International Journal of Innovative Research and Scientific Studies, 9(1) 2026, pages: 91-97

IJIRSS
International Journal of Innovative Research & Scientific Studies

ISSN: 2617-6548

URL: www.ijirss.com

Autism spectrum disorder throughout history: Paleogenetic analysis

Milen Zamfirov[1,2*], Dimitar Kenanov[3]

[1]*Department of Special Education, Faculty of Educational Studies and Arts Sofia University "St. Kliment Ohridski", Bulgaria.*
[2]*Center with an Autism Research Laboratory, Faculty of Educational Studies and Arts Sofia University "St. Kliment Ohridski", Bulgaria.*
[3]*Bioinformatics Institute, Agency for Science, Technology and Research, Singapore, Republic of Singapore.*

Corresponding author: Milen Zamfirov (*Email: mzamfirov@uni-sofia.bg*)

Abstract

This article provides a brief historical overview of the earliest publications on autism spectrum disorder and the subsequent scientific discussions. The main focus is on the analysis of data on genes that have been confirmed to be associated with this condition. The aim of the study is to demonstrate, by processing data from sequenced human genomes obtained from various databases. Methods used in the analysis: Data on missense SNPs for 1230 genes from SFARI GENE were extracted. Then a search was performed for matches in David Reich's Lab (provides genotypes and single nucleotide polymorphisms (SNPs). The matches found were compiled into a table using a custom Perl script. In the article we show that analysis of gene mutations through the paleogenetic approach is a method that can also be employed for other disorders with unknown etiology.

Keywords: Autism spectrum disorder, Databases, Genetic factors, Human genetic variation, Paleogenetics.

DOI: 10.53894/ijirss.v9i1.11173
Funding: This study is financed by the European Union - NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG- RRP-2.004-0008-SUMMIT-3.3.
History: Received: 20 November 2025 / **Revised:** 31 December 2025 / **Accepted:** 5 January 2026 / **Published:** 14 January 2026

Competing Interests: The authors declare that they have no competing interests.
Authors' Contributions: All authors contributed equally to the conception and design of the study. All authors have read and agreed to the published version of the manuscript.
Transparency: The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.
Publisher: Innovative Research Publishing

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental impairment that starts in early childhood and is characterized by communication deficits, abnormal social interaction, restricted interests, and repetitive behavioral patterns [1]. The mechanisms underlying ASD have been the subject of intense study and debate for decades. Common atypical behaviors and symptoms appear in all individuals with autism, but it has not been resolved how its pathogenesis is related to the formation of structural and metabolic abnormalities in the brain. Although its comprehensive etiopathogenesis is unresolved, ASD is considered to be a multifactorial disorder caused by combinations of genetic, epigenetic, and

environmental factors [2]. Brain developmental processes, such as cell proliferation, migration, differentiation, synaptogenesis, and myelination, are sensitive to damage caused by various environmental factors [3].

Autism Spectrum Disorder (ASD) is a common genetically based neurobehavioral disorder in which epigenetic and environmental factors are involved [4].

Children with ASD regularly experience social anxiety within various interactive scenarios.

The diagnostic profiles of children with autism spectrum disorder (ASD) reveal a spectrum of challenges that underscore the complexity of their educational requirements. Most notably, communication deficits manifest through limited social engagement and difficulties in comprehending verbal cues, necessitating individualised interventions tailored to each child's unique profile [5]. These profiles often highlight a reliance on specific support frameworks.

Comorbid psychiatric and behavioral disorders are common in individuals with ASD, including ADHD, mood disorders, anxiety, obsessive compulsive disorder, irritability, aggression, substance use disorders, self-injurious behaviors, gender dysphoria, suicidality, psychosis, catatonia, and schizophrenia spectrum disorders [6]. Currently, the diagnostics of ASD are symptomatic and according to the 5th edition of Diagnostic and Statistical Manual of MentalDisorders, it belongs to the group of neurodevelopmental disorders (NDDs) [7]. In the present medical nomenclature, ASD covers several NDDs: autism, atypical autism, Asperger's syndrome, and a pervasive developmental disorder not other-wise specified

The heterogeneity observed in social interactions indicates not only a need for targeted language development programs but also emphasizes fostering emotional regulation and cognitive skills, which are critical for academic achievement [8].

Since 1943, when Kanner [9] 'Autistic disturbances of affective contact', autism has been a subject of ongoing interest for 83 years [9].

Autism spectrum disorders (ASD) are observed in all racial, ethnic, and socioeconomic groups [10].

Over the years, the various symptoms that characterise this disorder have been defined quite clearly, yet one of the most intriguing questions for scientists and most distressing for parents, namely what causes autism, remains unanswered.

From a psychological point of view, the usual good practices are recommended for children with autism [11] which are supposed to result in effective adaptation of educational content within the framework of inclusive education [12] e.g., implementation of more visual support, which has been demonstrated to be effective in education, as well as development of effective language models, or social models.

Damyanov [12] identifies and describes some effective strategies that would be adequate for the improvement of the education system for students with SEN, including those with autism, which would also support the reduction of burnout among teachers [13]. Social anxiety can be especially noticeable in children with autism spectrum disorder (ASD)

Kanner [9] himself, in the conclusion of his study and description of the characteristics of children with autism, suggests that the possible cause may be due to problems in the family: "Even some of the happiest marriages are quite cold and formal. Three of the marriages are completely unsuccessful. The question arises whether or to what extent this fact has contributed to the condition of the children [9].

Despite the fact that Kanner [9] has been careful in his assumption and did not advance it as a definitive hypothesis, this did not prevent subsequent researchers from turning it into the main version of the cause and manifestation of autism symptoms in children.

In fact, the main contribution to the enforcement of the idea of the 'refrigerator mother' is not Kanner's, but Bruno Bettelheim's.

In 1959, Scientific American published his article Joey, A 'Mechanical Boy' [14], in which he described a boy who had become autistic due to a lack of maternal affection and had therefore developed a keen interest in machines, to the point of 'becoming a machine himself'.

Bettelheim stated that, thanks to his work, this boy succeeded to adapt to the other children.

Although Kanner [15] had remained cautious in his initial assessment of parental influence as a cause of autism in 1943, he took a more definitive stance on the matter in one of his subsequent articles, published in 1949: Problems of nosology and psychodynamics of early infantile autism [15].

It makes no sense to dwell on the whole story behind this idea, we can only mention that the idea of 'cold mothers' as a hypothesis had been circulating for many years and had left its stamp on many families around the world.

This brings us to one of the main questions being asked regarding autism, and one that provokes the greatest amount of discussion: what are the roots of the developmental condition known as autism? The answers vary, ranging from heredity and cold mothers to the environmental impact.

According to Pacheva [16] the etiology and pathogenesis of idiopathic autism, despite the numerous studies, remain unclear, with all kinds of hypotheses being considered-a combination of genetic factors, epigenetic factors, and the environment [16].

It can be assumed that the increasing number of children with autism is due to the decreasing number of children with mental retardation, but this is the way in which children with undifferentiated autism have been misdiagnosed.

The prevalence rate of Autism Spectrum Disorder (ASD) has reached over 1% world-wide prompting governments, health providers and schools to develop programs and policies to address this challenging disorder [2].

Neurodevelopment has been studied extensively, especially in respect to abuse, anoxia, nutritional status and prematurity/low birth weight. However, less attention has been paid to innate and environmental factors, as well as to inflammatory conditions that may adversely affect neurodevelopment and learning in children [3].

Common early signs and symptoms of ASD in a child's first 2 years of life include: no response to name when called, no or limited use of gestures in communication, and lack of imaginative play [1].

Understanding these characteristics is essential for recognizing the unique experiences of children with ASD, particularly as they navigate social landscapes that may evoke anxiety or reinforce introverted tendencies.

Regardless of the discussions to date, the causes of autism are not fully understood,they range from cold mothers to severe food allergies, folic acid, genetic components, etc. The lack of certainty has led to numerous unscientific theories about the causes of autism, such as vaccination or paracetamol.

In any case, these hypotheses, put forward in various publications, are incorrect, but thanks to this, discussions have been ongoing, regardless of the acrimony with which the authors have defended their ideas.

Such an understanding is critical for clinicians and researchers to make informed decisions about the direction of future research and practice.

2. Paleogenetic Analysis

There are various theories about the origin of autism, some of which are extremely misleading as discussed in previous section of this work. This has not gone unnoticed by researchers in various countries who are focusing on paleogenetic analysis to find explanations for the etiology of autism.

Prakash and Banerjee [17] for example, conducted a comparative analysis of ancient genomes with the aim of identifying their evolutionary patterns related to the evolution of autism, with the analysis of the ancient genome identifying conservative evolutionary selection clusters involved in cognitive function [17].

Esteller-Cucala, et al. [18] in their study related to Hyperactivity and Attention Deficit Disorder (HADD), which is part of the group of neurodevelopmental disorders, along with autism, propose several hypotheses to explain this disorder, mainly in the context of cultural change between the Paleolithic and Neolithic periods Esteller-Cucala, et al. [18]. Mozzi, et al. [19] in their study on Neanderthal introgressions, analyse human populations, apes, and genomic information on vertebrates to describe the evolution of two gene modules involved in neurodevelopmental disorders.

Pauly, et al. [20] consider the potential roles that Neanderthal single nucleotide polymorphisms (SNPs) may play in the predisposition to autism.

All of this suggests that the approach to seeking the causes of the mechanism of autism is relevant and contemporary, and that studies of ancient genomes to explain various disorders whose origins remain unclear have their place.

3. Practical Rationale

Research aim: The aim of the research is to demonstrate, based on sequenced human genome data from various databases, that genetic mutations associated with autism have existed long before Kanner [9] systematization of the condition in 1943, thereby demystifying some of the conspiracy theories based primarily on misinformation.

4. Methods, Research Data, and Workflow

4.1. Data Used for the Analysis

David Reich Lab data v54.1.p1 (Dataverse 8.0, March 6, 2023). Provides genotypes and single nucleotide polymorphisms (SNPs) [21] for ancient and modern individuals for up to 1.23 million positions in the human genome (coordinates hg19) [22].

NCBI dbSNP. Provides information on SNPs [23] and their annotation [24, 25]

NCBI ClinVar Provides clinical data [26] on human genetic variations [27]. SFARI GENE. Data on genes and their [28] relationship to autism [29].

5. Methods Used in the Analysis

5.1. dbSNP

Data on missense SNPs for 1230 genes from SFARI GENE were extracted. A comparison was made to identify which of these genes correspond to SFARI category 1 (235 genes). Then a search was performed for matches in Reich's data. The matches found were compiled into a table using a custom Perl script.

5.2. Workflow

- Extracting all gene names from SFARI GENE.
- Extracting data for these genes from dbSNP using a custom Perl script that utilizes Entrez eutils, specifically esearch.fcgi (https://www.ncbi.nlm.nih.gov/books/NBK25501).
- It was also necessary the period/era of each subject to be determined. ChatGPT was used to assist with the following classification [30]:

Table 1.
Period/era.

Era	From year	To year
Palaeolithic (or Old *Stone Age)*	-3 400 000	-10 000
Mesolithic (or *Middle Stone Age*	-10 001	-7 000
Neolithic (or New *Stone Age)*	-7 001	-3 300
Bronze Age	-3 301	-1 200
Iron Age	-1 201	500
Middle Ages	501	1500

- Each RSID was compared with Reich's data. Matches were collected and transformed into the final tabular format using a Perl script.

6. Data Analysis

Various research teams use the publicly available online database [31] to download, process, analyse, and publish data. The database currently contains a large number of genes. The available genes are grouped into the following categories:

- Genes established as being associated with autism, developing alongside other diseases affecting the body (so-called syndromic genes);
- Genes confirmed to be associated with autism;
- Genes 'suspected' of possibly being associated with autism;
- Genes of unclear significance.

Thus, 35 genes were systematized, established as related to autism and 'suspected' of of being possibly involved for the mechanism of autism.

Table 2.
Distribution of gene mutations by period/era.

Era	Palaeolithic	Mesolithic	Neolithic	Bronze Age	Iron Age	Middle Ages
Women	55	137	1102	2331	2019	1628
Men	119	162	1328	2702	2406	2206
Unspecified	5	4	16	84	39	46
Total	179	303	2446	5117	4464	3880

Table 2 presents the distribution of gene mutations by gender during different eras – Palaeolithic, Mesolithic, Neolithic, Bronze Age, Iron Age, and Middle Ages. One row has been added for gender that cannot be determined. Given the extremely low values in this row, it can be assumed that the data cannot be distorted.

Figure 1 illustrates that the highest values are recorded during the Bronze Age (period from -3,301 to -1,200) - 5117 results, followed by the Iron Age (from -1201 to 500) with 4464 results, the Middle Ages (from 501 to 1500) with 3880 results, and the Neolithic (from -7001 to -3300) with 2446 results. The Palaeolithic and Mesolithic periods have the lowest results, with 179 and 303 subjects, respectively.

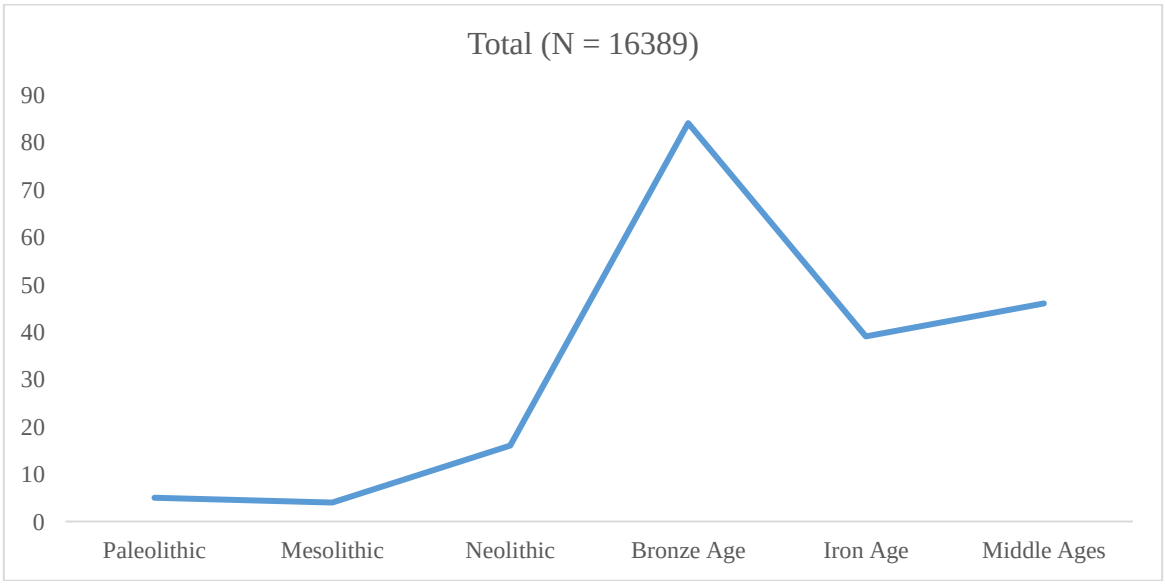

Figure 1.
General data for the periods.

Completely identical distributions are also reported in Figures 2 and 3 which refer to gender – men and women.

For women Figure 2 the highest values are recorded during the Bronze Age and Iron Age (2331 and 2019 totals), while the lowest are again during the Palaeolithic and Mesolithic periods, with 55 and 137 totals, respectively.

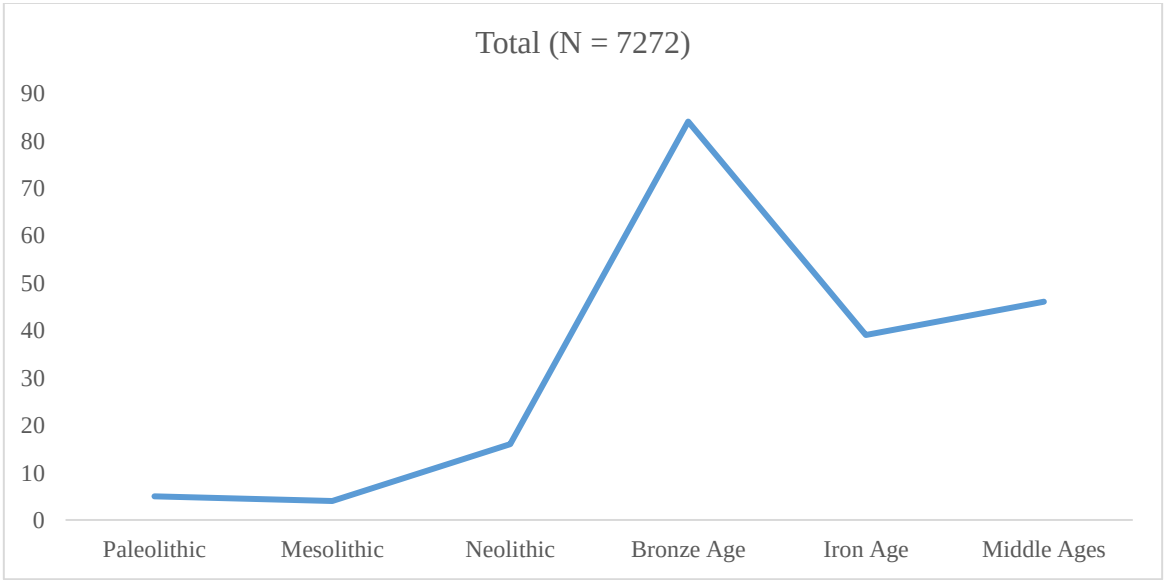

Figure 2.
Data by gender – women.

For males - 2702 and 2406 for the Bronze Age and Iron Age, respectively, and 119 and 162 totals for the Paleolithic and Mesolithic periods.

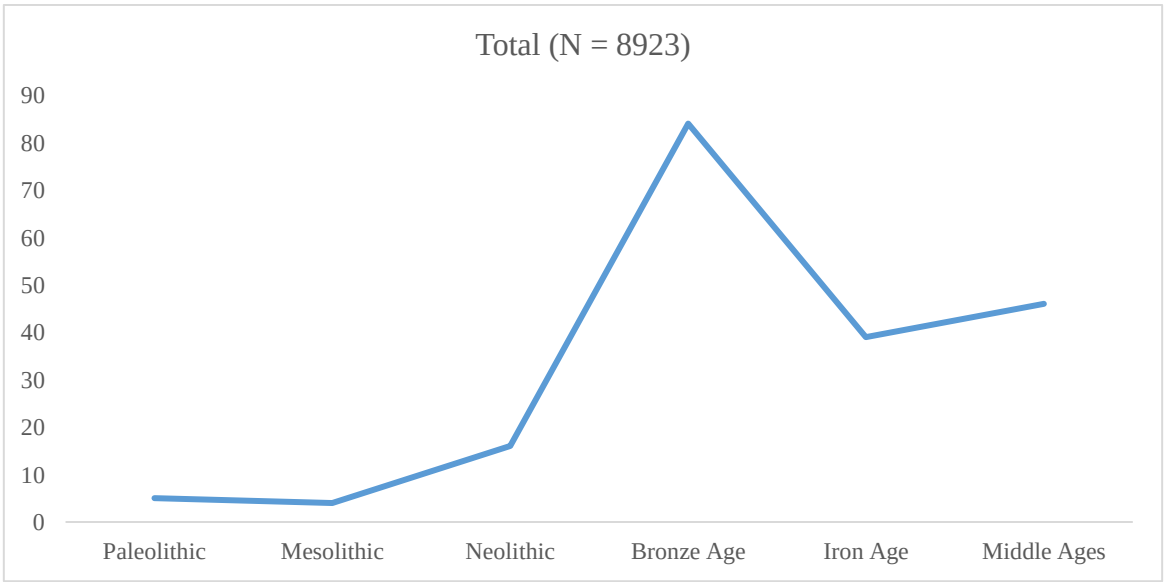

Figure 3.
Data by gender – men.

For unspecified gender data, the general trends are followed, with the exception of the differences between the Iron Age and the Middle Ages, where the ranks are rearranged.

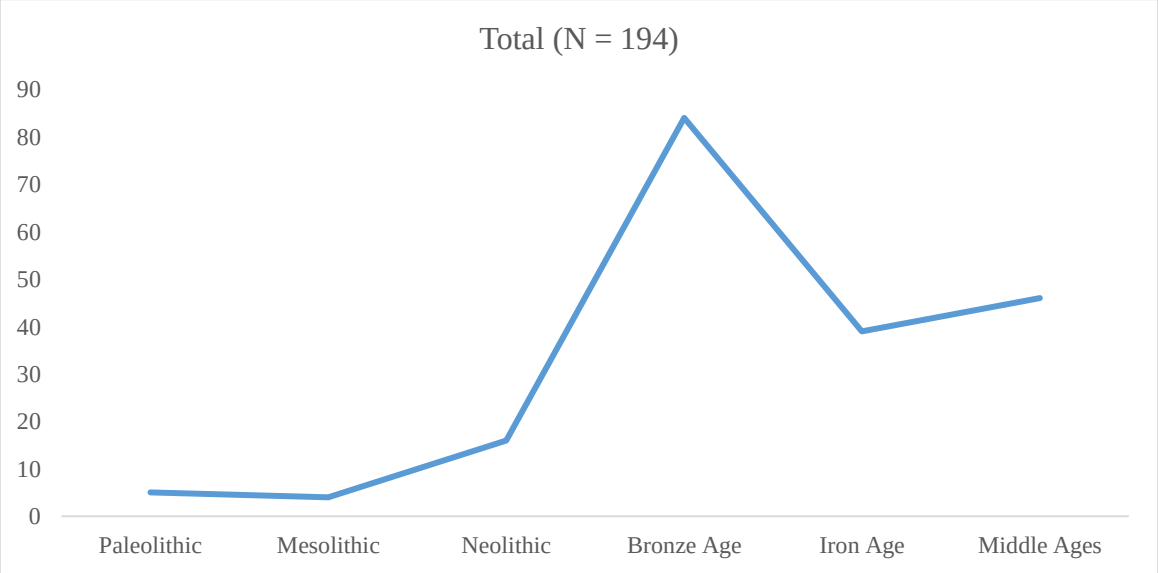

Figure 4.
Data by gender – unspecified.

Something else is worth noting. The literature references a gender ratio in relation to autism, where it is assumed that the prevailing ratio is in favour of males over females by a ratio of two to one [32] while another study indicates that the ratio of boys to girls with autism in a population study in Finland is 3.5:1 [33].

Our study, however, reveals different values. The gender ratio is not statistically significant, nor is it even percentage-wise significant. For example, at the highest values in the Bronze and Iron Ages, the ratio is not even 2:1, but 1.19 in favour of men in the Iron Age, 1.15 in the Bronze Age, and at the lowest values in the Palaeolithic and Mesolithic, they are 2.16 and 1.18, respectively.

This shows that the hypotheses about the prevailing ratio of men to women in genetic mutations are not confirmed, as the lines are almost identical.

7. Conclusion

The mechanism of autism is still unclear, and so far only inductive conclusions can be drawn about what does not cause this disorder.

The study confirms that hypotheses related to vaccines, cold mothers, paracetamol, etc., are not relevant.

It also refutes the claim that there is a ratio where the male profile predominates by 2 to 3 to 1. The data show that this ratio is not accurate, as autism is more common in boys, but the ratio is insignificant.

Overall, understanding diagnostic profiles is crucial for developing long-term support strategies to enhance the educational outcomes and social adaptation of children with ASD [8]

In conclusion, analysis of gene mutations through the paleogenetic approach is a method that can also be employed for other disorders with unknown etiology.

References

[1] T. Hirota and B. H. King, "Autism spectrum disorder: A review," *Jama*, vol. 329, no. 2, pp. 157-168, 2023. https://doi.org/10.1001/jama.2022.23661

[2] M. Styles *et al.*, "Risk factors, diagnosis, prognosis and treatment of autism," *Frontiers in Bioscience-Landmark*, vol. 25, no. 9, pp. 1682-1717, 2020. https://doi.org/10.2741/4873

[3] T. Theoharides, M. Kavalioti, and R. Martinotti, "Factors adversely influencing neurodevelopment," *Journal of Biological Regulators and Homeostatic Agents*, vol. 33, no. 6, pp. 1663-1667, 2019.

[4] M. Zamfirov, L. Belenska-Todorova, T. Todorov, and A. Todorova, "A low pass whole-genome sequencing revealed copy number variations in 7 out of 33 bulgarian patients having neurodevelopmental disorders with features of autism spectrum disorder," *Journal of Family Medicine and Primary Care April*, vol. 9, no. 1, pp. 1-5, 2025. https://doi.org/10.29011/2688-7460.100279

[5] T. Bagetti, V. S. d. Nascimento, G. G. d. Silva, and R. S. Lima, "Linguistic profile of children with language and speech disorders and family participation in the therapeutic process: An integrative literature review," *Revista CEFAC*, vol. 25, no. 3, p. e2623, 2023. https://doi.org/10.1590/1982-0216/20232532623

[6] A. Genovese and M. G. Butler, "The autism spectrum: Behavioral, psychiatric and genetic associations," *Genes*, vol. 14, no. 3, p. 677, 2023. https://doi.org/10.3390/genes14030677

[7] American Psychiatric Association, *Diagnostic and statistical manual of mental disorders*. Arlington, TX, USA: American Psychiatric Association, 2022.

[8] M. Zamfirov, M. Bakracheva, K. Damyanov, L. Belenska-Todorova, and P. Daskalova-Petkova, "Screening tool facilitating mainstream school practitioners to assess educational needs of children with autism spectrum disorders: The bulgarian case," *International Journal of Cognitive Research in Science, Engineering and Education*, vol. 13, no. 3, pp. 793-810, 2025. https://doi.org/10.23947/2334-8496-2025-13-3-563-835

[9] L. Kanner, "Autistic disturbances of affective contact," *Nervous Child*, vol. 2, no. 3, pp. 217-250, 1943.
[10] H. Ivanov, V. Stoyanova, N. Popov, T. Vachev, R. Yordanova, and I. Ivanov, "Genetics of autism spectrum disorder," presented at the In Pediatric Aspects of Autism in the Light of Evidence-based Medicine: Reports from the Second Multifaceted Conference on Child Development (pp. 39–59). Plovdiv, Bulgaria, 2015.
[11] M. Mihaylova *et al.*, *Response time for contour detection and reading in children and adolescents with autism spectrum disorder*. Singapore: Springer Nature Singapore, 2022.
[12] K. Damyanov, "Preparing teachers for adapting educational content for preschool children with special educational needs within the framework of inclusive education," *Special Education and Speech and Language Therapy Journal*, vol. 7, no. 1, pp. 36-49, 2023.
[13] M. Tsenov, "Emotional intelligence as a personality trait, and humor styles effect on teacher burnout," presented at the 16th International Conference on Education and New Learning Technologies, 2024.
[14] B. Bettelheim, "Joey: A mechanical boy," *Scientific American*, vol. 200, no. 3, pp. 116–127, 1959.
[15] L. Kanner, "Problems of nosology and psychodynamics of early infantile autism," *American journal of Orthopsychiatry*, vol. 19, no. 3, pp. 416–426, 1949.
[16] I. Pacheva, "Autism – etiology and pathogenesis: Hypotheses and evidence," presented at the Pediatric Aspects of Autism in the Light of Evidence-based Medicine: Reports from the Second Multifaceted Conference on Child Development (pp. 69–82). Plovdiv, Bulgaria, April 3–4, 2015.
[17] A. Prakash and M. Banerjee, "Genomic selection signatures in autism spectrum disorder identifies cognitive genomic tradeoff and its relevance in paradoxical phenotypes of deficits versus potentialities," *Scientific Reports*, vol. 11, p. 10245, 2021. https://doi.org/10.1038/s41598-021-89798-w
[18] P. Esteller-Cucala *et al.*, "Genomic analysis of the natural history of attention-deficit/hyperactivity disorder using Neanderthal and ancient Homo sapiens samples," *Scientific Reports*, vol. 10, p. 8622, 2020. https://doi.org/10.1038/s41598-020-65322-4
[19] A. Mozzi, D. Forni, R. Cagliani, U. Pozzoli, M. Clerici, and M. Sironi, "Distinct selective forces and Neanderthal introgression shaped genetic diversity at genes involved in neurodevelopmental disorders," *Scientific Reports*, vol. 7, p. 6116, 2017. https://doi.org/10.1038/s41598-017-06440-4
[20] R. Pauly, L. Johnson, F. A. Feltus, and E. L. Casanova, "Enrichment of a subset of Neanderthal polymorphisms in autistic probands and siblings," *Molecular Psychiatry*, vol. 29, no. 11, pp. 3452-3461, 2024. https://doi.org/10.1038/s41380-024-02593-7
[21] S. Mallick *et al.*, "The Allen Ancient DNA Resource (AADR) a curated compendium of ancient human genomes," *Scientific Data*, vol. 11, p. 182, 2024. https://doi.org/10.1038/s41597-024-03031-7
[22] Harvard Dataverse, "The allen ancient DNA resource (AADR): A curated compendium of ancient human genomes," 2025. https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/FFIDCW&version=8.0
[23] L. Phan *et al.*, "The evolution of dbSNP: 25 years of impact in genomic research," *Nucleic Acids Research*, vol. 53, no. D1, pp. D925-D931, 2025. https://doi.org/10.1093/nar/gkae977
[24] D. F. Sherry, "Neuroecology," *Annual Review of Psychology*, vol. 57, no. 2006, pp. 167-197, 2006.
[25] National Center for Biotechnology Information, "dbSNP: Short genetic variations database," 2025. https://www.ncbi.nlm.nih.gov/snp
[26] M. J. Landrum *et al.*, "ClinVar: improving access to variant interpretations and supporting evidence," *Nucleic acids research*, vol. 46, no. D1, pp. D1062-D1067, 2018. https://doi.org/10.1093/nar/gkx1153
[27] National Center for Biotechnology Information, "ClinVar: Archive of reports of the relationships among human variations and phenotypes," 2025. https://www.ncbi.nlm.nih.gov/clinvar
[28] B. S. Abrahams *et al.*, "SFARI Gene 2.0: A community-driven knowledgebase for the autism spectrum disorders (ASDs)," *Molecular autism*, vol. 4, p. 36, 2013. https://doi.org/10.1186/2040-2392-4-36
[29] Simons Foundation Autism Research Initiative, "SFARI gene: Database for autism research," 2025. https://gene.sfari.org/
[30] OpenAI, "ChatGPT," 2025. https://chat.openai.com
[31] SFARI Gene, "SFARI Gene is an evolving database for the autism research community that is centered on genes implicated in autism susceptibility." https://gene.sfari.org/
[32] I. Ivanov, "A pediatric perspective on autism: Meaning, frequency, symptoms, behavior," presented at the Pediatric Aspects of Autism in the Light of Evidence-based Medicine: Reports from the Second Multifaceted Conference on Child Development (pp. 9–38). Plovdiv, Bulgaria, April 3–4, 2015.
[33] L. Timonen-Soivio *et al.*, "The association between congenital anomalies and autism spectrum disorders in a F innish national birth cohort," *Developmental Medicine & Child Neurology*, vol. 57, no. 1, pp. 75-80, 2015. https://doi.org/10.1111/dmcn.12581