**Review**

Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2026; 18(2):438-451

doi: 10.18863/pgy.1634506

# Sources of Phenotypical Variability in Autism Spectrum Disorder and Their Effects on Treatment

## Otizm Spektrum Bozukluğunda Fenotipik Değişkenliğin Kaynakları ve Tedavi Üzerindeki Etkileri

Gökçe Koçak[1], Dilara Özdemir[1], Asya Afacan[1], Buse Akıncı[1], Yasemin İmrek[1], Ali Evren Tufan[1]

[1]Bolu Abant İzzet Baysal University, Bolu

## ABSTRACT

Autism Spectrum Disorder (ASD) is a clinically and etiologically heterogeneous neurodevelopmental disorder. Approaching ASD as a single categorical diagnosis without addressing heterogeneity may limit intervention efficacy. A narrative, critical review was conducted using the PubMed database for studies between 2020-2025 and using "autism" AND "heterogeneity" (n= 3869) and "ASD" AND "heterogeneity" (n= 2391). A total of 435 references were selected based on titles, 167 based on abstracts, and 89 based on text reviews. Finally, 59 studies were reviewed. The DSM-5 criteria and their evolution, genetics, gender, environmental/epigenetic risk factors, comorbidities, development, syndromic vs. non-syndromic presentations, simplex vs. multiplex families, and autistic regression were the main sources of heterogeneity in the studies. The "deficit" term in the DSM-5 should be operationalized in conjunction with disability levels. ASD should be better characterized in female samples. Studies on genetic, environmental, and epigenetic risk factors should model these interactions. Protective factors should also be evaluated in future studies. Comorbidities may be grouped according to type (psychiatric vs. medical) and degree (symptom vs. syndrome), and temporal changes in symptoms can be modelled. Incident ASD cases should be screened using genetic tests and evaluated for dysmorphology. International databases of simplex/multiplex families and regressive ASD cases may help better characterize samples.

**Keywords:** Autism spectrum disorder, autism, phenotype, genetics, developmental regression, multiplex

## ÖZ

Otizm Spektrum Bozukluğu (OSB) klinik ve etiyolojik olarak heterojen bir nörogelişimsel bozukluktur. Heterojenliği ele almadan OSB'ye tek bir kategorik tanı olarak yaklaşmak, müdahalelerin etkilerini sınırlayabilir. 2020-2025 yılları arasındaki çalışmalar için PubMed veri tabanı kullanılarak ve "autism" AND "heterogeneity" (n= 3869) ve "autism spectrum disorder" AND "heterogeneity" (n= 2391) kullanılarak anlatısal, eleştirel bir inceleme yapılmıştır. Toplam 435 referans başlıklara göre, 167'si özetlere göre ve 89'u metinler gözden geçirilerek seçilmiştir. Son olarak, 59 çalışma gözden geçirilmiştir. DSM-5 kriterleri ve bunların değişimi, genetik, cinsiyet, çevresel/epigenetik risk faktörleri, komorbiditeler, gelişim, sendromik ve sendromik olmayan sunumlar, simpleks ve multipleks aileler ve otistik regresyon heterojenliğin ana kaynaklarıydı. DSM-5'teki "eksiklik" terimi, engellilik düzeyleri ile birlikte operasyonel hale getirilmelidir. OSB kadın örneklemler arasında daha iyi karakterize edilmelidir. Genetik, çevresel ve epigenetik risk faktörleri üzerine yapılan çalışmalar, bunların etkileşimlerini modellemelidir. Koruyucu faktörler de değerlendirilmelidir. Komorbiditeler türlerine (psikiyatrik ve tıbbi) ve derecelerine (semptom ve sendrom) göre gruplandırılabilir ve semptomlardaki zamansal değişiklikler modellenebilir. OSB vakaları genetik testlerle taranmalı ve dismorfoloji açısından değerlendirilmelidir. Simpleks/ multipleks ailelerin ve gerileyen OSB vakalarının uluslararası veri tabanları, örneklerin daha iyi karakterize edilmesine yardımcı olabilir.

**Anahtar sözcükler:** Otizm spektrum bozukluğu, otizm, fenotip, genetik, gelişimsel gerileme, multipleks

**Address for Correspondence:** Yasemin İmrek, Bolu Abant İzzet Baysal University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Bolu, Türkiye **e-mail:** dr.yaseminimrek@gmail.com

**Received:** 10.02.2025 | **Accepted:** 09.07.2025

## Introduction

Autism Spectrum Disorder (ASD) is a clinically and etiologically heterogenous neurodevelopmental disorder presenting with impairments in communication/ social interaction, restrictive interests, repetitive behaviors, insistence on sameness and sensory regulation problems (APA 2013, Lazar et al. 2024). The etiology of ASD is thought to be multifactorial, and a complex interplay between genetic, epigenetic, and environmental factors is suspected (Genovese and Butler 2023). The current global prevalence is estimated to be 0.7 % with a male: female ratio of 4.3 (Talantseva et al. 2023, Olusanya et al. 2023). Successive iterations of diagnostic classification systems (i.e., DSM) have been associated with increases in the prevalence of ASD, especially among higher-income countries (APA 2013, Genovese and Butler 2023, Talantseva et al. 2023, Olusanya et al. 2023, Lazar et al. 2024). ASD and associated symptoms and comorbidities continue to affect people and their families throughout their lifespan, leading to functional impairment, may be associated with elevated rates of mortality, and impose a substantial economic burden (Roy et al. 2023, Zhao et al. 2024). Approaching ASD as a single, categorical diagnosis without addressing heterogeneous developmental histories, etiologies, intellectual abilities, comorbidities, and symptom levels may limit the effects of interventions (Mottron and Bzdok 2020). Therefore, this narrative, critical review aimed to address the sources of phenotypical variability in ASD and their effects on treatment and provide suggestions for further research (Sukhera 2022). A perusal of the literature suggests DSM-5 criteria and their evolution, genetics, gender, environmental/ epigenetic risk factors, comorbidities, development, syndromic vs. non-syndromic presentations, simplex vs. multiplex families and autistic regression as main sources of phenotypical heterogeneity (APA 2013, Mottron and Bzdok 2020, Genovese and Butler 2023, Lazar et al. 2024). ASD is a complex disorder that can occur through the complex interaction of risk and protective factors, the timing of the onset of symptoms can vary, and it can encompass hundreds of phenotypes. A multidimensional approach is required for assessment and interventions. In this study, we aimed to identify the sources of phenotypic variables in autism.

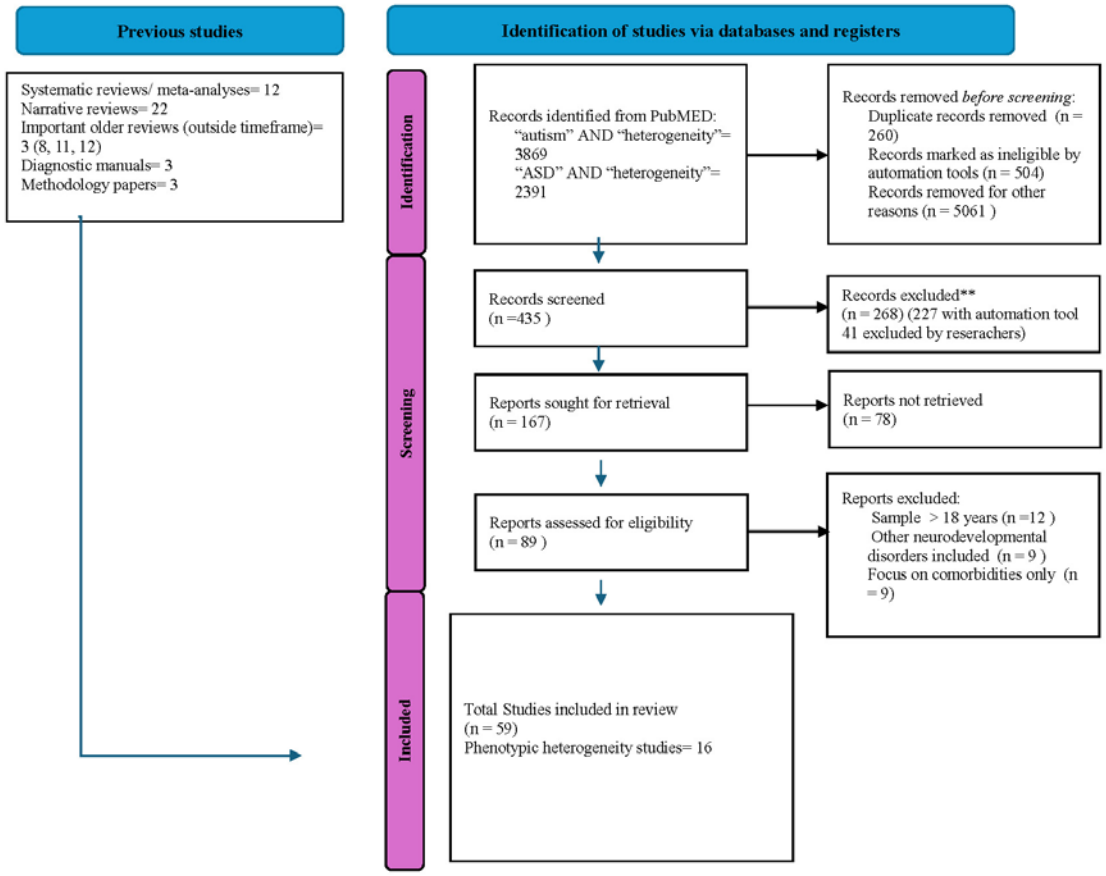


**Figure 1. PRISMA flow chart**

A PubMed (https://pubmed.ncbi.nlm.nih.gov/) search was conducted for publications between January 2021- May 2025 using the search terms "autism" AND "hetereogeneity" and "ASD" AND "heterogeneity". The flowchart according to the PRISMA statement (Page et al. 2021) is shown in Figure 1.

# Effects of Distinct Sources on Phenotypical Variability in ASD

## DSM-5 Criteria

Current DSM-5 criteria for ASD consist of deficits in understanding and using social communication and interaction (as manifested by all three of nonverbal communicative behaviors used for social interaction, social-emotional reciprocity, and in developing and maintaining relationships appropriate to developmental level beyond those with caregivers) and restricted, repetitive patterns of behavior/interests/activities (two of the following: stereotyped/repetitive speech/motor movements/use of objects, excessive adherence to routines/ritualized patterns of verbal or nonverbal behavior/excessive resistance to change, highly restricted, fixated interests that are abnormal in intensity or focus, and hyper/hypo-reactivity to sensory input/unusual interest in sensory aspects of environment) not accounted for by general developmental delays (APA 2013). With these seven criteria and the inclusion of specifiers for intellectual disability, deficits in language development, known medical/genetic/environmental etiologies, and catatonia, a wide range of presentations is possible (APA 2013, Mottron and Bzdok 2020). Specifically, with seven criteria and five specifiers at least 180 permutations are possible and A and B criteria for ASD can display six combinations (https://stattrek.com/online-calculator/combinations-permutations, accessed on 26.05.2024).

Earlier definitions of ASD were monothetic (requiring fulfillment of all criteria) and underlined the importance of gross deficits in language development, while from DSM-III-R, diagnostic criteria became polythetic (no requirement for fulfillment of all criteria) with specifiers and deemphasized the importance of early language problems (DSM-III-R, Happe and Frith 2020, Lombardo and Mandelli 2022). DSM-IV lists three symptom domains for ASD (qualitative impairment in social interaction, qualitative impairment in communication, and restricted/repetitive and stereotyped patterns of behaviour/interests/activities), each consisting of four criteria (DSM-IV). For diagnosis, at least one criterion from each domain should be met, for a total of at least six criteria. This requirement allowed 924 combinations (https://stattrek.com/online-calculator/combinations-permutations, accessed on 26.05.2024). The lack of clinical cut-offs for "deficit" along with specifiers in the DSM-5 also contributes to phenotypical variability (APA 2013, Lombardo and Mandelli 2022). The change from DSM-IV-TR to DSM-5 mostly affected the group diagnosed with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), and a majority of those with this diagnosis were reclassified as having Social Pragmatic Communication Disorder (SPCD) introduced in DSM-5 (DSM-IV-TR, DSM-5, Blázquez Hinojosa et al. 2021). The rate of children with PDD-NOS who were diagnosed with SPCD according to the DSM-5 varied widely in studies between 1.0–97.0 %, although a conservative estimate is 25.0-30.0 % with probably ≤ 10.0 % losing both diagnoses (Blázquez Hinojosa et al. 2021, DSM-5, Lombardo and Mandelli 2022). This change may have affected those with less severe social-communication impairments and a milder course (DSM-5). Therefore, ASD diagnostic criteria may contribute to phenotypical variability in ASD. The successive changes in diagnostic criteria went in tandem with acceptance of ASD as the extreme (but not rare) end of a population-wide, normally distributed expression of underlying quantitative traits, its lifelong and complex nature, a reduction on emphasis of the medical model (i.e., neurodiversity) and increasing recognition of male-biased definitions of the disorder which further introduced variability (APA 2013 , Mottron and Bzdok 2020, Lombardo and Mandelli 2022, Dwyer 2022, Ochoa-Lubinoff et al ark 2023).

## Genetic Factors

Twin and family studies have found that ASD is one of the most genetically determined neurodevelopmental disorders, with a heritability of 0.7-0.8 (Kereszturi 2023). Family members without a clinical diagnosis of ASD display a "broad autism phenotype" with subclinical traits (Happe and Frith 2020,

Kereszturi 2023, Godoy-Gimenez et al. 2024). Recurrence rates for later-born siblings may vary between 3.0-7.0 %, although even higher rates have been reported in prospective studies (Happe and Frith 2020). The concordance rates for monozygotic (MZ) and dizygotic (DZ) twins were 98.0 % and 53.0 %, respectively (Godoy-Gimenez et al. 2024). Accordingly, 60.0–90.0 % of the variance in ASD etiology may be genetic, while variance rates explained by shared and non-shared environments may vary between 0.0–20.0 % and 10.0–30.0 %, respectively (Kereszturi 2023).

**Table 1. Common genetic variants associated with autism spectrum disorder (ASD), odds ratios (OR) according to genetic models and their roles in phenotypic variability**

| Gene | Protein | Allele | Model and OR | Phenotypic variability |
|---|---|---|---|---|
| CNTNAP2 | Contactin Associated Protein 2 | rs2710102 | HZ, 1.30<br>HeZ, 1.21<br>Dominant, 1.28<br>Allelic, 1.17 | Age at first word, A allele reduced social function and gaze contact |
| | | rs7794745 | HeZ, 1,30<br>Dominant, 1.28 | Language processing and social interaction domains |
| MTHFR | Methylenetetrahydrofolate Reductase | C677T | HZ, 1.63<br>HeZ, 1.82<br>Dominant, 1.66<br>Recessive, 2.03<br>Allelic, 1.59 | Increased ASD risk especially in Han Chinese, severity of ASD symptoms, folate metabolism |
| | | A1298C | Dominant, 1.19<br>Allelic, 1.17 | Increased ASD risk, folate metabolism |
| OXTR | Oxytocin Receptor | rs2254298 | HZ, 1.49 | Social deficits, oxytocin levels, possibly with Asperger Syndrome/ High Functioning Autism |
| GABRB3 | Gamma-aminobutyric acid type A receptor subunit beta3 | rs7180158, rs7165604, rs12593579 | Allelic, - | Possibly with Asperger Syndrome/ High Functioning Autism |
| VDR | Vitamin D Receptor | rs731236 | -, 1.30 | Increased ASD risk |
| | | rs2228570 | -, 1.30 | Increased ASD risk especially in Han Chinese, hyperactivity |
| | | rs7975232 | HZ, 0.67 | G allele may be protective against ASD |

OR: Odds Ratio, HZ: homozygote, HeZ: heteroygote ASD: Autism Spectrum Disorder

Between-family variability and within-family similarity for ASD traits may contribute to phenotypic variations (Taylor et al. 2023). Underlying genetic abnormalities may be detected in up to 20.0- 35.0 % of those with ASD (Mottron and Bzdok 2020, Happe and Frith 2020, Genovese and Butler 2023, Godoy-Gimenez et al. 2024). Common variants are associated with a low risk, whereas rarer variants are associated with a higher risk (Godoy-Gimenez et al. 2024). Rare copy number variations (CNVs) may be elevated among those with ASD, although they may be responsible for only 1.0-5.0 % of total cases (Godoy-Gimenez et al. 2024). These CNVs usually affect neuroligin or neurexin gene families related to synaptic connections and functioning (Happe and Frith 2020, Genovese and Butler 2023, Godoy-Gimenez et al. 2024). SHANK family genes (SHANK 1/ 2/ 3 coding proline-rich synapse-associated protein) may be sources of variability in ASD along with ADNP (coding activity-dependent neuroprotector homeobox protein), CHD8 (coding chromodomain helicase DNA binding protein 8), DYRK1A (coding dual specificity tyrosine phosphorylation regulated kinase 1A), SCN2A (coding sodium voltage-gated channel alpha subunit 2), and GRIN2B (glutamate ionotropic receptor NMDA type subunit 2B, Taylor et al. 2023, Hudac et al. 2024). Patients with ASD with ADNP, CHD8, DYRK1A, and SCN2A variations may display elevated sensory sensitivities, while those with GRIN2B may display lower sensory avoidance (Hudac et al. 2024). Genetic variations may also affect the

cognitive profiles and severity of deficits in children with ASD. Accordingly, cognitive and adaptive outcomes in those with CHD8 variations may be highly variable, with some displaying minimal impairment, while others may have intellectual disability (ID) in addition to ASD. Children with ASD and GRIN2B and DYRK1A mutations almost invariably have ID. DYRK1A mutations may also be associated with microcephaly, delayed speech, motor problems, and dysmorphic features (Arnett et al. 2020).

Common genetic variants associated with ASD include CNTNAP2 (Contactin Associated Protein 2), MTHFR (Methylenetetrahydrofolate Reductase), OXTR (Oxytocin Receptor) and VDR (Vitamin D Receptor, Fang et al. 2023). The odds ratios (OR) of these genes according to various genetic models and their roles in phenotypic variability in ASD are illustrated in Table 1.

Advanced paternal age may increase the risk of ASD among offspring by increasing the rates of de novo mutations and epigenetic alterations (Happe and Frith 2020, Genovese and Butler 2023, Godoy-Gimenez et al. 2024). De novo mutations may increase the comorbidity of intellectual disability with ASD (Genovese and Butler 2023, Godoy-Gimenez et al. 2024). Additionally, sex may interact with heritability, with the risk of recurrence being elevated for female probands compared to male probands, and female probands displaying mutations with higher penetrance (Dougherty et al. 2022, Sandin et al. 2024, Leow et al. 2024). These results may partially explain the "female protective effect" where females with ASD would require greater cumulative risks to display the same degree of impairment as males with ASD (Dougherty et al. 2022, Godoy-Gimenez et al. 2024, Sandin et al. 2024, Leow et al. 2024). Further complicating the ASD phenotype, a gene may be variably involved in protein synthesis (i.e., "penetrance"), it may lead to seemingly diverse, multiple outcomes (i.e., "pleiotropy"), may have differing effects according to parent of origin (i.e., "imprinting"), may suppress (i.e., "epistasis") or increase (i.e., "additive effect") the effects of another gene or may lead to different symptoms in different individuals (i.e., "variable expression") (Genovese and Butler 2023, Godoy-Gimenez et al. 2024). Lastly, genes that increase the risk for ASD also increase the risk for schizophrenia, bipolar disorder, learning disability, and epilepsy, illustrating the complexity of downstream effects (Peal et al. 2024). In accordance with the results of these studies, family of origin, genetic basis/associated genetic syndromes, and proband sex may be listed among the important sources of phenotypical variability for ASD.

## Gender

Recent studies suggest that ASD may be more common than previously thought among females and that sex differences in symptoms, along with male-biased criteria listed in diagnostic manuals, may lead to delayed or missed diagnoses (Ochoa-Lubinoff et al. 2023, Cook et al. 2024). Females with ASD may have greater awareness of the need for social communication and greater motivation to do so. They may imitate others to minimize their social problems ("social camouflaging") and may have close friends. A recent meta-analysis suggested that the rates of ASD among females may be affected by social camouflaging Cruz et al. 2024). Girls with ASD may have an increased capacity for symbolic play, and their restricted interests may focus on famous people, television series, and pets, which may be more acceptable to their peers. Rates of internalizing (e.g., anxiety and depression) and eating disorders may be higher among females with ASD than among males (Ochoa-Lubinoff et al. 2023, Cook et al. 2024). Conversely, externalizing and behavioral disorders may be more common among males with ASD.

Social camouflaging is cognitively exhausting, increases stress, and may lead to burnout. This may be expressed as fatigue, anger, social withdrawal, an increase in symptoms, forgetfulness, problems in executive functions, reduced motivation, and self-grooming, as well as gastrointestinal problems among females with ASD following a period of intense social relationships and communication (Zhuang et al. 2023). These results suggest that sex is an important source of phenotypical variability in ASD and that further studies are needed to discern the ASD phenotype among females.

## Environmental/Epigenetic Risk Factors

The current consensus on the environmental risk factors for ASD is strongest for higher parental (especially paternal) age and preterm birth (Torres et al. 2023, Botelho et al. 2024). For air pollution,

immune-related factors, maternal prenatal nutritional status, pesticides, interval between successive births, pregnancy and labor complications, maternal use of antiepileptics during pregnancy, maternal metabolic disorders (e.g., obesity, diabetes, and hypertension), and maternal nutritional status, including dietary supplements (e.g., vitamins), are considered potential risk factors for ASD; however, data are limited, and further studies are needed (Botelho et al. 2024). Several studies have shown that prenatal and postnatal antibiotic exposure may be a risk factor for ASD in children, while some antibiotics have been reported to have a positive effect on social skills development and improvement in irritability and hyperactivity subscales in children with ASD (Njotto et al. 2023). For chemicals in the environment, maternal use of selective serotonin reuptake inhibitors/beta blockers during pregnancy and heavy metal intoxication data are controversial (Mathew et al. 2022, Torres et al.2023, Botelho et al. 2024, Netto et al. 2024, Suprunowicz et al. 2024). A recent meta-analysis found that although excessive screen use may pose developmental risks, screen time is not a risk factor for ASD (Ophir et al .2023). Table 2 illustrates the results of studies on environmental/epigenetic risk factors for ASD and their contribution to phenotypic variability.

**Table 2. Environmental/epigenetic risk factors associated with autism spectrum disorder (ASD), strength of evidence and their roles in phenotypic variability**

| Factor | Association | Strength of evidence | Phenotypic variability |
|---|---|---|---|
| Advanced paternal age | (+) risk | Strong | May be prominent especially for female children and high functioning ASD |
| Prenatal valproate exposure | (+) risk | Strong | (+) ID and motor delays, (+) RRB, dysmorphic features |
| Birth complications (trauma, ischemia, hypoxia) | (+) risk | Strong | (+) ID, greater language impairment/ motor problems, elevated comorbidities (especially epilepsy and ADHD) |
| Maternal obesity | (+) risk | Moderate | Elevated ID comorbidity, (+) executive function problems |
| Maternal diabetes (including gestational) | (+) risk | Moderate | |
| Prematurity/ low birth weight | (+) risk | Moderate | (+) sensory problems, hyperactivity, motor coordination problems |
| Caesarean section | (+) risk | Weak | (+) ID, greater language impairment/ motor problems, elevated comorbidities (especially epilepsy and ADHD) |
| Maternal bleeding in pregnancy | (+) risk | Weak | (+) ID, greater language impairment/ motor problems, elevated comorbidities (especially epilepsy and ADHD) |
| IU infections/ maternal immune response | (+) risk | Weak | Elevated ID comorbidity, social-communication problems, regressive ASD |
| Air pollutants | (+) risk | Subtle, emerging | Potentially sex-specific effects, language delay |
| Immigrant status | (+) risk | Subtle, emerging | Underdiagnosis of milder forms, greater problems in adaptive functioning and language, (+) behavioral/ emotional dysregulation (possibly due to trauma) |

(+): increase, ID: intellectual disability, RRB: repetitive motor behavior/ restrictive interests, ASD: Autism spectrum disorder, ADHD: attention deficit/ hyperactivity disorder, IU: intrauterine

According to studies in the literature, environmental risk factors for ASD may also contribute to phenotypical variability, although it should be emphasized that these factors are not unique to ASD, their effects may not be clearly demarcated from genetic effects, they affect development by means of epigenetic factors, and the results of these studies may be affected by confounding variables (Mathew et al. 2022, Ophir et al. 2023, Torres et al. 2023, Botelho et al. 2024, Netto et al. 2024, Suprunowicz et al.

2024). Lastly, it should be noted that risk factors do not act in isolation and interact with protective factors in determining the phenotype (Pugsley et al. 2022).

## Comorbidities

Comorbidity is the rule rather than the exception in childhood neurodevelopmental/psychiatric disorders, and ASD is no exception (Micai et al. 2023, Bougeard et al. 2024). The most prevalent neurodevelopmental/psychiatric comorbidities in ASD include developmental coordination (DCD, 87.0 %), attention deficit/hyperactivity (ADHD, 37.0 %), anxiety (35.0 %), feeding/eating (32.0 %), and disruptive behavior (28.0 %) disorders. Intellectual disability is present in one-third of patients with ASD. At subthreshold levels, symptom rates may be even higher; for example, almost four-tenths of youth with ASD may experience sleep problems. Among medical/ neurological comorbidities highest rates were reported for elimination (29.0 %), gastrointestinal disorders (21.0 %), and with epilepsy (16.0%). Similar to neurodevelopmental/psychiatric comorbidities, the rates of subthreshold somatic symptoms are high (Micai et al. 2023, Bougeard et al. 2024). Furthermore, sex and age affect rates of comorbid disorders, with ADHD and externalizing disorders being more common among males, internalizing/eating disorders and epilepsy being more common among females, and rates of anxiety and ADHD increasing until adolescence (Micai et al. 2023, Bougeard et al. 2024). ASD and psychiatric/neurodevelopmental comorbidities may also share genetic etiology, especially for genes involved in synaptic functioning, immune signaling, and transcriptional regulation (Micai et al. 2023). The effects of comorbidities and their genetic etiologies on phenotypic variability are illustrated in Table 3.

**Table 3. Genetic risk factors shared among autism spectrum disorder (ASD) and psychiatric/ neurodevelopmental comorbidities and their roles in phenotypic variability**

| Genetic Basis | Type | Phenotype |
|---|---|---|
| Rare, de novo mutation, high penetrance | Chromosomal, 15q11-q13 dup | ASD + Epilepsy/ ID |
| | Chromosomal, 16p11.2 del/ dup | ASD+ obesity/ macrocephaly |
| | Single gene, FMR1 (FXS) | Most common inherited cause of ASD (app. 2.0 -5.0 %) + ADHD/ anxiety + hyperarousal |
| | Single gene, TSC1/ TSC2 (TSC) | ASD + epilepsy |
| | PTEN | ASD + macrocephaly + increased cancer risk |
| | SHANK3 (Phelan-McDermid Syndrome) | ASD + severe ID + language delay |
| | CHD8 | ASD + macrocephaly + GIS problems |
| | SCN2A | ASD + severe epilepsy + motor delay + ID |
| | GRIN2B | ASD + speech delay + epilepsy + ADHD |
| | CACNA1C | ASD + mood instability/ schizophrenia |
| | ANK3 | ASD+ impulsivity |
| Common variants | SNPs in synaptic genes, NRXN1, NLGN3/ 4X | ASD + schizophrenia |
| | SNPs in synaptic genes, CNTNAP2 | ASD + ADHD + Epilepsy |
| | Immune/ glia related genes, MET | ASD + GIS problems |
| Copy Number Variants | Del 22q11.2 (Di George Syndrome) | ASD+ psychosis/ ID |
| | Del/ Dup 1q21.1 | ASD+ schizophrenia/ microcephaly |

dup: duplication, del: deletion, ID: intellectual disability, app.: approximately, ADHD: attention deficit/ hyperactivity disorder, FXS: Fragile X Syndrome, TSC: Tuberous Sclerosis Complex, GIS: gastrointestinal system, SNPs: single nucleotide polymorphisms , ASD:Autism Spectrum Disorder, FMR1:Fragile X Mental Retardation 1, FXS: Fragile X Syndrome , TSC1:Tuberous Sclerosis Complex 1, TSC2: Tuberous Sclerosis Complex 2, PTEN:Phosphatase and TENsin homologue, SHANK3: SH3 and multiple ankyrin repeat domains 3, CHD8: Chromodomain Helicase DNA Binding Protein 8, SCN2A :Sodium Voltage-Gated Channel Alpha Subunit 2, GRIN2B : Glutamate Ionotropic Receptor NMDA Type Subunit 2B, CACNA1C :Calcium Voltage-Gated Channel Subunit Alpha1 C, ANK3 :Ankyrin 3, SNP :Single Nucleotide Polymorphism , NRXN1 : Neurexin 1, NLGN3 :Neuroligin 3, NLGN4X :Neuroligin 4 X-linked, CNTNAP2 :Contactin Associated Protein 2, MET :Mesenchymal-Epithelial Transition factor, Del: Deletion, Dup: Duplication, GIS: Gastrointestinal System

Accordingly, comorbid medical and neurodevelopmental/psychiatric disorders may contribute to phenotypic variability in ASD. This variability may be addressed by dividing the population of patients with ASD into homogenous subgroups. These groups may be divided according to the type (physical vs. neurodevelopmental/psychiatric) and degree (syndrome vs. symptoms) of comorbidity and functional status. One such group may be "profound autism" denoting individuals with ASD and an intellectual disability (intelligence quotient < 50), minimal-to-no language, and requiring 24-hour supervision and assistance with activities of daily living (Wachtel et al. 2023).

## Syndromic versus Non-Syndromic Autism

ASD rates are known to be elevated in some genetic syndromes. As an example among Klinefelter, Down, Dup15q, DiGeorge, Williams-Beuren, CHARGE, Cornelia de Lange, Tuberous Sclerosis, Rett, Fragile X, Neurofibromatosis and Noonan syndromes the rates of ASD may vary between 6.0- 80.0 % (Godoy-Gimenez et al. 2024). However, among those with ASD, these syndromes are rarer (i.e., less than one-third) (Godoy-Gimenez et al. 2024). Angelman, Joubert, Smith-Lemli-Opitz, and Timothy syndromes are rare examples of genetic disorders associated with ASD. Strongest associations with ASD are reported for Rett and Cohen syndromes where more than half of patients are diagnosed with ASD (Happe and Frith 2020, Godoy-Gimenez et al. 2024).

"Syndromic autism" refers to ASD associated with clinically defined genetic syndromes related to deletions or duplications of specific genes (Genovese and Butler 2023, Taylor et al. 2023, Genovese ve Butler 2024, Lazar et al. 2024). In this context, the ASD phenotype is observed in the context of neurodevelopmental delays. Approximately one-tenth of all ASD cases may be syndromic and are often associated with congenital malformations or dysmorphic features. Although "idiopathic" ("primary," "non-syndromic") ASD has a male preponderance, syndromic ASD has a more balanced sex ratio (Genovese and Butler 2024). This distinction may also contribute to phenotypical variability in ASD. The detractors of the syndromic versus non-syndromic distinction in ASD argue that any neurodevelopmental condition with a sufficient degree of intellectual disability and behavioral problems may fulfill the criteria for ASD, and that novel genetic discoveries will diminish the non-syndromic group while increasing the number of identified syndromes.

Furthermore, the genetic and pathophysiological basis of syndromic and non-syndromic ASD may not overlap, leading to heterogeneous samples (Taylor et al. 2023, Genovese and Butler 2024). To reduce the effects of this heterogeneity, genetic evaluations of incident cases of ASD should be routine, and the results should be recorded according to the DSM-5 specifiers. Because resources for genetic panels may vary between laboratories and may be limited among centers from low-middle income countries (LMIC), dysmorphological features may be recorded along with DSM-5 specifiers (such as by using the Autism Dysmorphology Measure or similar scales) (Shapira et al. 2019). Smartphone applications, such as Face2Gene (https://www.face2gene.com/), may benefit clinicians in this endeavor.

## Number of Offspring with ASD

Most studies on ASD have been conducted on simplex families in which only one child was diagnosed with ASD. However, there is another group termed multiplex families in which multiple children are diagnosed with ASD (Anbar et al. 2023). The results of studies on the effects of simplex vs. multiplex status on the phenotype of children with ASD are conflicting, with some reporting no difference, while others report better expressive language and cognitive abilities and milder ASD symptoms among multiplex offspring (Anbar et al. 2023, Cohenour et al. 2023). Additionally, the genetic architecture of ASD may differ among families. Accordingly, inherited single nucleotide variations (SNVs) and CNVs may be common among simplex families, whereas multiplex families may have higher rates of both inherited and de novo CNVs (More et al. 2023). Future studies on the genetic and neurobiological basis of ASD may address this distinction by forming homogeneous groups of simplex and multiplex families. International databases of simplex and multiplex families (similar to the Simons Simplex Collection; https://www.sfari.org/resource/simons-simplex-collection/) may be helpful in this regard.

## Development and Age

Rather than remaining stable over time, ASD symptoms change in severity, becoming milder over time in a substantial proportion of individuals. This change varies across studies, with a group displaying stable levels of symptoms over time (Waizbard- et al. 2023, Hong et al. 2023). Variation is observed both between and within individuals and between symptom domains. As reported, the most common pattern is a reduction, followed by stability of symptoms, although a minority of patients with ASD display increasing symptoms with age. Even for groups of people displaying the same temporal trends, the pace of change may differ. The reduction in symptoms may be faster at younger ages and may slow or plateau with time within individuals. Temporal trends may also differ for social communication symptoms and restrictive/ repetitive behaviors (Waizbard-Barov et al. 2023, Hong et al. 2023). Restrictive/repetitive behaviors (RRB) are especially prominent in early childhood and become less overt with age. High-functioning children with ASD display a faster reduction in RRB, while this reduction may be delayed among those with comorbid ADHD. In contrast, social communication symptoms emerge from middle childhood onwards (Waizbard-Barov et al. 2023).

Intriguingly, some studies hint at a group with later emerging ASD symptoms, although data on this group are limited (Riglin et al. 2021). This group may comprise approximately 6.5 % of those with ASD and may be characterized by minimal/subthreshold ASD symptoms in early childhood, prominence of social-communication problems in adolescence triggered by increasing demands, higher baseline IQ, fewer overt, early RRBs with gradual emergence of cognitive rigidity later, increased use of "social camouflaging," elevated rates of anxiety/depression and ADHD (especially inattentive type), and female predominance (Riglin et al. 2021). Consequently, age seems to be an important contributor to phenotypical variability in ASD, which may be decomposed into between- and within-individual and between-domain variability (Riglin et al. 2021,Waizbard-Barov et al. 2023, Hong et al. 2023). Future studies on developmental variability in ASD symptoms may employ more complex methodologies (e.g., accelerated longitudinal designs) to address this problem (Geurts et al. 2021).

**Table 4. Common features of regressive autism contributing to phenotypic variability in autism spectrum disorders**

| Feature | Description |
|---|---|
| Symptom onset | Loss of previously acquired skills (e.g., language, social engagement) after age 12/ 18–24 months |
| Course | Normal or near-normal development until regression, sudden/ gradual loss |
| Prevalence | Approximately 20.0- 30.0 % of all ASD |
| Language and Social Skills | More severe language impairment after regression, more likely to remain non-verbal |
| Cognitive functioning | Higher rates of ID after regression, may plateau in development thereafter |
| Repetitive behaviors | More severe RRBs after regression |
| Biological and Genetic Etiology | Stronger association with seizures, more frequent in TSC and mitochondrial disorders, may be associated with SNAP25 alleles |
| Neuroinflammation | Higher rates of immune dysregulation |
| Prognosis | Poorer compared to non-regressive ASD |

ID: intellectual disability, RRB: restrictive/ repetitive behaviors, TSC: tuberous sclerosis complex, ASD: Autism Spectrum Disorder, SNAP-25: Synaptosomal-Associated Protein 25

## Regression

Almost one-third of children with ASD may have "regressive autism" characterized by developmental regression and loss of previously acquired skills between 18-24 months of age (mean=19.8 months) (Furley et al. 2023). Loss is mainly in the social and language domains, with isolated reports of cases with regression at later ages. Children with ASD and developmental regression have lower cognitive abilities, increased comorbidity of intellectual disability, elevated ASD symptom levels, lower receptive/expressive language outcomes, and more sleep problems (Furley et al. 2023, Hu et al. 2022). They also experience

higher rates of epilepsy( Tonekaboni et al. 2025). Genetic studies also suggest that children with regressive ASD may differ from those with non-regressive ASD (Bolognesi et al. 2023). After one year of behavioral training, the symptom scale scores of children with ASD in the non-regressive group decreased more significantly than those in the regressive group. These findings suggest that regressive phenotypes significantly affect the rehabilitation of children with ASD (Hu et al. 2024). Accordingly, regression may be listed as another source of phenotypic variability in ASD, and its contribution to phenotypic variability is illustrated in Table 4.

This narrative review aimed to define the main sources of phenotypic variability in patients with ASD. Based on the literature review, nine sources of variability were identified. The sources of variability and their effects on treatment are presented in Table 5.

**Table 5. Sources of phenotypical variability in Autism Spectrum Disorder, their effects on treatment and suggestions for future research**

| Source | Effect on phenotype | Effect on treatment | Suggestions for future research |
|---|---|---|---|
| DSM-5 criteria | Male- biased criteria, delayed/ missed diagnosis among females, lack of clinical cut-offs for “deficit”, combinations/ permutations leading to variable clinical presentations | Heterogenous samples biasing studies of intervention, effect of gender on interventional studies are not addressed | More homogenous samples, grouped according to functioning levels and comorbidities may increase validity of results (e.g., “profound autism”), Validity of criteria among female samples should be tested at different ages and stages of development, Studies should employ both categorical diagnostic groups and quantitative evaluations of traits |
| Genetic factors | Family of origin, genetic basis (CNVs, SNVs, mutations/ duplications/ deletions), associated syndromes, interaction of environmental/ epigenetic and genetic factors leading to heterogeneity | Heterogenous samples biasing studies of intervention, effects of environmental/ epigenetic and genetic factors are confounded, within family similarity and between family variability may affect results, syndromic and non-syndromic ASD may differ in pathophysiology | Familial clustering of traits may be addressed, genetic factors may be evaluated considering gender, genetic studies may evaluate both categorical diagnosis of ASD and quantitative evaluations of traits, Presentations of ASD in genetic syndromes should be defined both categorically and quantitatively |
| Gender | Male- biased criteria, delayed/ missed diagnosis among females, | Results of interventional studies may not be valid for female samples | Further studies on female samples are required, the validity of ASD criteria as well as quantitative traits should be evaluated among females, further studies on ASD traits among females with internalizing/ eating disorders and personality disorders are required |
| Environmental/ epigenetic factors | Environmental/ epigenetic factors may increase heterogeneity | Results of interventional studies may be affected by environmental/ epigenetic factors | Effects of supposed environmental/ epigenetic factors should be tested among other neurodevelopmental disorders (.e.g, ADHD, LD, ID), Preclinical studies should discern the epigenetic/ genetic results of supposed environmental risk factors, Moderating effects of gender and developmental timing should be tested, Rather than focusing solely on |

**Table 5. Sources of phenotypical variability in Autism Spectrum Disorder, their effects on treatment and suggestions for future research**

| Source | Effect on phenotype | Effect on treatment | Suggestions for future research |
|---|---|---|---|
| Comorbidities | Comorbid medical and neurodevelopmental/ psychiatric disorders as well as symptoms increase heterogeneity | Results of interventional studies may be affected by comorbid medical and neurodevelopmental/ psychiatric disorders as well as symptoms | Homogenous sub-groups may be formed according to type (physical vs. neurodevelopmental/ psychiatric) and degree (syndrome vs. symptom) of comorbidity and functionality, |
| Syndromic vs. non-syndromic ASD | ASD associated with known genetic syndromes (i.e., "syndromic") may differ from non-syndromic ASD increasing heterogeneity | Results of interventional studies may be affected by syndromic/ non-syndromic ASD distinction | Genetic evaluations of incident cases should be routine,<br>dysmorphological features may be recorded along with DSM-5 specifiers,<br>smartphone applications may be used to evaluate dysmorphology, |
| Number of offspring with ASD | "simplex families" (one child with ASD) may differ from "multiplex families" (multiple children with ASD) increasing heterogeneity | Results of interventional studies may be affected by simplex/ multiplex ASD distinction | Homogenous groups of simplex and multiplex families may be enrolled in studies,<br>International databases of simplex/ multiplex families may be initiated |
| Development and age | ASD symptoms change with time, change is variable both within and between persons and among symptom domains increasing heterogeneity, | Results of interventional studies may be affected by age of participants, | Studies should be designed to evaluate temporal variability (i.e., accelerated longitudinal designs, prospective cohorts, time series etc.),<br>Children with subtle symptoms/ risk factors may be followed over time to discern "late emergent ASD" |
| Developmental regression | Regressive ASD may be phenotypically and genetically distinct, increasing heterogeneity | Results of interventional studies may differ for those with regressive ASD | Homogenous samples with regressive ASD may be evaluated in studies |

DSM-5: Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition, ASD: Autism Spectrum Disorder, CNVs: Copy Number Variations, SNVs: Single Nucleotide Variations, ADHD: attention deficit/ hyperactivity disorder, LD: learning disorder, ID: intellectual disability

## Discussion

This narrative, critical review aimed to address the sources of phenotypic variability in ASD and their effects on treatment and provide suggestions. A review of PubMed database was conducted for publications between January 2021- May 2024 using the key terms "autism" AND "heterogeneity" and "ASD" AND "heterogeneity." DSM-5 criteria, genetics, gender, environmental/epigenetic risk factors, comorbidities, development, syndromic vs. non-syndromic presentations, simplex vs. multiplex families, and autistic regression were found to be the main sources of phenotypical variability.

Successive iterations of the DSM have led to a broader, polythetic definition of ASD and increased the heterogeneity of the samples. Arguably, the symptom triad of the DSM-IV allowed a greater number of possible combinations of symptoms, and the DSM-5 went in the right direction in reducing the number of combinatorial possibilities. However, there is room for further improvements. First, the "deficit" in the criteria for social-emotional reciprocity, non-verbal communicative behaviors, and social relationship skills may be operationalized to reduce ambiguity. This operationalization may be defined, for example, by scoring below three standard deviations from the norm in a standardized test of nonverbal communication. Similarly, the criterion for sensory responsiveness may be revised to reflect the quantitative performance in a sensory responsiveness test. "Clinically significant impairment" may be operationalized with the Children's Global Assessment Scale (CGAS) or its modifications (Wagner et al. 2007). Although the table illustrating examples of severity levels of ASD in the DSM-5 is helpful, more examples of behaviors (or even

better, reformatting the table to a scale form) may help clinicians better understand and report functioning. In addition, the validity of the DSM-5 criteria should be tested in female ASD samples.

ASD has one of the strongest genetic bases among neurodevelopmental disorders; however, the plethora of associated genes, polymorphisms, and genetic syndromes increases the sample variability. Future studies on genetic sources of the ASD phenotype may also test for within-family similarity/between-family variability and moderating effects of gender. The latter may also be important for the ASD phenotype and may change the associated comorbidities. Future studies should evaluate the validity of ASD criteria among female samples, as well as ASD symptoms among females with internalizing, eating, and cluster B personality disorders (Pires et al. 2023). Social camouflaging, autistic burnout, and their myriad symptoms should be better characterized.

The strongest evidence of environmental/epigenetic risk factors for ASD exists for advanced paternal age and preterm birth, and all these factors seem to contribute to the phenotypic variability. However, the available studies on these factors seem to be affected by bias and confounding by genetic factors. Future studies on environmental risk factors should also evaluate their interactions with protective factors and focus on putative epigenetic/genetic mediators that lead to the ASD phenotype. Comorbid neurodevelopmental/ psychiatric and physical disorders, as well as subthreshold symptoms, frequently accompany ASD, leading to heterogeneous samples. Comorbidities may be divided according to type and degree to increase the homogeneity of the subgroups. Syndromic and non-syndromic ASD may differ in terms of phenotype and pathophysiology. Careful and routine genetic screening of incident ASD cases, as well as evaluations for dysmorphology, may help clinicians form more homogenous groups. Simplex and multiplex ASD appear to differ in their phenotypes and pathophysiology. Databases of both ASD groups may be formed by multiple centers from various countries, increasing sample sizes and leading to a better characterization of these groups. ASD symptoms also seem to change with age and development, necessitating a study design to model temporal variability.

Finally, the regressive ASD group should be studied further, and its relationships with regressive syndromes arising from other neurodevelopmental disorders (for example, Down Syndrome Regressive Disorder) should be delineated (Santoro et al. 2022). Future studies may use Research Domain Criteria (RDoC) for social disorders to better characterize ASD samples and evaluate affiliation/attachment, social communication, perception/self and perception/others domains, as well as social endophenotypes (Tiede et al. 2021, Mundy et al. 2023).

The results of this narrative and critical review should be evaluated within the scope of these limitations. First, the broad focus of the review necessitated a narrative methodology to delineate potential avenues of research, and we depended on one database and a narrow timeframe for our research. Therefore, systematic reviews and meta-analyses focusing on multiple databases and longer timeframes should be conducted to evaluate the effect sizes of the sources of variability listed in this study. Second, we relied mostly on other reviews and meta-analyses, which was necessary because of our methodology. Further systematic reviews and meta-analyses of epidemiological and clinical studies may be more informative regarding the sources of ASD variability. Third, our results may be limited to studies published in English and may not be valid for studies in other languages. Fourth, we did not evaluate grey literature, conference proceedings, or abstracts on the ASD phenotype. Fifth, we did not evaluate the methodological rigor of the studies we reviewed, and bias or confounding may have affected the studies we reviewed regarding environmental and epigenetic risk factors.

## Conclusion

Regardless of its limitations, in this narrative critical review, we found that DSM-5 criteria, genetic factors, sex, environmental and epigenetic factors, comorbidity, syndromic versus non-syndromic and simplex versus multiplex status, development/age, and regressive ASD were the main sources of phenotypic variability, and we provided suggestions to reduce heterogeneity among study samples. Future systematic reviews should address the mediators and moderators of phenotypic variability in patients with ASD.

# References


APA (1987) Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Revised (DSM-III-R). Washington DC, American Psychiatric Association.

APA (1994) Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). Washington DC, American Psychiatric Association.

APA (2013) Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5). Washington DC, American Psychiatric Association.

Arnett AB, Beighley JS, Kurtz-Nelson EC, Hoekzema K, Wang T, Bernier RA et al. (2020) Developmental predictors of cognitive and adaptive outcomes in genetic subtypes of autism spectrum disorder. Autism Res, 13:1659-1669.

Blázquez Hinojosa A, Lázaro Garcia L, Puig Navarro O, Varela Bondelle E, Calvo Escalona R (2021) Sensitivity and specificity of dsm-5 diagnostic criteria for autism spectrum disorder in a child and adolescent sample. Rev Psiquiatr Salud Ment (Engl Ed), 14:202-211.

Botelho RM, Silva ALM, Borbely AU (2024) The autism spectrum disorder and ıts possible origins in pregnancy. Int J Environ Res Public Health, 21:244.

Bougeard C, Picarel-Blanchot F, Schmid R, Campbell R, Buitelaar J (2024) Prevalence of autism spectrum disorder and co-morbidities in children and adolescents: a systematic literature review. Focus (Am Psychiatr Publ), 22:212-228.

Cook J, Hull L, Mandy W (2024) Improving diagnostic procedures in autism for girls and women: a narrative review. Neuropsychiatr Dis Treat, 20:505-514.

Cruz S, Zubizarreta SC, Costa AD, Araújo R, Martinho J, Tubío-Fungueiriño M et al. (2024) Is there a bias towards males in the diagnosis of autism? a systematic review and meta-analysis. Neuropsychol Rev. doi:10.1007/s11065-023-09630-2. [In Press]

Dougherty JD, Marrus N, Maloney SE, Yip B, Sandin S, Turner TN et al. (2022) Can the "female protective effect" liability threshold model explain sex differences in autism spectrum disorder? Neuron, 110:3243-3262.

Dwyer P (2022) The neurodiversity approach(es): what are they and what do they mean for researchers? Hum Dev, 66:73-92.

Fang Y, Cui Y, Yin Z, Hou M, Guo P, Wang H et al. (2023) Comprehensive systematic review and meta-analysis of the association between common genetic variants and autism spectrum disorder. Gene, 887:147723.

Genovese A, Butler MG (2023) The autism spectrum: behavioral, psychiatric and genetic associations. Genes (Basel), 14:677.

Godoy-Giménez M, García-Pérez Á, Cañadas F, Estévez AF, Sayans-Jiménez P (2024) The Broad Autism Phenotype-International Test (BAP-IT): A two-domain-based test for the assessment of the broad autism phenotype. Autism, 28(9), 2362-2380.

Happé F, Frith U (2020) Annual research review: looking back to look forward – changes in the concept of autism and implications for future research. J Child Psychol Psychiatry, 61:218–232.

Hudac CM, Friedman NR, Ward VR, Estreicher RE, Dorsey GC, Bernier RA et al. (2024) Characterizing sensory phenotypes of subgroups with a known genetic etiology pertaining to diagnoses of autism spectrum disorder and ıntellectual disability. J Autism Dev Disord, 54:2386-2401.

Kereszturi É (2023) diversity and classification of genetic variations in autism spectrum disorder. Int J Mol Sci, 24:16768.

Lazar SM, Challman TD, Myers SM (2024) Etiologic evaluation of children with autism spectrum disorder. Pediatr Clin North Am, 71:179-197.

Leow KQ, Tonta MA, Lu J, Coleman HA, Parkington HC (2024) Towards understanding sex differences in autism spectrum disorders. Brain Res, 1833:148877.

Lombardo MV, Mandelli V (2022) Rethinking our concepts and assumptions about autism. Front Psychiatry, 13:903489.

Mathew S, Bichenapally S, Khachatryan V, Muazzam A, Hamal C, Velugoti LSDR et al. (2022) Role of serotoninergic antidepressants in the development of autism spectrum disorders: A systematic review. Cureus, 14:e28505.

Micai M, Fatta LM, Gila L, Caruso A, Salvitti T, Fulceri F et al. (2023) Prevalence of co-occurring conditions in children and adults with autism spectrum disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev, 155:105436.

Mottron L, Bzdok D (2020) Autism spectrum heterogeneity: fact or artifact? Mol Psychiatry, 25:3178-3185.

Netto BB, da Silva EP, de Aguiar da Costa M, de Rezende VL, Bolan SJ, Ceretta LB et al. (2024) Critical period of exposure to mercury and the diagnostic of autism spectrum disorder: A systematic review. J Neurochem., 168(9), 2092-2104.

Njotto LL, Simin J, Fornes R, Odsbu I, Mussche I, Callens S et al. (2023) maternal and early-life exposure to antibiotics and the risk of autism and attention-deficit hyperactivity disorder in childhood: a swedish population-based cohort study. Drug Saf, 46:467-478.

Ochoa-Lubinoff C, Makol BA, Dillon EF (2023) Autism in women. Neurol Clin, 41:381-397.

Olusanya BO, Smythe T, Ogbo FA, Nair MKC, Scher M, Davis AC (2023) Global prevalence of developmental disabilities in children and adolescents: A systematic umbrella review. Front Public Health, 11:1122009.

Ophir Y, Rosenberg H, Tikochinski R, Dalyot S, Lipshits-Braziler Y (2023) screen time and autism spectrum disorder: a systematic review and meta-analysis. JAMA Netw Open, 6:e2346775.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372:n71.

Peall KJ, Owen MJ, Hall J (2024) Rare genetic brain disorders with overlapping neurological and psychiatric phenotypes. Nat Rev Neurol, 20:7-21.

Pugsley K, Scherer SW, Bellgrove MA, Hawi Z (2022) Environmental exposures associated with elevated risk for autism spectrum disorder may augment the burden of deleterious de novo mutations among probands. Mol Psychiatry, 27:710-730.

Roy M, Strate P (2023) autism spectrum disorders in adulthood-symptoms, diagnosis, and treatment. Dtsch Arztebl Int, 120:87-93.

Sandin S, Yip BHK, Yin W, Weiss LA, Dougherty JD, Fass S et al. (2024) examining sex differences in autism heritability. JAMA Psychiatry,81(7), 673-680.

Suprunowicz M, Tomaszek N, Urbaniak A, Zackiewicz K, Modzelewski S, Waszkiewicz N (2024) Between dysbiosis, maternal ımmune activation and autism: ıs there a common pathway? Nutrients, 16:549.

Sukhera J (2022) Narrative reviews: flexible, rigorous, and practical. J Grad Med Educ, 14:414-417.

Talantseva OI, Romanova RS, Shurdova EM, Dolgorukova TA, Sologub PS, Titova OS et al. (2023) The global prevalence of autism spectrum disorder: A three-level meta-analysis. Front Psychiatry, 14:1071181.

Taylor CM, Finucane BM, Moreno-De-Luca A, Walsh LK, Martin CL, Ledbetter DH (2023) Phenotypic shift in copy number variants: Evidence in 16p11.2 duplication syndrome. Genet Med, 25:151-154.

Torres G, Mourad M, Iqbal S, Moses-Fynn E, Pandita A, Siddhartha SS et al. (2023) Conceptualizing epigenetics and the environmental landscape of autism spectrum disorders. Genes (Basel), 14:1734.

Wachtel LE, Escher J, Halladay A, Lutz A, Satriale GM, Westover A et al. (2024) Profound autism: An ımperative diagnosis. Pediatr Clin North Am, 71:301-313.

Zhao Y, Lu F, Wang X, Luo Y, Zhang R, He P et al. (2024) The economic burden of autism spectrum disorder with and without intellectual disability in China: A nationwide cost-of-illness study. Asian J Psychiatr, 92:103877.

Zhuang S, Tan DW, Reddrop S, Dean L, Maybery M, Magiati I (2023) Psychosocial factors associated with camouflaging in autistic people and its relationship with mental health and well-being: A mixed methods systematic review. Clin Psychol Rev, 105:102335.

**Authors Contributions:** The author(s) have declared that they have made a significant scientific contribution to the study and have assisted in the preparation or revision of the manuscript
**Peer-review:** Externally peer-reviewed.
**Ethical Approval:** This review study does not require ethical clearance.
**Conflict of Interest:** No conflict of interest was declared.
**Financial Disclosure:** No financial support was declared for this study..