterogeneity. Modern molecular genetic studies confirm the key role of hereditary factors in the formation of pathological changes in neural networks. Genetic disorders affect the processes of synaptogenesis, synaptic plasticity, regulation of neuronal excitability, and interneuronal adhesion. Of particular importance are de novo mutations, variations in the number of gene copies, single nucleotide polymorphisms, and epigenetic changes that affect the expression of genes regulating the development of the central nervous system. The paper systematizes current data on the molecular mechanisms by which genetic defects disrupt the formation of neural networks and discusses the prospects for genetically oriented diagnostics and targeted therapy.

Keywords: Autism spectrum disorders, neural networks, SHANK, SCN2A, synaptogenesis, epigenetics.

Introduction

Autism spectrum disorders are among the most complex neurodevelopmental pathologies, characterized by impaired social communication, limited interests, and stereotypical behaviors. The prevalence of ASD worldwide is steadily increasing due to improved diagnostic criteria and greater awareness among specialists. The etiology of ASD is multifactorial, but genetic mechanisms play a leading role. According to twin studies, the heritability of the disorder reaches 60–80%, indicating a significant contribution of genetic predisposition. The modern concept considers ASD to be a polygenic disorder resulting from a combination of rare mutations with a large effect and a multitude of common genetic variants with a small contribution to the risk of disease.

Disruptions in genes involved in the formation of neural networks lead to defects in synaptic transmission, an imbalance between excitatory and inhibitory influences, and impaired functional connectivity between different parts of the brain. As a result, molecular changes are transformed into cognitive, behavioral, and sensory characteristics typical of patients with ASD.

Objective

To systematize current data on the role of genetic disorders in the formation of neural networks in autism spectrum disorders and to analyze the molecular mechanisms of their influence on the development of synaptic dysfunction.

Materials and methods

A systematic analysis of current scientific publications on the genetic aspects of autism spectrum disorders (ASD) and their impact on the formation of neural networks was conducted. The main sources of information were international and Russian databases: PubMed, Scopus, Web of Science, eLibrary, Medline, as well as current peer-reviewed journals and official clinical recommendations of the Russian Federation.

Results and Discussions

Large GWAS studies have identified more than 100 candidate genes and over 1,000 rare de novo mutations associated with ASD, including more than 70 previously unknown mutations that affect disease risk. Particular attention is paid to genes involved in the formation and functioning of neural networks, as their disruption leads to an imbalance of excitation and inhibition, impaired synaptic plasticity, and cognitive function. Gene data are presented in Table 1.

Table 1

Gene	Main function	Consequences of mutation
SHANK3	Postsynaptic density, structural organization of synapses	Impaired dendritic spine formation, excitation/inhibition imbalance
SCN2A	Sodium channel Nav1.2, action potential generation	Impaired neuronal excitability, abnormal synaptic plasticity
NRXN1	Presynaptic adhesion protein	Disruption of connections between neurons, instability of synapses
NLGN3/4	Postsynaptic adhesion proteins	Defects in synapse stabilization, reduced signal transmission efficiency
CHD8	Transcription regulator, neuron formation	Impaired neuron differentiation, altered gene expression
FMR1	Regulation of synaptic protein trafficking	Decreased plasticity, cognitive and behavioral impairments

Disruptions in these genes lead to a number of pathological changes at the neuronal level: a decrease in the density and stability of synaptic connections, an imbalance between excitatory and inhibitory signals, and disturbances in functional connectivity between different areas of the brain. These mechanisms manifest themselves in the form of cognitive, sensory, and behavioral characteristics typical of ASD, confirming the hypothesis that disturbances in neural networks are a key pathogenetic component of the disorder.

In addition, large-scale studies confirm the significant genetic heterogeneity of ASD. For example, in one of the largest cohort studies, geneticists showed that genetic predisposition accounts for approximately 11% of the age of ASD diagnosis, and that the phenotypes of “early” and “late” autism probably have different genetic bases. This emphasizes that the genetic architecture of ASD is complex and multifaceted and includes not only genes directly involved in synaptic function, but also those that influence regulatory processes and the timing of symptom onset. Thus, understanding the role of genetic disorders in the formation of neural

networks in ASD is a fundamental problem in modern neuroscience and medical genetics. The difference between ASD and other neurodevelopmental disorders lies not only in the specificity of clinical manifestations, but also in the pathogenetic mechanisms at the level of molecules and neural networks. Elucidation of these mechanisms not only expands fundamental knowledge about the nature of the disorder, but also forms the basis for the development of more accurate diagnostic tools and targeted therapeutic strategies focused on specific genetic profiles of patients. ASD is a polygenic and heterogeneous disorder, where a combination of multiple genetic variants contributes to an increased risk of developing the disease. Genetic disorders affecting neural networks provide a link between molecular mechanisms and cognitive/social-behavioral manifestations. For example, SHANK3 mutations reduce the number of dendritic spines, disrupting the balance of excitation/inhibition and affecting cognitive flexibility and social behavior. SCN2A abnormalities alter the electrical activity of neurons, reducing network synchronization and the brain's adaptive response to external stimuli. NRXN1 and NLGN3/4 ensure synaptic stability; defects in these genes disrupt signal transmission and cognitive function. CHD8 and FMR1 mutations affect gene expression and synaptic plasticity, forming severe phenotypic manifestations of ASD. Taken together, these data confirm that the genetic architecture of ASD is complex and multifaceted, involving both genes directly involved in synaptic function and regulatory genes that influence the development of neural networks.
Understanding these mechanisms allows us to:
- predict clinical manifestations based on genetic profiles;
- develop targeted diagnostic methods;
- formulate individualized therapeutic strategies focused on specific genetic changes.

Conclusion

Autism spectrum disorders have a complex genetic basis and develop under the influence of multiple genetic factors, including rare mutations and polygenic combinations. These changes disrupt neural circuitry, synaptic function, and excitation/inhibition balance, which affects cognitive and social-behavioral functions. The SHANK3, SCN2A, NRXN1, NLGN3/4, CHD8, and FMR1 genes play a key role. Understanding the genetic mechanisms of ASD is important for early diagnosis, prognosis, and the development of individualized approaches to therapy, opening up new opportunities to improve patients' quality of life.

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