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Genetic Aspects Of Autism Spectrum Disorder

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Abstract:
Autism spectrum disorder is a clinically and etiologically heterogeneous group, affecting 1 in 59 children. The etiopathogenesis of these, basically, neurodevelopment disorders, has been the subject of research by numerous researchers for more than two decades, and involves complex genetic, environmental, and epigenetic mechanisms. Hundreds of genes have been identified that contribute to serious deficits in communication, social relations and patient behavior. So the main objective of the paper is to explain the way in which genetic modifiers and epigenetic changes have a key role in modulating the phenotypic spectrum of patients with autism spectrum disorder. The systematic review of literature is based on a review of the available scientific papers. Following PRISMA's instructions, a systematic review of published papers in the period from 2016 to 2024 was performed. Our study included literature published in the MEDLINE/PubMed database in which the following keywords were used during the search: "autismspectrum disorder", "pervasive developmental disorder", "risk factors", "genetics", "phenotypic spectrumof ASD", "genes", "epigenetic mechanisms". The obtained results show that the genetic factor increases the risk for development of autism spectrum disorder. More genes have been identified that are involved in the development of autism spectrum disorder, such as: ADNP, ANK2, CHD2, CNTN4, DSCAM, etc. In addition to genetic variants, there is also evidence of de novo gene variants. At the same time, chromosomal deletions or duplications were found in patients, such as the following: 15q11.2, BP1-BP2, 16p11.2 and 15q13.3. Copy number variations are submicroscopic, structural variants in chromosomes that include duplications, deletions, translocations, and inversions, sometimes stretching several kilo bases. Many genes may be affected with these changes, but not all are necessarily drivers of disease. Epigenetic mechanisms, DNA methylation and chemical histone modification are mechanisms that affect gene expression without changing the primary structure of genes. Genetic research so far has enabled us to consider autism spectrum disorder from a different angle, and understand its etiopathogenesis as a complex interaction between genes and environmental factors as a predisposition for its occurrence.

Keywords: *autism spectrum disorder, genetic modifiers, epigenetic, gene-environment interaction.*

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I. Introduction

The autism spectrum disorder is a heterogeneous group of neurodevelopmental disorders with certain common characteristics: a qualitative disorder in reciprocal social interactions, in verbal and non-verbal communication, as well as a poor, stereotyped, repetitive repertoire of interests and activities, which are observable in the functioning of the individual in all situations. Very often there are changes in affect, imagination, flexibility, cognition and attention.

The causes for the occurrence of ASD are not completely known and clear to date. It is a psychopathological disorder that occurs as a consequence of various biological or psychological factors, with an emphasis on genes and environmental risk factors[1]. Twin studies prove that identical twins, who share nearly identical genetic material and also include interactions between gene, environment, and epigenetic factors, show a significantly higher likelihood of both individuals having ASD compared to non-identical twins[2]. The studies also confirm the involvement of genetic (hereditary) and non-genetic (environmental) factors.

With advances in molecular genetics, specific genetic variations associated with an increased risk of autism have been identified. Although no single gene is solely responsible, numerous genetic variations contribute to the wide spectrum of symptoms that occur in autism spectrum disorder. Different variants in specific genes are associated with development of neurons, synaptic function and communication between brain cells, which have an important role in the pathogenesis of ASD. The polygenic nature of ASD allows researchers to explore heterogeneity within the autistic population, providing the basis for personalized interventions, whereby the unique genetic profile of each individual is considered, which leads to more efficient treatment.

II. Method

In order to study how genetic modifiers and epigenetic changes play an important role in modulating the phenotypic spectrum of patients with ASD, we determined the following steps:

1. Systematic review of the literature from the MEDLINE/PubMed database, as well as study of professional literature.
2. Data extraction and study quality assessment.

Literature search procedure

A systematic search and review of literature was conducted in accordance with the Systematic Reviews and Meta-Analysis (PRISMA) Procedures. A pre-designed protocol was used for search, data abstraction, inclusion-exclusion criteria, and research quality assessment. Following PRISMA's instructions, a systematic review of published studies from 2016 to 2024 was conducted. We included literature published in the PubMed database during the literature search while using the following keywords: "autism spectrum disorder", "pervasive developmental disorder", "risk factors", "genetics", "phenotypic spectrumof ASD", "genes", "epigenetic mechanisms". A pre-designed search strategy was used, as well as inclusion and exclusion criteria.

After the conducted search in the PubMed database, we obtained 62 studies and one printed study that refer to neurodevelopment disorder. After filtering and specifying the criteria of the PubMed database, the number of studies changed, hence 27 studies remained as reviews, which were manually reviewed by using the skimming reading technique and finding results in each paper, which were analyzed for this overview.

After filtering the keywords that refer only to autism spectrum disorder based on the inclusion and exclusion criteria, we obtained a total of 8 papers that are included in this paper. The papers were reviewed and analyzed by means of manual review of each paper individually, according to the skimming reading technique without any language restrictions. After excluding papers that did not meet the criteria for their inclusion as papers in the research, we obtained a total of 12 papers that are included in the quantitative analysis, and during manual comprehensive and final review of the papers, 8 papers remained that were included in the qualitative analysis of this systematic review.

Paper inclusion and exclusion criteria

In this systematic review, we included a total of 8 studies that were used in the final analysis and that were published in the period from 2016 to 2024. The specific reasons why the papers were included in the systematic review consist of the following: (1) peer-reviewed studies; (2) studies with higher homogeneity of respondents (due to the heterogeneity of the disease itself); (3) studies with free full-text and full-text were reviewed; (4) only papers published in English were included in the review, even though that was not one of the inclusion criteria in the review; (5) papers related to genetic factors in the development of autism spectrum disorder; (6) papers providing results in support of the genetic hypothesis of ASD. Each paper was reviewed, information/data were extracted based on the following characteristics: author's name, title, year, publication format (academic thesis or scientific publication), study type, sample size, age, monogenetic and polygenetic mechanisms, epigenetic mechanisms, phenotypic changes of patients with ASD.

Papers that were excluded in the systematic review: (1) we excluded studies that did not have processed data, (2) and confirmed genetic changes, (3) and due to limited time and human resources.

III. Results

The initial results in the research of the scientific bases provided us access to 62 papers. In the second step, the year of publication of the paper was analyzed, whereby 27 papers were available. In the third step, the papers that corresponded to the title, were written in English and were available with a full text were analyzed. In the fourth step, the analyzed papers included papers with indicated genetic modifiers and epigenetic changes that have an important role in modulating the phenotypic spectrum of patients with ASD.

The included papers determined the direction of genetic heterogeneity and genetic factors related to autism spectrum disorder. This heterogeneity results in a variety of personality changes, making each individual with ASD unique in their symptom profile. Understanding genetic diversity enables a more appropriate approach to diagnosis and intervention, thus confirming that behavioral changes in individuals with autism result from a complex interplay of genetic influences. Contemporary research aims to identify subtypes of ASD based on different genetic profiles[3]. Genetic subtyping may offer an insight into the different types of behavioral symptoms in ASD. By categorizing individuals with ASD into subgroups, researchers are able to discover more about the relationship between ASD, behavior and genetic changes.

Single-gene disorders associated with ASD

Several individual characteristics of a single gene are associated with an increased risk of developing autism spectrum disorder. Tuberous sclerosis (TSC) and fragile X-syndrome (FRAXA) are the mostmentioned

in literature, and phenylketonuria (PK) and Smith-Lembi-Opizt syndrome (SLO) are less common. Tuberous sclerosis (TSC) is an autosomal neurocutaneous disorder in which mutations are found in the TSC1 gene on chromosome 9q34 and the TSC2 gene on chromosome 16p13. Studies of children have shown that autism in children with tuberous sclerosis is 100 times more common than expected, thus confirming that tuberous sclerosis is a risk factor of ASD[4]. One meta-analysis confirms the association between fragile X chromosome (FRAXA) and autism in boys[5]. The molecular basis of this syndrome is an unstable expansion of the CGG tripletrepeat (more than 200 repeats) in the 5'-untranslated region of the FMR1 gene localized on chromosome Xp27. Approximately 2-5% of children and adolescents with ASD carry a complete FRAXA mutation or mosaicism in this region.

Genome-wide association studiesand candidate genes

The genes that increase the predisposition to develop autism spectrum disorder are not clearly defined. This is the result of the potential participation of several genes, each of which is a risk factor for the occurrence of the disease, the increased degree of heterogeneity and the lack of clear pathophysiological evidence in regard to the respective candidate genes. For this reason, the numerous researches dedicated to the etiology of autism belong to the so-called GWAS studies (Genome-Wide Association Studies). Throughout the past decade, there have been a large number of papers that have studied the chromosomal regions involved in the etiopathogenesis of ASD[6].

GWAS studies examine the association of ASD and genetic variants including copy number variation (CNV) and single nucleotide polymorphism (SNP). Genetic variants can be inherited or arise from de novo mutations. Copy number variations are usually insertions, deletions, and sequence repeats that alter the gene function[7]. In addition, a meta-analysis confirmed that common single nucleotide polymorphism acting additively, increase the risk for ASD, with a heritability of about 60% in "multiplex families", i.e. families in which several cases of ASD are present[8].

In their paper Uddin et al. (2021) confirm that CNTNAP2 mutations are usually associated with behavioral changes in ASD resulting from impaired synaptic neurotransmission[9]. Actually, CNTNAP2 is a member of the neurexin superfamily and is a synaptic protein. The rs271010C and rs794745 polymorphisms of CNTNAP2 increase the risk of developing ASD.

Neurolignin 3 and 4, as well as SHANK3, are important molecules for cell adhesion at the synapse, and mutations in the genes of neurolignin 3 (NLGN3) and 4 (NLGN4x and NLGN4Y) have been found in individuals with autism, by means of base pair deletion or a cytosine to thymine transition. The SHANK3 gene participates in coding a synaptic protein that binds to neurolignins and plays an important role in cognitive development, speech development and social contacts[10].

Multiple gene candidates are found on chromosome 7 that are associated with the development of ASD. Mutations of the FOXP2 gene (Forkhend Box 2) lead to reduced verbal communication, while the RELN gene is important in synaptogenesis and formation of specific parts of the cortex[11]. According to some researches, a repeat of a three nucleotide polymorphism in the 5' untranslated region of the RELN gene is associated with ASD[12].

The A1298C and C667D polymorphisms of the MTHFR gene are associated with reduced enzyme activity that affects the folate metabolism, which is reflected in fetal brain development[13]. Brain dysfunction is indicated in the etiology of ASD. At the same time, the OXTR gene is one of the most frequently studied genes associated with ASD[14]. Oxytocin plays an important role in human behavior, especially social interaction and communication.

On chromosome 15 in the 15q11-13 region, the genes responsible for encoding gamma-aminobutyric acid (GABA) receptors are associated with the development of ASD, as their level is reduced in the hippocampus. However, currently there is insufficient evidence about these genes, as well as the possible candidate genes for ATPase, type 10C (ATP10C) and ubiquitin-protein ligase E3A (UBE3A) located on the maternal expression domain, because the 15q11-13 region is very complex, due to high recombination between mother and father changes[15].

Copy number variations of the synaptic genes SYNGAP and DLGAP are involved in the process of neurogenesis and disruption of the GTPase/Ras signaling pathway[16].

A severe form of autism in girls is associated with mutations in the regulatory CTNND2 gene that affects neural development. This finding is very significant, because it can help us explain why autism in girls, although less common, is usually more severe[17].

Epigenetic mechanisms in autism spectrum disorder

Epigenetic markers, such as DNA methylation, histone methylation and acetylation, determine the chromatin state and regulate the expression of many genes without affecting the primary DNA sequence. Certain studies reveal the association of autism with SNP (single nucleotide polymorphism) in the MTHFR

gene (gene for methylenetetrahydrofolate reductase), involved in DNA methylation in lymphoblastoid cells of autistic patients[18,19].

In addition, LoParo and Waldman (2016) based on analysis of methylated DNA by sequencing, after bisulfide treatment of DNA, come to the conclusion that the CpG sequences of the gene for the oxytocin receptor (OXTR) in a sample taken from the temporal cortex of an autistic patient have more methylated CpG sequences compared to the control samples[20]. The CpG sequences regulate the expression of the OXTR gene in the temporal cortex. Hypermethylation of this gene leads to its silencing, therefore the synaptic pathway of oxytocin is impaired.

IV. Discussion

We have seen that autism spectrum disorder is an etiologically heterogeneous syndrome[21]. The genetic mechanisms that predispose to autism are unknown, since neither the level of familial risk nor the very different concordance rate in monozygotic and dizygotic twins is compatible with a simple monogenic model of transmission. It is possible that Mendelian monogenic inheritance takes part in a small number of individuals, but in most cases it seems to be due to multiple susceptible genes, known as polygenic inheritance[22].

A specific characteristic confirmedly meta-analytic research is the relationship between autism spectrum disorder and genetic factors. The autism spectrum disorder shows a polygenic nature, since the interaction of several genetic factors is involved. Although no single gene is solely responsible, the cumulative effect of the numerous genetic variations contributes to the increased susceptibility to ASD. This complexity has an influence on changes in behavior, since these genetic factors affect the brain, the synaptic function and the neural connectivity. The polygenic nature of ASD results in a wide range of symptoms and behavioral changes such as: social communication difficulties, repetitiveactivities and sensory difficulties[23]. The polygenic nature of autism allows researchers to explore the heterogeneity of the autistic population, providing the basis for personalized interventions that consider each individual's unique genetic profile, thereby providing more effective and tailored treatments to improve the behavior of individuals with ASD.

Epigenetic mechanisms such as DNA methylation regulate gene expression during personality development. Understanding the epigenetic landscape of ASD provides a better perspective in regard to the interaction between genetic and environmental factors in shaping the behavioral symptoms typical of autism. Usually, epigenetic changes refer to modifications that affect gene expression without changing the basic DNA sequence.

A metaanalysis offers one approach to obtain maximum information from various studies. Currently, the 15q region provides weaker evidence for linkage, but a relatively high incidence of chromosomal abnormalities does support a role for this region in autism etiology, although the effect of this locus may be limited to a smaller subgroup of autism cases. An interesting fact is that the 15q and 7q regions contain imprinted genes suggesting that abnormal imprinting may be implicated in the etiology of autism[24].

Therefore, after discovering the nature of gene functions, the next step involves identifaction of the risk process according to which abnormalities of gene function lead to the autism phenotype. This would require research to understand the functioning of the biological system (molecular cell biology), but will also involve determining how genetic risk interacts with developmental processes or environmental hazards (external factors) of some kind,requiring research in the field of molecular epidemiology.

V. Conclusion

ASD is characterized by the presence of pronounced genetic heterogeneity, including both locus and allelic heterogeneity, which is both a problem and a challenge for researchers. There is still no answer when it comes to the relationship between genetic variations and phenotype, because identical mutations can cause different phenotypes in different individuals.

In the next few years, we can expect new genomic screenings and an increase in existing family cohorts. It may also predict the use of more sophisticated analytical approaches to extract full genetic information from family data, by measuring milder autistic phenotypes and by dimensioning the various phenotypic components for use in quantitative trait locus analysis. The identification of the first autism susceptibility gene may accelerate the discovery of other genes and allow targeting of mechanisms underlying abnormal development and brain function. The leap in our knowledge will be of primary importance for the development of new prevention and treatment strategies.