Revista ARACÊ
ISSN: 2358-2472

GENETIC CONTRIBUTIONS TO AUTISM SPECTRUM DISORDER: A REVIEW OF RECENT ADVANCES

https://doi.org/10.56238/arev7n3-092

Date of submission: 12/02/2025 **Date of publication:** 12/03/2025

Mariana Oliveira Silva[1], Flávia Melo Rodrigues[2], Marc Alexandre Duarte Gigonzac[3] and Thaís Cidália Vieira Gigonzac[4]

ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with a multifac-torial origin and significant genetic contribution. It is characterized by difficulties in social interaction, communication, and the presence of repetitive behaviors, often associated with comorbidities such as intellectual disability and Attention Deficit Hyperactivity Disorder (ADHD). This integrative review analyzed articles published in the last five years to explore relevant genes related to ASD and neurodevelopment. Genes such as MYT1L, ZNF292, AUTS2, and regulatory genes involved in the production of microRNAs were highlighted, demonstrating their rela-tionship with critical processes such as neurogenesis and synaptogenesis. Genes such as FGFR2 and KMT5B have been strongly associated with neurodevelopmental disorders, including autism and ADHD, underscoring their importance in understanding the genetic basis of these conditions. Additionally, the identification of specific variants, such as PTEN p.Ile135Leu, and their rela-tionship with changes in neurogenesis, neural maturation, and synaptic function highlights the need for more in-depth studies on the molecular pathways regulating these genes expression. The findings reinforce the genetic heterogeneity of ASD and suggest potential targets for personalized therapies within the context of precision medicine. However, the importance of incorporating epigenetic and environmental factors into analyses is emphasized to achieve a more compre-hensive understanding of gene-environment interactions and their clinical implications.

Keywords: Autism Spectrum Disorder. Genetic Heterogeneity. MicroRNAs. Neurodevelopment. Precision Medicine. Regulatory Genes.

[1] Master's Degree in Genetics, Pontifical Catholic University of Goiás, Goiânia, Goiás, Brazil
E-mail: mrnoliveirasilva@gmail.com
[2] Academic Institute of Health and Biological Sciences - IACSB, State University of Goiás (UEG) Master's Degree in Genetics, Pontifical Catholic University of Goiás, Goiânia, Goiás, Brazil
E-mail: rflamelo@gmail.com
[3] Academic Institute of Health and Biological Sciences - IACSB, State University of Goiás (UEG) Master's Degree in Genetics, Pontifical Catholic University of Goiás, Goiânia, Goiás, Brazil
E-mail: m.gigonzac@gmail.com
[4] Academic Institute of Health and Biological Sciences - IACSB, State University of Goiás (UEG) Master's Degree in Genetics, Pontifical Catholic University of Goiás, Goiânia, Goiás, Brazil
E-mail: thaiscidalia@gmail.com

Revista ARACÊ
ISSN: 2358-2472

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, communication, and restricted and repetitive behavioral patterns [1]. Its global prevalence has been increasing, reaching 2.3% in children in the United States in 2018 [2]. Comorbidities such as neurodevelopmental delay (NDD), intellectual disability (ID), and attention-deficit hyperactivity disorder (ADHD) are widely docu-mented among individuals with ASD, illustrating its clinical heterogeneity [3].

Although the origin of ASD involves both environmental and genetic factors, mutations in specific genes, such as those involved in the regulation of brain development and synaptic function, are associated with distinct manifestations of the disorder [4]. These mutations influence the severity of behavioral traits and the presence of comorbidities, such as epilepsy and mood disorders [2].

Advances in genetic sequencing techniques, such as genome-wide association studies (GWAS) and exome sequencing, have enabled the identification of genetic variants that help map the complexity of the clinical spectrum of ASD [5]. These discoveries reveal a multifaceted network of genes associated with neurodevelopment, neuronal communication, and synaptic plasticity, indicating that ASD is a genetically heterogeneous disorder with a direct impact on the observed clinical manifestations [6].

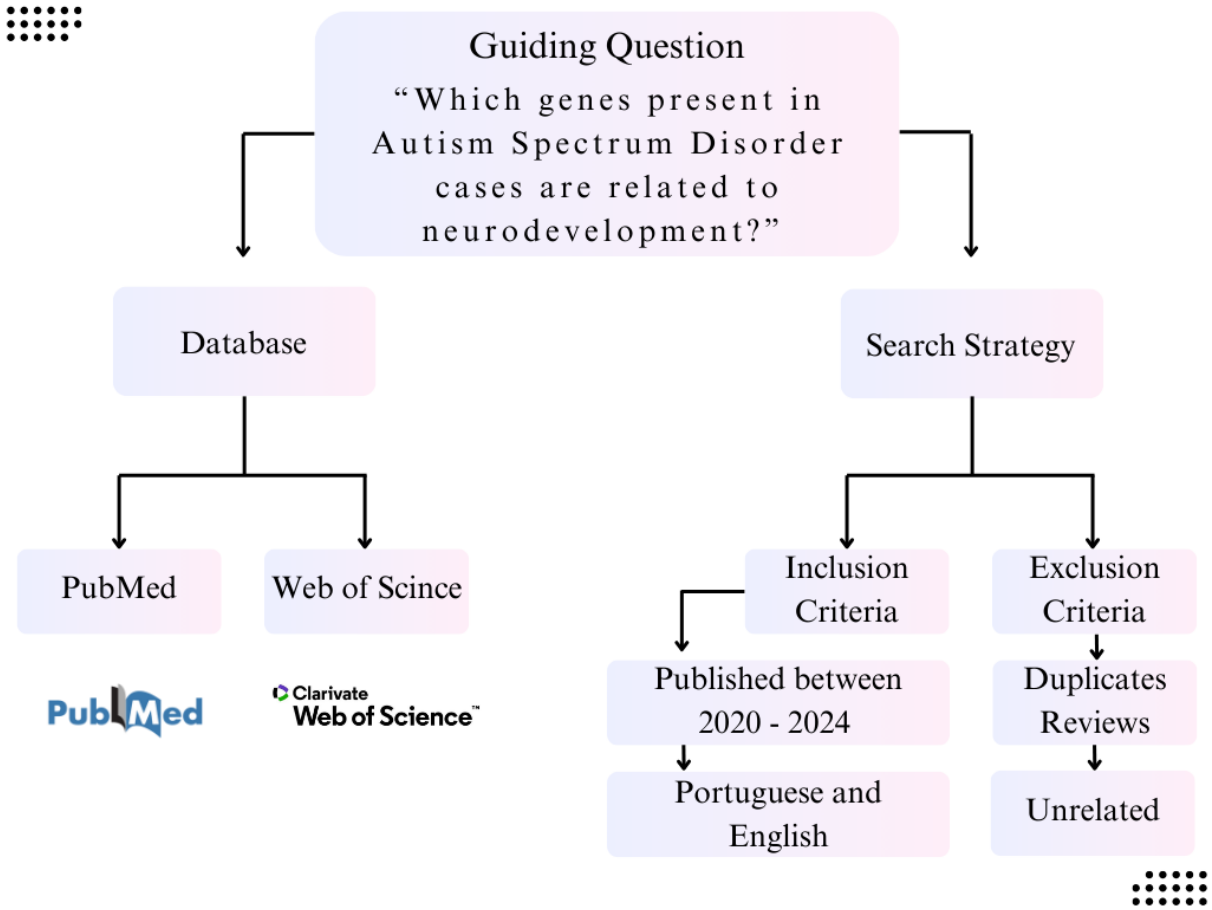
This integrative review aims to explore the main genes associated with ASD and their relationships with neurodevelopment, highlighting how these factors contribute to the varied clinical manifestations of the disorder, based on recent literature.

MATERIALS AND METHODS

The data were obtained through a search conducted in two electronic databases: US National Library of Medicine (PubMed) and Web of Science. The search terms used were combined as follows: “Autism” OR "Autism Spectrum Disorder" OR “ASD” AND “genes” OR "genetic mutation" OR "gene variant" OR "gene expression" AND “neurode-velopment” OR "brain development" OR "neural development." The descriptors were de-fined by the guiding research question: “Which genes present in Autism Spectrum Disor-der cases are related to neurodevelopment?”. Studies published between January 2020 and April 2024, in Portuguese and English, were included. Duplicated articles, narrative and integrative reviews, as well as studies unrelated to the topic, were excluded. (Figure 1)

Revista ARACÊ
ISSN: 2358-2472

Figure 1. Flowchart outlining the guiding question and search strategy, including the selected databases, inclusion, and exclusion criteria.

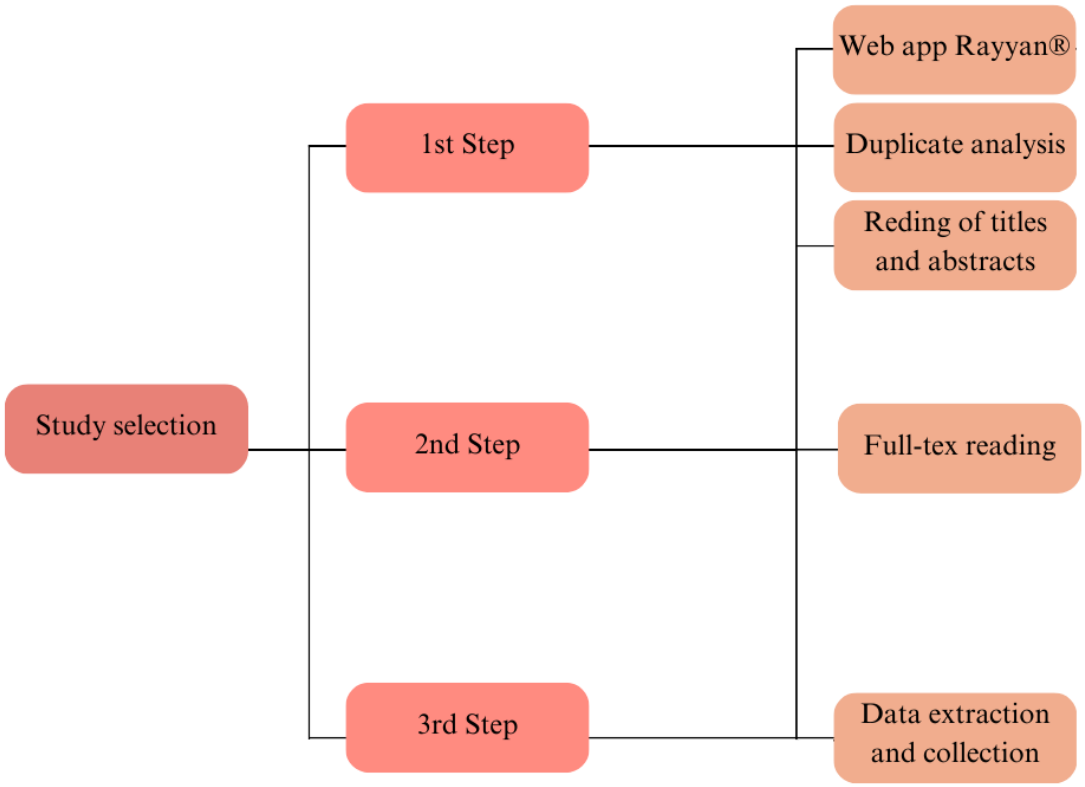


Source: Own authorship.

The study selection process was carried out in three stages. In the first stage, the studies found were submitted to the Web app Rayyan®, where they underwent a dupli-cate check. In the second stage, the titles and abstracts of the articles were read to identify potentially relevant studies. In the third and final stage, the articles that passed the initial screening were read in full to confirm their relevance and inclusion in the review. Data ex-traction was performed after reading the selected articles, identifying genes associated with autism spectrum disorder and neurodevelopment. (Figure 2)

Revista ARACÊ
ISSN: 2358-2472

Figure 2. Flowchart of the study selection process, including duplicate check, title and abstract screening, and full-text reading for inclusion confirmation.



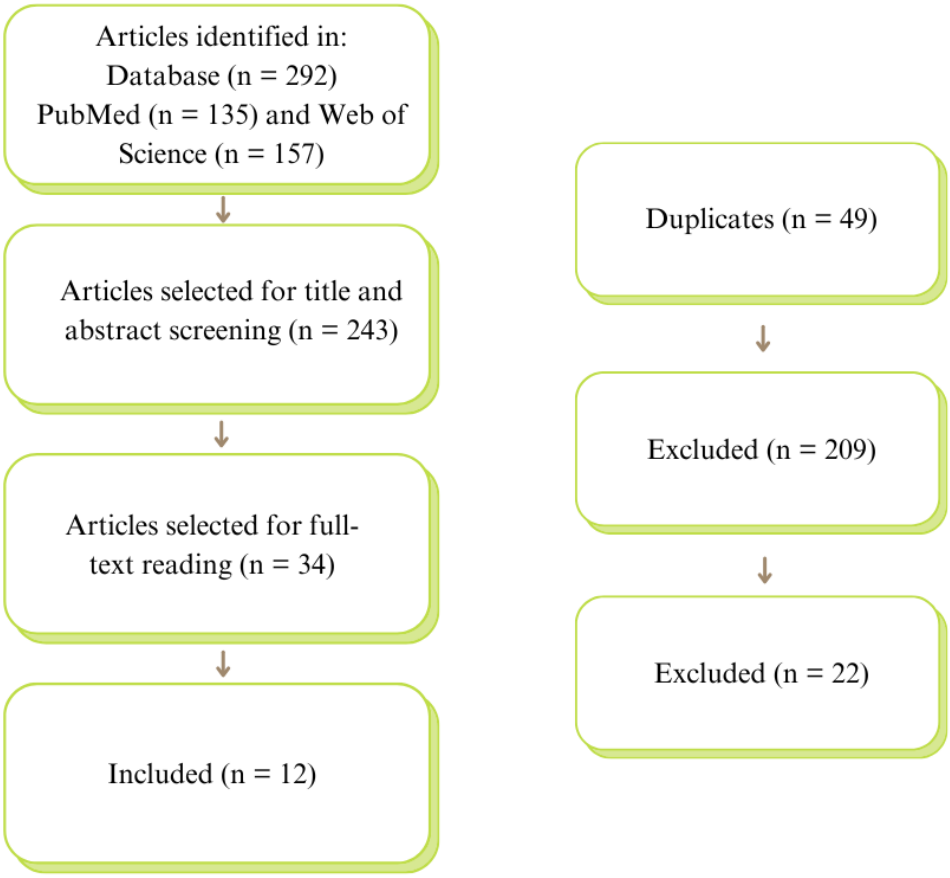
Source: Own authorship.

RESULTS

A total of 292 articles were obtained, distributed as follows: 157 articles from the Web of Science database and 135 articles from the PubMed database. Forty-nine duplicated ar-ticles were excluded. After reading the titles and abstracts, 209 articles were excluded, and 34 remained for the next phase. After the full reading of the selected studies, 12 articles proceeded to the data extraction phase. (Figure 3)

Revista ARACÊ
ISSN: 2358-2472

Figure 3. Flowchart of the article selection process, showing the distribution of 292 articles between Web of Science and PubMed, with 49 duplicates and 209 articles exclud-ed after screening, resulting in 12 articles for data extraction.



Source: Own authorship.

The results reveal significant findings on the proposed topic. In a clinical case analysis, a deleterious variant in the MYT1L gene was identified, associated with autism and intellectual disability (ID), highlighting the importance of genomic analysis through WGS and the rigorous collection of phenotypic data [7]. Additionally, de novo and inherited variants in the ZNF292 gene were associated with a spectrum of neurodevelopmental characteristics, including ID, ASD, and ADHD [4]. (Table 1)

Table 3: Results table of studies on genes associated with neurodevelopment and autism.

Study	Identified Genes	Associations	Functions
Wong et al. (2022)	TUB, SCP2, ONECUT2, OSBPL7, RBM24, UQCC2	Autism Spectrum Disorder (ASD), neurodevelopment	Neuronal signaling, lipid transport, neural differentiation, apoptosis regulation
Hori et al. (2022)	AUTS2	Autism, intellectual disability, ADHD, schizophrenia	Related to neural and psychological disorders
Bruel et al. (2022)	ITSN1	Neurodevelopment and ASD	Present in ASD cases

Revista ARACÊ
ISSN: 2358-2472

van Jaarsveld et al. (2022)	KDM2B	Neurodevelopment and ASD	Found in ASD cases
Yip et al. (2022)	MYT1L	Autism and intellectual disability	Identified deleterious variant, relevant in genomic analysis
Mirzaa et al. (2020)	ZNF292	Intellectual disability, ASD, ADHD	De novo or inherited variants associated with neurodevelopment
Li et al. (2020)	GABRA5, GABRB3, NTN1, SNRPN, OTX1, FOXG1, TSHZ3, CDH8, GABRB3, GATM, HTR2A, DHRS7, NRF2	Autism	Associations with the neural system and autism
Nicotera et al. (2023)	FGFR2	Neurodevelopmental disorders, autism, and ADHD	Associated with ASD and ADHD
Odaka et al. (2023)	KMT5B	Neurodevelopmental disorders, autism, and ADHD	Associated with ASD and ADHD
Feu et al. (2023)	PTEN (variant p.Ile315Leu)	ASD	Accelerated neural maturation, neurogenesis dysregulation, gliogenesis, and synaptic function
Park et al. (2024)	F2RL2, TRIM16L, PANX2	ASD	NRF2 pathway activation, which may impact neurodevelopment
Geng et al. (2024)	AUTS2	Autism, schizophrenia, and ADHD	Related to neural and psychological disorders

Source: Own authorship.

The investigation of genes associated with autism, combined with differential brain expression data, revealed GABRA5, GABRG3, NTM, SNRPN, OTX1, FOXG1, TSHZ3, CDH18, GABRB3, GATM, HTR2A, DHCR7, and NLRP2. All of these genes have associations with the neural system and are linked to autism [8]. (Table 2)

Table 2: Genes with described associations with neurodevelopmental alterations.

Gene	OMIM Code	Genomic Coordinates	Clinical Information
MYT1L	613084	2:1,789,113-2,331,275	DI (Developmental Delay)
ZNF292	616213	6:87,155,565-87,265,943	DI (Developmental Delay)
GABRG5	137190	15:26,994,573-27,074,973	Epilepsy
GABRG3	137192	15:26,971,181-27,541,984	Epilepsy
NTM	607938	11:131,370,615-132,336,822	Congenital Malformations
SNRPN	182279	15:25,799,840-25,807,303	Prader-Willi Syndrome
OTX1	600372	2:63,049,735-63,057,831	Microcephaly
FOXG1	164874	14:28,766,787-28,770,277	Microcephaly
TSHZ3	614427	19:31,149,876-31,350,877	Anxiety
CDH18	603019	5:19,471,296-20,575,713	ADNPM (Developmental Disorder)
GABRB3	137192	15:26,514,275-26,986,768	Epilepsy
GATM	602360	15:45,361,124-45,402,227	Neuro-muscular Disorder
HTR2A	182135	13:46,831,546-46,898,082	Schizophrenia, Depression, OCD
DHCR7	602858	11:71,427,287-71,449,043	Smith-Lemli-Opitz Syndrome

Revista ARACÊ
ISSN: 2358-2472

NLRP2	609364	19:54,965,284-55,001,138	Neuroinflammation

Source: Own authorship.

Additionally, genes associated with the production of microRNAs (miRNAs), a class of small non-coding RNAs that play a regulatory role in post-transcriptional gene expres-sion, have been identified. These miRNAs influence various molecular pathways, includ-ing those related to neurodevelopment and neuromodulation . Among the key genes highlighted are TUB, SCP2, ONECUT2, OSBP, RBM24, and UGCG, with implications for ASD (Autism Spectrum Disorder) and neurodevelopmental processes. (Table 3)

Table 3: Regulatory genes associated with neurodevelopmental disorders. WLI (Written Language Impairment), ADHD (Attention Deficit Hyperactivity Disorder), SRI (Social Response Impairment), OLI (Oral Language Impairment).

Gene	Location	Neurodevelopmental Consequences	Inheritance
TUB	11p15.4	WLI	Dominant
SCP2	1p32.3	WLI, ADHD	Dominant
ONECUT2	18q21.31	SRI	Dominant
OSBP	11q12.1	WLI	Dominant
RBM24	6q22.3	ADHD, OLI	*De novo*
UGCG	9q31.3	WLI, OLI	Dominant

Source: Own authorship.

DISCUSSION

The findings of this review reinforce the central role of genetics in understanding Au-tism Spectrum Disorder (ASD). Genes such as FGFR2 and KMT5B, highlighted by Nicotera et al. [6] and Odak et al. [9] , are strongly associated with neurodevelopmental disor-ders like ASD and ADHD, underscoring their relevance for understanding the genetic ba-sis of these disorders. The association of specific variants, such as the PTEN p.Ile135Leu variant, with alterations in neurogenesis, neural maturation, and synaptic function, as reported by Fu et al. [10] and Park et al. [11], points to the importance of detailed mecha-nistic studies. These findings suggest that the dysregulation of essential processes such as neurogenesis and gliogenesis may significantly contribute to the clinical variability ob-served in ASD.

Furthermore, the identification of mutations in the AUTS2 locus and genes like ITSN1 and KDM2B reinforces the complexity of the molecular mechanisms of ASD, linking them not only to neurodevelopment but also to other conditions such as schizophrenia and ADHD [12–15]. The identification of new candidate genes for ASD, especially those related to post-transcriptional regulation, such as microRNAs (TUB, SCP2, UGCG, among others), enhances our understanding of the molecular networks involved. These non-coding RNAs

Revista ARACÊ
ISSN: 2358-2472

play critical roles in modulating neural differentiation, apoptosis, and neuronal signaling, emerging as potential therapeutic targets [16].

The use of specialized databases was essential for consolidating the findings of this review. OMIM (Online Mendelian Inheritance in Man) is a comprehensive database that gathers information about genes and their relationships to genetic conditions, serving as an indispensable tool for identifying genes associated with ASD. ClinVar, in turn, pro-vides detailed information about the clinical significance of genetic variants, facilitating the correlation between mutations and their clinical impacts. NCBI (National Center for Biotechnology Information) was widely used for genomic sequence consultation and lo-cus analysis, while Decipher proved to be fundamental in investigating rare variants and their associations with specific phenotypes. These resources not only centralize critical information but also enable integrative analyses, contributing to the robustness of the con-clusions drawn.

The data presented highlight that specific genetic variants play a central role in the development of ASD, with implications extending beyond diagnosis, offering insights for new therapeutic approaches. The integration of genomic information with emerging technologies, such as cortical organoids and gene-editing studies, may represent a signif-icant advance in the field. The relevance of genes related to neurodevelopment, as well as pathways regulated by miRNAs, emphasizes the need for further exploration of the mo-lecular mechanisms of ASD, focusing on targeted interventions.

CONCLUSION

The presented review demonstrates the genetic complexity of Autism Spectrum Dis-order, revealing important genes such as MYT1L, ZNF292, AUTS2, PTEN, and genes re-lated to regulation by microRNAs, all linked to key neurodevelopmental processes such as neurogenesis, synaptogenesis, and neuronal regulation.

The selection of relevant studies, highlighting the diversity of molecular mechanisms contributing to ASD, from specific deleterious variants to dysregulation in gene expres-sion, has expanded the knowledge of genetic factors associated with neurodevelopment. However, the analysis could benefit from greater integration with epigenetic and envi-ronmental factors, enhancing the understanding of gene-environment interactions. De-spite this, the findings provide a solid foundation for the development of new therapeutic approaches, pointing to genes and molecular pathways as potential targets for personal-

Revista ARACÊ
ISSN: 2358-2472

ized clinical strategies, reflecting the relevance of genomics in advancing precision medicine in the field of neurodevelopment.

Revista ARACÊ
ISSN: 2358-2472

REFERENCES

1.Pavinato L, Vedove AD, Carli D, et al. CAPRIN1 haploinsufficiency causes a neurodevelopmental disorder with language impairment, ADHD and ASD. *Brain : a journal of neurology*. 2023;146(2):534-548. doi:10.1093/BRAIN/AWAC278

2.Li H, Zhang Q, Wan R, et al. PLPPR4 haploinsufficiency causes neurodevelopmental disorders by disrupting synaptic plasticity via mTOR signalling. *Journal of cellular and molecular medicine*. 2023;27(21):3286-3295. doi:10.1111/JCMM.17899

3.Takahashi N, Harada T, Nishimura T, et al. Association of Genetic Risks With Autism Spectrum Disorder and Early Neurodevelopmental Delays Among Children Without Intellectual Disability. *JAMA network open*. 2020;3(2). doi:10.1001/JAMANETWORKOPEN.2019.21644

4.Mirzaa GM, Chong JX, Piton A, et al. De novo and inherited variants in ZNF292 underlie a neurodevelopmental disorder with features of autism spectrum disorder. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*. 2019;22(3):538-546. doi:10.1038/S41436-019-0693-9

5.Deng J, Wang Y, Hu M, et al. Deleterious Variation in BR Serine/Threonine Kinase 2 Classified a Subtype of Autism. *Frontiers in Molecular Neuroscience*. 2022;15:904935. doi:10.3389/FNMOL.2022.904935/FULL

6.Nicotera AG, Amore G, Saia MC, et al. Fibroblast Growth Factor Receptor 2 (FGFR2), a New Gene Involved in the Genesis of Autism Spectrum Disorder. *Neuromolecular medicine*. 2023;25(4):650-656. doi:10.1007/S12017-023-08759-W

7.Yip S, Calli K, Qiao Y, Trost B, Scherer SW, Lewis MES. Complex Autism Spectrum Disorder in a Patient with a Novel De Novo Heterozygous MYT1L Variant. *Genes*. 2023;14(12). doi:10.3390/GENES14122122

8.Li J, Lin X, Wang M, et al. Potential role of genomic imprinted genes and brain developmental related genes in autism. *BMC Medical Genomics*. 2020;13(1):1-13. doi:10.1186/S12920-020-0693-2/TABLES/4

9.Odak L, Vulin K, Meašić AM, Šamadan L, Batoš AT. Neurodevelopmental disorder caused by an inherited novel KMT5B variant: case report. *Croatian Medical Journal*. 2023;64(5):334. doi:10.3325/CMJ.2023.64.334

10.Fu S, Bury LAD, Eum J, Wynshaw-Boris A. Autism-specific PTEN p.Ile135Leu variant and an autism genetic background combine to dysregulate cortical neurogenesis. *American journal of human genetics*. 2023;110(5):826-845. doi:10.1016/J.AJHG.2023.03.015

11.Park HR, Azzara D, Cohen ED, et al. Identification of novel NRF2-dependent genes as regulators of lead and arsenic toxicity in neural progenitor cells. *Journal of hazardous materials*. 2024;463. doi:10.1016/J.JHAZMAT.2023.132906

Revista ARACÊ
ISSN: 2358-2472

12.Bruel AL, Vitobello A, Thiffault I, et al. ITSN1: a novel candidate gene involved in autosomal dominant neurodevelopmental disorder spectrum. *European journal of human genetics : EJHG*. 2022;30(1):111-116. doi:10.1038/S41431-021-00985-9

13.Geng Z, Tai YT, Wang Q, Gao Z. AUTS2 disruption causes neuronal differentiation defects in human cerebral organoids through hyperactivation of the WNT/β-catenin pathway. *Scientific Reports 2024 14:1*. 2024;14(1):1-13. doi:10.1038/s41598-024-69912-4

14.Hori K, Shimaoka K, Hoshino M. AUTS2 Gene: Keys to Understanding the Pathogenesis of Neurodevelopmental Disorders. *Cells 2022, Vol 11, Page 11*. 2021;11(1):11. doi:10.3390/CELLS11010011

15.Jaarsveld RH van, Reilly J, Cornips MC, et al. Delineation of a KDM2B-related neurodevelopmental disorder and its associated DNA methylation signature. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2023;25(1):49-62. doi:10.1016/J.GIM.2022.09.006

16.Wong A, Zhou A, Cao X, et al. MicroRNA and MicroRNA-Target Variants Associated with Autism Spectrum Disorder and Related Disorders. *Genes*. 2022;13(8). doi:10.3390/GENES13081329