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GENES INVOLVED AND COMBINATION OF PHENOTYPICAL HETEROGENEITY IN PATIENTS DIAGNOSED WITH AUTISTIC SPECTRUM DISORDER (ASD): A LITERATURE REVIEW

GENES ENVOLVIDOS E COMBINAÇÃO DE HETEROGENEIDADE FENOTÍPICA EM PACIENTES DIAGNOSTICADOS COM TRANSTORNO DO ESPECTRO AUTÍSTICO (TEA): UMA REVISÃO DE LITERATURA

GENES IMPLICADOS Y COMBINACIÓN DE HETEROGENEIDAD FENOTÍPICA EN PACIENTES CON DIAGNÓSTICO DE TRASTORNO DEL ESPECTRO AUTISTA (TEA): UNA REVISIÓN DE LA LITERATURA

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ABSTRACT

Autism Spectrum Disorder (ASD) is characterized by cognitive impairment and impairment in behavioral and social interaction. Of complex etiology, considering interactions between genetic and epigenetic factors. Objective: The research proposes to investigate the genetic contribution underlying Autism Spectrum Disorder (ASD). Methods: A systematic literature review methodology is used in the PubMed, Scientific Electronic Library Online (Scielo) and VHL databases via DeCS/MeSH descriptors in any language. Results and discussions: The findings highlight the strong predominance of genetic influences in ASD, evidencing the alteration of more than 800 documented genes, whose heritability is greater than 80%. Covering a diverse plexus regarding its functionality with changes in chromatin remodeling, transcription factors/regulators, mRNA traffic regulators, protein modification, cell proliferation, and synaptic architecture. Genomic interactions that include deletion, translocation, polymorphism and specific mutations found in the genes: MTHFR, GABRB3, RELN, OXTR, RTTN, SOCS6, CBLN2, and the alteration of the chromosomal chromosomes in the numbers :1, 2, 3, 7, 16, 22, with a predominance of 17, were highlighted. Responsible for altering the formation of proteins and neurotransmitters indispensable for the development of physical, social and behavioral skills. In addition, association with RETT and X-fragile syndromes. Conclusion: Therefore, this research highlights the genetic complexity of ASD with a high degree of heritability, the insufficiency of genetic testing, reliable biological markers, and the pressing need for additional advances in diagnosis, clinical management, and early therapeutic approaches.

Keywords: Genetics. Genes. Autism.

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RESUMO
O Transtorno do Espectro Autista (TEA) é caracterizado por comprometimento cognitivo e prejuízo na interação comportamental e social. De etiologia complexa, considerando interações entre fatores genéticos e epigenéticos. Objetivo: A pesquisa propõe investigar a contribuição genética subjacente ao Transtorno do Espectro Autista (TEA). Métodos: Utilizou-se a metodologia de revisão sistemática de literatura nas bases de dados PubMed, Scientific Electronic Library Online (Scielo) e BVS via descritores DeCS/MeSH em qualquer idioma. Resultados e discussões: Os achados destacam a forte predominância de influências genéticas no TEA, evidenciando a alteração de mais de 800 genes documentados, cuja herdabilidade é superior a 80%. Abrangendo um plexo diverso quanto à sua funcionalidade com alterações na remodelação da cromatina, fatores/reguladores de transcrição, reguladores do tráfego de mRNA, modificação de proteínas, proliferação celular e arquitetura sináptica. Interações genômicas que incluem deleção, translocação, polimorfismo e mutações específicas encontradas nos genes: MTHFR, GABRB3, RELN, OXTR, RTTN, SOCS6, CBLN2, e a alteração dos cromossomos cromossômicos nos números: 1, 2, 3, 7, 16, 22, com predominância de 17, foram destacadas. Responsáveis por alterar a formação de proteínas e neurotransmissores indispensáveis ao desenvolvimento de habilidades físicas, sociais e comportamentais. Além disso, associação com síndromes RETT e X-frágil. Conclusão: Portanto, esta pesquisa destaca a complexidade genética do TEA com alto grau de herdabilidade, a insuficiência de testes genéticos, marcadores biológicos confiáveis e a necessidade urgente de avanços adicionais no diagnóstico, manejo clínico e abordagens terapêuticas precoces.

Palavras-chave: Genética. Genes. Autismo.

RESUMÉN
El Trastorno del Espectro Autista (TEA) se caracteriza por deterioro cognitivo y deterioro en la interacción social y conductual. De etiología compleja, considerando interacciones entre factores genéticos y epigenéticos. Objetivo: La investigación propone indagar en la contribución genética subyacente al Trastorno del Espectro Autista (TEA). Métodos: Se utiliza una metodología de revisión sistemática de la literatura en las bases de datos PubMed, Scientific Electronic Library Online (Scielo) y BVS mediante descriptores DeCS/MeSH en cualquier idioma. Resultados y discusión: Los hallazgos resaltan el fuerte predominio de influencias genéticas en el TEA, evidenciando la alteración de más de 800 genes documentados, cuya heredabilidad es superior al 80%. Abarcando un plexo diverso en cuanto a su funcionalidad con cambios en la remodelación de la cromatina, factores/reguladores de transcripción, reguladores del tráfico de ARNm, modificación proteica, proliferación celular y arquitectura sináptica. Se destacaron interacciones genómicas que incluyen deleción, translocación, polimorfismo y mutaciones específicas en los genes MTHFR, GABRB3, RELN, OXTR, RTTN, SOCS6 y CBLN2, así como la alteración de los cromosomas 1, 2, 3, 7, 16 y 22, con predominio del 17. Estos genes alteran la formación de proteínas y neurotransmisores indispensables para el desarrollo de habilidades físicas, sociales y conductuales. Además, se observó asociación con los síndromes de Rett y X frágil. Conclusión: Por lo tanto, esta investigación destaca la complejidad genética del TEA, con un alto grado de heredabilidad, la insuficiencia de pruebas genéticas y marcadores biológicos fiables, y la apremiante necesidad de avances adicionales en el diagnóstico, el manejo clínico y las estrategias terapéuticas tempranas.

Palabras clave: Genética. Genes. Autismo.

1 INTRODUCTION

Autism Spectrum Disorder (ASD), known as Autism, is defined as a neuropsychomotor disorder, characterized by cognitive and behavioral deficits with impaired social interaction, interest in restricted and repetitive activities[1,2]. However, it encompasses a phenotypic complexity, which may vary in form and intensity, as it presents degrees of impairment, mild (Level 1), moderate (Level 2) and Severe (Level 3)[2,3]. According to the World Health Organization (WHO), it has a record in the ICD-10 (International Classification of Diseases) of subcategories such as: childhood autism, atypical autism, Rett syndrome, Asperger's syndrome, childhood disintegrative disorder, and unspecified general developmental disorder[3,4].

Its etiology is complex and multifactorial, with a strong genetic influence. Unlike other syndromes, it is not only linked to 1 specific gene, but more than 800 genes with some association have been documented. Including, hundreds of chromosomal aberrations, syndromes interconnected to the same chromosome, and genetic interaction influenced by the environment linked to epigenetic factors[4,5,6].

This disorder affects 1 in 54 live births, data from the United States, predominates in males and affects about 4 to 1. Interconnected to genetic alterations, associated with some syndromes such as RETT and fragile X, sought respectively in girls and boys. In addition to having a high degree of heritability, studies with monozygotic twins, who share the same DNA, have shown hereditary percentages higher than 80%[6,7].

Therefore, this research systematically addresses an integrated bibliographic review of the last 5 years. Highlighting the identification of the most prevalent genes, chromosomal alterations, and syndromes involved with ASD. And, the difficulty in identifying these genes, linked to a deficiency of advanced genomic technologies. In addition, it is difficultto identify the disorder due to the typical nonspecific presentation, varying degrees of impairment, and the need for continuous follow-up.

METHODOLOGY

The present study is a systematic approach to literature review. In order to investigate the genetic influence on ASD. The searches were carried out in a wide academic database, including PubMed, Scientific Electronic Library Online (Scielo) and VHL via DeCS/MeSH descriptors: genetics, genes, autism, Autism Spectrum Disorder

(ASD). Specifications were used as full texts, from the last 5 years, between the years 2019 to 2024, in any language. In the analysis, 16 articles were considered essential and relevant to ensure the approach of the study in question.

RESULTS AND DISCUSSION

Among observed studies, ASD is mainly linked to genetic alterations, chromosomal aberrations or may be associated as a characteristic of a syndrome. Some genes appear to be more affected and are categorized according to their chromatin remodeling functionality (ANKRD11, ARID1B, ASXL3, ATRX, AUTS2, DCC2, DCC7, DCC8, CREBBP, EHMT11, MBD5, MECP2, SETD5), transcription factors/regulators (ADNP, FOXG1, FOXP1, FOXP2, MED13L, POGZ, RAI1, TBR1), Mrna trafficking regulators (FMR1, TCF4, ZBTB20), protein modification (CDKL5), cell proliferation (DYRK1A, NF1, PTEN,SYNGAP1, TSC1/TSC2), synaptic architecture and functionality[7,9].

Others that stand out are: Reelin (RELN), via the RhoA and mTOR pathways, and OXTR. RLN is essential for central nervous system (CNS) lamination to occur. The mTOR pathway is responsible for neurodevelopment and neural cutting. The Rhoa pathway, on the other hand, is responsible for the motility and cellular transmission of the cytoskeleton in the CNS[6,8,16]. In addition, the OXTR gene, located on chromosome 3q, acts as a coder for the oxytocin receptor, a hormone with the function of stimulating uterine contractions, lactation, hormone-peptide binding, and intense modulator of behavior (stress, anxiety, binomial relationship between mother and child) and reproductive, popularly cited as the "love hormone" precisely because it increases affective interactions. 2 polymorphic alterations stand out, rs1042778 (G allele, responsible for binding the MAZ transcription factor) and rs53576, with decreased expression of the OXTR gene, favor clinical phenotypes of autism, such as: seizures, aggressive behavior, phobias, difficulty in social interactions[4,15,16].

Recent references demonstrate chromosomal alterations by Microarray analysis with a 2,9-Mb deletion in the 18q22 region, in which the RTTN, SOCS6, CBLN2 genes are located, and the alteration of chromosome 15q24, which has been described as a recurrent genomic imbalance in individuals with ASD and intellectual deficit[4]. The latter is responsible for encoding the neogenin protein in the NEO1 gene. It acts as a membrane receptor and entangled with the communication of the

transmigration of cortical neurons and with axonal orientation[4]. Among other chromosomes that stand out in autism, there are also those with numbers: 1, 2, 3, 7, 16, 17, 22. Grade 17 is characterized as one of the genetic loci most associated with ASD, being investigated more frequently[5,9,12].

A possible connection to the association with ASD would be the mutation of the MTHFR gene (enzyme Methylenetetrahydrofolate reductase). This acts as a fundamental cofactor in the regulation of homocysteine, important in neurological development, acting as a transporter of the methyl group. The MTHFR C677T polymorphism is characterized by missense alteration, where the exchange of thymine for cytosine at the base position 677, consequently occurs the exchange of the amino acid alanine for valine at position 222 of the MTHFR protein. Collaborating to reduce the enzymatic activity of MTHFR (60%), causing an increase in homocysteine (20%), found in the plasma of patients with ASD, in the fasting state. In particular, the presence of the T allele mutation in the MTHFR gene represents a significant percentage of 90% of patients with ASD and increases the risk of developing the disorder by 5 to 20 times[8,12].

Alterations in the GABA-adrenergic system have a very strong relationship with the symptoms presented in autism. Among them are the GABRB3 mutation that acts directly on gamma-aminobutyric acid (GABA), a fundamental neurotransmitter as a CNS inhibitor, being essential in early neural development. This, consequently, favors synaptic dysfunctions and manifests autism phenotypes. Duplications can also be found on chromosome 15q11-q13, associated with paternal duplications or supernumerary isodicentric chromosomes responsible for directly interfering with GABA receptors[3,11].

Much is discussed about frequent syndromes perceived in autism, such as fragile X syndrome and Rett syndrome. In principle, genetic tests are requested in clinical practice in girls with suspected Rett syndrome, and in boys with suspected fragile X syndrome[4,8]. The mutation of the FMR1 gene, located on the X chromosome, causes deficiency of the FMRP protein and impairs gene expression and the formation of brain synapses[10].

Therefore, major impasses in the identification of autism-related genes would be in the analysis of enormous demands for genetic samples and the deficiency of advanced genomic technologies5. Since the lack of specific physical phenotypes and the involvement of different levels of neuropsychomotor involvement, hinder the identification of the disorder. These variables of non-characterization of the disorder

have a direct impact on the daily life of autistic people, in which early support measures are necessary for better development.

CONCLUSION

Autism is mainly involved with genetic alterations and has high heritability rates. However, the insufficiency of effective tests and reliable biological markers to distinguish affected and unaffected individuals make the identification of autistic genes an additional challenge. Linked to this, the presentation of nonspecific physical phenotypes and the involvement of varying degrees of neuropsychomotor involvement make it difficult to identify the disorder.

From this perspective, more research needs to be developed to help in early diagnosis, clinical management, and multiprofessional therapeutic approaches, to offer a better quality of life to this specific audience.

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