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Review Article

Dichotomous Classification of Autism Spectrum Disorders: Syndromal and Non-Syndromal Forms

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Abstract

In foreign literature on research into the etiopathogenesis of autism spectrum disorders (ASDs), the division of this group of diseases into two forms is getting more and more frequent. These two forms are «syndromal» and «non-syndromal» forms of autistic disorders. The literature review aims to cover the issues of the dichotomous classification of ASDs based on the genetic and molecular psychiatric views on the etiopathogenesis of this group of diseases. It also covers the purpose of this classification, the opportunities of its usage in routine clinical practice and the network resources, which allow classifying a form of ASD correctly. Special attention is paid to the multidisciplinary approach to dichotomous classification and its difference from the clinical view on the systematization of autism and the importance of this method for selection of target therapy.

Keywords: *Autism Spectrum Disorder; Genetic Association Studies; Genome-Wide Association Study; Review*

Introduction

Autism is a mental development disorder, the prevalence of which is estimated in 1 case per 68 people [1], the ratio of men to women is 4: 1. According to modern concepts, the concept of autism includes a wide range of diseases characterized by impaired social interaction and stereotypical behavior [2]. Autistic disorders appear in the main two modern classification systems - DSM-5 (Diagnostic and Statistical Manual of Psychology diseases, 5th edition, published in 2013) and ICD-10 (International Classification of Diseases, 10th edition). Both classifications are based only on the clinical diagnosis of autism, without taking into account data relating to the etiology and pathogenesis. Currently, the 11th edition of the ICD is being prepared for release. It is assumed that autism in it will be considered as a spectrum of poly- etiologic diseases - autism spectrum disorder (ASD). In this article, autism is considered in the terminology given in DSM-5, i.e. as PAC[1]. In the course of time and the development of modern methods of instrumental diagnostics in recent studies, a new approach to the classification of forms of autism has also been formed - the division into syndromic and non-syndromic forms, but this has been reflected mainly in foreign literature.

[1]RAC methods in 2016 in the PubMed resource tesarius, the concept status (MeShTerm) was assigned [3].

Syndromic and non-syndromic forms of ASD

Over the past 10 years, the possibilities for diagnosing ASD have greatly expanded due to the advent of new research: mass spectrometric analysis, chemiluminescent methods, full-exon and genome-wide sequencing. So, the new-generation sequencing (NGS) that has appeared, a feature of which is the ability to determine the nucleotide sequence of DNA and RNA, simultaneously analyzes several sections of the genome. The technique allowed us to speak with confidence about the polygenic etiology of ASD. In 2011, one of the first studies was conducted [4] using the full-exon sequencing technique, which revealed genes that are significant for the etiopathogenesis of ASD, for example, encoding the β-subunit 2 of the glutamate ionotropic NMDA receptor (GRIN2B); gene α-subunit 1 potential-activated sodium channels (SCN1A), etc. Thanks to the latest approaches, by 2012, about 20% of ASD had acquired the most probable genetic etiology [5], which led to an increase in the understanding of the pathogenesis of ASD.

It should be noted that the range of questions studied in the field of etiology and pathogenesis of ASD is wide: from environmental factors, the impact of which may be key at any stage of development - from the formation of a zygote to the postnatal period (for example, the most likely risk factors are complications during childbirth - fetal hypoxia, birth trauma [6], etc.), metabolic disorders (for example, changes in plasma amino acid indices [7]) to genetic and epigenetic [8] disorders. At the same time, the most significant etiological factors are still genetic disorders [9]. This is due to the fact that genetic aberrations ultimately lead to impaired formation of nerve tissue and brain structures, immunological, metabolic and functioning of signaling pathways, direct and indirect synaptic transmission mechanisms, and also cause compensatory and protective functions of the body in response to the impact of environmental factors [6-8]. The converse is also true: under the influence of external factors, all changes lead to disturbances in the gene and epigenic structure (the so-called gene - environment interaction [10]). These findings are confirmed by studies [11-13], which determine the high importance of the gene component in the formation of ASD from 38 to 90% (depending on the study parameters).

By mid-2017, more than 880 genes were studied, mutations in which were considered as risk factors for the development of ASD [14]. However, such a large base for studying heterogeneous genetic etiology is the reason for the formation of an increasing number of questions regarding both the etiology and pathogenesis of ASD. Due to the huge amount of information and difficulties in identifying specific genes responsible for the manifestations of autistic disorders, researchers began to single out such forms of disorders as syndromic and non-syndromic. The dichotomous classification is more likely genetic than psychiatric, since in clinical practice, the formation of the diagnosis is in accordance with the symptoms, and not the results of a genetic study. Based on such a classification system, it became possible to conduct a comparative genetic analysis of syndromic and nonsyndromic (i.e. idiopathic) forms of diseases [15], determining what molecular signaling pathways are involved in the genesis of autistic disorders in general and a specific disorder of this spectrum in particular. At the same time, from a clinical point of view, without the use of sequencing methods to determine gene disorders, the syndromic and idiopathic forms may turn out to be the same form of the disease. Thus, the syndromic forms of autism are a specific syndrome of pathological development, in which, in addition to autistic manifestations, other specific dysontogenic disorders are determined. Within the framework of syndromic forms, the so-called syndromic genes responsible for the formation of this pathology of development are considered. Syndromic forms of ASD were the first group to initiate a dichotomous classification, since their etiology was easier to determine due to the monocausal nature. Initially, the group consisted of about 35 diseases, but with the development of modern technologies, their number is constantly growing. However, it should be remembered that disorders in the syndromic genes do not always lead to the development of autistic symptoms [16]. This allows researchers to identify molecular mechanisms (in particular, by elimination) that are responsible specifically for the autistic spectrum of clinical manifestations.

Conventionally, syndromic forms are also usually distinguished into monogenic and due to mutations according to the type of variation in the number of copies (CNV: duplication or deletion). Monogenic forms include fragile X chromosome syndromes [17], cortical dysplasia - local epilepsy (CDFE syndrome [18]), tuberous sclerosis types 1 and 2 (TSC1 and TSC2 [16]), Rett [19, 20] and others, in which a single key gene is determined as an etiological developmental factor. Forms due to CNV do not have an established key gene but are determined

by a specific chromosome site [13]. A striking example is Phelan - McDermid syndrome (deletion of the 22q13 region [21]). However, researchers play a key role in the formation of this syndrome as the deletion of the SHANK3/PROSAP2 gene. This hypothesis is due to the very function of the gene. SHANK3 expression (also called ProSAP2) is found in many areas of the brain, and the protein encoded by it helps maintain synaptic structural integrity. SHANK - multi-domain support proteins located in postsynaptic compaction that connect the receptors of neurotransmitters, ion channels and other membrane proteins associated with the signaling pathway of the actin cytoskeleton and signaling pathways associated with the G-protein. SHANK proteins can play an important role in the formation of synapses and the maturation of dendritic spines. It is the changes in these structures that are responsible for the mechanisms of synaptic transmission that the formation of autistic symptoms [21-23] and other signs of a phenotype similar to the Rett and Phelan - MacDermid syndromes [24-26] are prescribed. At this stage, SHANK is one of the most actively investigated syndromic genes involved in the pathogenesis of ASD, since violations in it lead to dysfunction of the mT OR-PI3K-Akt signaling pathway.

The list of syndromic forms is wide and includes both denovo mutations and inherited ones. In the literature, one can find Angelman syndrome [27], PTEN syndrome [28], type 1 neurofibromatosis (NF1) [29] related to the syndrome; macro-encephalic/autistic syndrome and Cowden syndrome [30-32], caused by abnormalities in the same gene as the PTEN syndrome. However, not all forms of syndromes have specific nomenclature names - the syndrome of deletion or duplication of genes in the region 15q11-13 [33]; syndromes caused by deletion or duplication of the 16p11.2 region [34,35]; microdeletion syndrome 2q23.1 [36], etc.

Non-syndromic (or idiopathic, sporadic) forms of ASD are most often understood as forms, the etiology of which has not been elucidated or cannot be established precisely. All genes associated with idiopathic forms that are not syndromic are also non-syndromic. Such a separation of genes is important for understanding the mechanisms of activity of the nervous system and the pathogenesis of neuropsychiatric disorders.

Identification of non-syndromic genes became possible thanks to large-scale studies of a large array of genetic information in people with ASD: both rare denovo mutations and the most common genetic aberrations [37]. The study of large arrays of pathogenic genes with varying degrees of significant significance of their role in the development of non-syndromic forms of ASD [38-43] makes it possible to identify not only violations of certain metabolic pathways, but also the significance of inheritance of pathogenic genes in the etiology of ASD. In 2016, a large meta-analysis of twin studies was conducted [44], covering more than 6,000 subjects. He demonstrated that in families with pro-gangs for ASD, the heritability coefficient was in the range of 64 - 91%. Thus, the isolation of nonsyndromal genes makes it possible to identify those genes that may be pathogenic enough to become a reason for the development of a nonsyndromic form of ASD. According to rough estimates, syndromes with reliably known etiopathogenesis represent only about 5-10% of all cases of ASD [45,46].

It should be noted that the classification into syndromal and non-syndromic forms of autism is of scientific and practical interest, since it can be one of the most important aspects in the development of new methods of drug therapy [8,46-48].

Genetic analysis - the basis of the dichotomous classification of ASD

Differential diagnosis with genetic analysis is becoming increasingly important. From the point of view of clinical practice, ASD are polygenic and etiologically complex diseases, which are characterized by a wide range of clinical manifestations. Thus, according to ICD-10, childhood autism (column F84.0) [49] is characterized by abnormal or impaired development, which manifests itself before the age of 3 years (impaired receptive or expressive speech, the development of selective social attachments, functional or symbolic game). It is also characterized by limited interests and activity, repetitive and stereotypic behavior. Such a definition is clinically important, but does not reflect the etiopathogenetic form, which would make it possible to prescribe the most adequate therapy, taking into account the "dropped out molecular links" of the functioning of higher nervous activity. In the framework of the DSM-5 classification, gradation is additionally observed according to the severity of symptoms, estimated on the basis of the amount of care required [2].

At the same time, the analysis of genetic information and the syndrome-non-syndromic classification are increasingly mentioned and used, although mainly for research purposes to determine the pathogenesis of ASD, as well as the development of new methods of treatment and selection of etiopathogenetic therapy.

In this regard, there is a need for the formation of an accessible genetic search and analysis of data on the possible etiology of ASD for the differentiation of forms of disorders. The dichotomous classification proposed by researchers is based on the discovery of specific pathways that cause autism symptoms. Due to the complexity of the molecular biological pathways in the nervous system, finding the causes of autism has proven to be quite a challenge. The number of genes and proteins encoded by them in biological pathways (from tens to hundreds of genes involved) required researchers and practicing clinicians who can detect a new syndromic form of ASD to create tools for conducting "network gene analysis" [50], as well as certain interaction algorithms. The amount of resources to supplement knowledge of signaling paths, available both for free and on the basis of a commercial license [51], is growing every year. Consider the basic resources that allow us to assess the role of genetic disorders in the framework of ASD and the possibility of their application.

One of the most complete paintings, reflecting the entire spectrum of genetic disorders associated with autism, has a resource created within the framework of the Simons Simplex Collection project [14] - SFARIGene. This is a database with a categorical division of genes into syndromal and non-syndromic, as well as distributing them on a scale of confidence and significance in the development of ASD (from 1 - "high confidence" to 6 - "there is no evidence confirming the role in the development of disease vania"). The resource also has research data on animal models, a glossary of terms, and is constantly updated. As part of this resource, one of the main approaches to the detection of molecular pathways involved in the formation of ASD, usually associated with genetic aberrations, which consists in the analysis of protein-protein interactions (PPI) to identify key proteins in the list, was additionally demonstrated. ke proteins interacting with each other. The SFARI Gene resource describes an algorithm for such an analysis. PPI analysis involves the use of databases based on experimentally confirmed or possible PPI [52]. PPI also allows one to determine "binding moments" in pathogenetic processes, strongly interacting proteins that may be key in specific molecular pathways, which can help in the search for etiopathogenesis of a specific ASD. However, this technique has its drawbacks and warnings among researchers. Firstly, the lack of knowledge about tissue-specific PPI, in particular, in the dichotomy classification of autistic disorders 110EvlatarVV collection in the ISVOVkrlVV, 4, 2018 of nerve tissue of the brain. Often this problem is solved by combining PPI databases with data on RNA expression in a specific tissue, therefore, when genetic analysis of encoded proteins and their interactions is necessary to make sure that only those proteins that are in a specific tissue are taken into account. Additional opportunities used to identify the most likely paths in the gene list are the databases of the Gene Ontology Consortium [53] and tools to supplement knowledge of signaling pathways. So, the "Gene ontology" project [51] essentially represents a unified dictionary of genes and their biological roles.

The most popular among researchers, a platform based on commercial analysis is IPA (Ingenuity Pathway Analysis [54]). It is used for analysis, integration and interpretation of scientific research data obtained from genetic (including RNA), metabolic and proteomic results of experimental work. A significant drawback of the platform is its commercial component. However, there are also several important points that should be considered when using these resources in clinical and research practice: data processing methods (both manually and computerized); algorithms used to create maps of signaling paths, and types of map data (according to the specificity of the metabolic pathway and tissue), as well as the volume of the knowledge base [50].

To assess the extent of the necessary analysis of molecular disorders in ASD, it should be understood that genetic disorders trigger a change in signaling pathways [55], such as mT OR- and PI3K-AKT- [56], Wnt-β-catenin - [57], calcium/calmodulin-signaling pathways [58], the neurotrophin signaling pathway (aka nerve growth factor) [50]. These are just those of them, changes in which are most likely the pathogenetic mechanism of ASD. The number of studied signaling pathways, whose influence may be significant in the pathogenesis of this group of disorders, only increases with time. For example, the possible effect of disturbances in the oxytocin signaling pathway has recently been examined [59].

The signaling pathways and their genetic basis are most fully recorded in the signaling pathway database KEGG (KEGG: Kyoto Encyclopedia of Genes and Genomes [60]). However, it should be remembered that these pathways can be considered not only in humans and do not always take into account the tissue-specific nature of the interaction. The advantages of this system are a schematic presentation of information, separation into signaling pathways and areas of their influence by pathology, a complete description of genes and the proteins encoded by them. Especially the visibility of this resource is manifested during a detailed study of signal paths. It becomes obvious that most of the metabolic pathways are interconnected by the main links (for example, the Wnt signaling pathway is linked via the GSK-3 protein kinase by the regulatory function of metabolism to mT OR and AKT protein kinases), which allows a broader look at the etiopathogenetic mechanisms ASD and conclude that most changes in the genes of these signaling pathways lead to impaired functioning and/or development of neural tissue due to pathogenetic mechanisms such as apoptosis, cell disorders are cycle neurons, changing the formation and development of synapses, as well as the disruption of the normal functioning of neurotransmitters.

In many respects, the genetic analysis of this spectrum of diseases is complicated by the fact that some of the genes that vary in various degrees affect the development of ASD are common with other disorders of the human mental activity (anxiety disorders, attention deficit and hyper-activity, mental retardation, bipolar disorder and schizophrenia) [61-63]. This is not surprising, since the comorbidity of mental disorders is pronounced in the framework of ASD [64]. However, the development of tools such as SFARI Gene, Gene Ontology, KEGG made it possible to differentiate genetic abnormalities, identify new syndromic forms, and along with this, it became possible to objectify the differential diagnosis, prescription or withdrawal of drug therapy, and in general, there has been a change in the approach to treatment from symptomatic to etiopathogenetic.

Conclusion

Summarizing the above, it can be argued that over the past 10 years, ideas about the etiopathogenetic mechanisms of ASD have expanded significantly thanks to the discovery of new methods of instrumental diagnosis of genetic disorders. The use of modern methods and resources for network analysis of data allowed us to formulate the concept of dichotomous genetic classification, which includes syndromic and non-syndromic forms of RAS. The modern dichotomous classification of ASD in the near future will provide an opportunity not only to determine the presence or absence of a specific development syndrome in a patient with ASD, but also to detect a dysfunctional link in the affected molecular signaling pathway responsible for furs isms direct and indirect synaptic transmission signal or other, important for the normal functioning of the nervous processes of de yours elf.

Conflict of Interest

The authors declare no conflict of interest.

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