Proceedings of the 5th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2025.24079

The Genetic Basis and Molecular Mechanisms of Autism Spectrum Disorder

Tengyue Cao

Department of Biology, Washington University in St. Louis, St. Louis, USA
c.tengyue@wustl.edu

Abstract: Autism Spectrum Disorder (ASD) represents a neurodevelopmental disorder with a robust genetic etiology and intricate molecular mechanisms, characterized by key features such as social communication deficits, repetitive behaviors, and abnormal sensory responses. Earlier studies have demonstrated that the etiology of ASD is influenced by genetic, epigenetic, and environmental factors, which presents challenges for research in this field. This paper seeks to explore the genetic basis and molecular mechanisms of ASD, emphasizing key genes, signaling pathways, and their regulatory processes. Through the review and analysis of relevant literature, the study highlights genetic mutations, DNA methylation, changes in microRNAs, and synaptic transmission dysregulation. The genetic basis of ASD is intricate, involving various genes and mutations, with notable clinical variations associated with different genetic variations. Besides, molecular mechanisms, such as synaptic transmission dysregulation, abnormal gene expression regulation during neurodevelopment, and disturbances in specific signaling pathways, play a pivotal role in the onset and progression of ASD. The results indicate that genetic mutations, epigenetic changes, and environmental factors all contribute to ASD. Nevertheless, given that these genes are also implicated in other neurological disorders, further investigation is required. Integrating behavioral therapy with targeted molecular interventions holds promise for more effective management of ASD symptoms.

Keywords: Autism Spectrum Disorder (ASD), Genetic Basis, Molecular Mechanisms, Clinical Treatment, Epigenetics

1. Introduction

Autism Spectrum Disorder (ASD), a profoundly intricate neurodevelopmental disorder, has garnered considerable global attention in recent years, driven by its complexity and the growing awareness of its huge impact within scientific and clinical communities [1]. Through advances in genetics, neuroscience, and epigenetics, a deeper understanding of the genetic foundations and molecular mechanisms of ASD has been achieved. Research has demonstrated that the onset of ASD is influenced not only by genetic factors but also by epigenetic and environmental factors. However, many questions remain unresolved, particularly regarding the interactions between these factors, with a primary focus on gene-environment interactions in the pathogenesis of ASD. Despite the identification of several gene mutations associated with ASD in existing research, systematic studies on the roles of multiple genes, epigenetic changes, and synaptic dysfunction remain relatively limited. Therefore, investigating the genetic and molecular mechanisms underlying ASD and elucidating the

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.24079

complex relationships involved is essential for further advancing research in this domain. Through a review of recent literature, this paper critically examines key genes, signaling pathways, and their regulatory processes associated with ASD, providing novel insights into its underlying mechanisms. Furthermore, it analyzes genetic variations linked to the onset of ASD, explores how molecular mechanisms contribute to clinical manifestations, and evaluates the interactions between genetic, epigenetic, and environmental factors, offering valuable references for the early diagnosis and therapeutic interventions of ASD.

2. The genetic foundations of Autism Spectrum Disorder

2.1. Genetic factors and heritability of ASD

Genetic factors play a significant role in the development of ASD. Twin and family studies provide key evidence regarding the heritability of autism. Research indicates that the likelihood of autism diagnosis is higher in monozygotic (MZ) twins compared to dizygotic (DZ) twins, supporting the genetic basis of autism. For example, approximately 36% of MZ twins have at least one child diagnosed with autism, whereas no cases of autism were observed in DZ twins [2]. These findings suggest that ASD is a highly heterogeneous genetic disorder, caused by multiple contributing factors. Further exploration of whole-genome sequencing (WGS) studies have provided additional evidence for uncovering the genetic basis of ASD. One thousand-four families have been studied by WGS to further explore the contribution of rare and common inherited variations to ASD. As a result, the size of biological parents of both autistic and nonautistic children who were sequenced and passed QC is more than double compared to the early study. In addition, recent genetic research on autism highlighted that genetic variations in ASD result in significant phenotypic variability, with different variations leading to diverse clinical outcomes.

However, the inheritance of autism is affected by both genetic mutations and environmental factors and prenatal conditions. Parents infected with viruses such as rubella, measles, mumps, influenza, and chickenpox during pregnancy may increase the risk of ASD in their offspring. Additionally, advancing maternal age is positively correlated with the occurrence of ASD. In particular, women over the age of 55 have twice the risk of having a child with autism compared to women under 30, which is associated with an increased rate of de novo mutations in germ cells. Furthermore, nutritional deficiencies during pregnancy, particularly zinc deficiency, have been identified as a potential risk factor for autism, and zinc deficiency may affect the normal development of the embryo, thus increasing the risk of ASD.

2.2. Genetic markers and candidate genes in ASD

The relationship between ASD and genes is an important area of current genetic research. Numerous candidate genes, such as FOXP2, CHD8, and others, have been found to be closely related to ASD. The FOXP2 gene is primarily involved in oral motor skills and language development, and mutations in this gene result in mild cognitive impairments and severe speech and language disorders, which greatly affect individuals with ASD. The CHD8 gene, involved in neural development and gene expression regulation, is strongly associated with the occurrence of ASD. Studies have shown that mutations in CHD8 are connected to more severe clinical symptoms in ASD patients, including delays in speech development and cognitive impairments [3].

Furthermore, different genetic variations play a crucial role in the clinical manifestation of ASD. For example, variations in the RAY1/ST7 gene locus are not yet fully understood, but research suggests that this gene may affect certain manifestations of autism [3]. Genes such as SPCH1 and AUTS1 are linked to language impairments and autism. Mutations or deletions in these genes significantly impact patients' language abilities, thus worsening the clinical symptoms of ASD [3].

DOI: 10.54254/2753-8818/2025.24079

Besides, gene deletions or duplications at loci such as 16p11.2 and 22q11.2 are commonly linked to ASD clinical presentations, with some patients displaying more complex cognitive and social impairments [4]. At present, research on genetic markers for ASD has achieved considerable progress, but several challenges remain. Despite the identification of several genetic loci linked to ASD, such as 5p14.1, 10q24.32, and rs910805, the connection between these genes and clinical symptoms is not yet fully clarified [4]. The complexity of ASD's genetic basis, including the interaction of multiple genes and environmental factors, has made it challenging to establish clear associations. Moreover, the phenotypic differences between individuals further complicate the research. Thus, further genome-wide association studies (GWAS) and functional research are key to overcoming these challenges.

2.3. Genetic models used in ASD

Animal models play a crucial role in the study of ASD. Current commonly used ASD animal models include genetic models, copy number variation (CNVs)-induced models, idiopathic models, as well as environmentally induced models [5]. These models provide important experimental foundations for the in-depth study of the genetic mechanisms of ASD. In particular, mice and rats are the most commonly used experimental models for ASD due to their genetic manipulability and ability to exhibit behavioral deficits associated with ASD, allowing the exploration of structural, biochemical, and physiological abnormalities related to ASD. For example, Fragile X syndrome, one of the most common genetic causes of intellectual disability, is strongly linked to ASD due to mutations in the FMR1 gene. FMR1 gene knockout mice display autistic traits, providing important insights into the pathogenesis of ASD, including elevated phosphorylation levels of gene-regulatory molecules and abnormal protein synthesis in the hippocampus [6]. Besides, zebrafish, a highly social species with considerable physiological and genetic homology to humans, have emerged as a widely utilized model in ASD research. Experimental studies on zebrafish have indicated that drugs such as phencyclidine, MDMA, and ethanol can induce social behavior deficits similar to those observed in ASD, thereby confirming their effectiveness and sensitivity as models for autism [7]. However, existing animal models still have significant limitations in replicating the pathology of ASD. As ASD is a multifactorial and complex neurological disorder, current animal models cannot fully encompass all of its pathological features. Animal models primarily study specific neural pathways and struggle to accurately reproduce the complex interactions between genes and the environment. Therefore, although animal models offer valuable insights into the genetic foundation and pathophysiology of ASD, yet they face significant limitations in fully recapitulating the complexity of human ASD pathology [6].

3. Molecular mechanisms underlying Autism Spectrum Disorder

3.1. Signaling pathways and synaptic dysfunction in ASD

Key signaling pathways associated with synaptic dysfunction and neural signaling play a pivotal role in the pathogenesis of ASD. Studies have highlighted pathways such as the Wnt and mTOR pathways as potential therapeutic targets in ASD. For instance, the Wnt signaling pathway is crucial for processes such as cell fate determination, migration, cell polarity, and organogenesis, and its abnormal activation can lead to the stimulation of small GTPases, such as RhoA and RAC. Dysregulation of this pathway is critical in early brain development and linked to neurological disorders, including ASD [8]. Similarly, the mTOR pathway also plays a key role in ASD-related neural signaling. mTOR controls cell growth and survival in response to nutrients like glucose and amino acids, and is involved in synaptic plasticity, axonal guidance, neuronal repair, and memory consolidation [9]. Additionally, the second messenger PIP3 recruits Akt and promotes its

DOI: 10.54254/2753-8818/2025.24079

phosphorylation by PDK1, while MTORC2 regulates the mTOR signaling pathway, activating mTOR activity [9].

Furthermore, dysregulation of these signaling pathways impacts neural development and synaptic plasticity, thereby leading to the manifestation of ASD symptoms. MECP2, a pivotal transcriptional regulator, is involved in a range of nuclear processes, including transcriptional repression, microRNA processing, and the regulation of RNA splicing [1]. Its deficiency can lead to synaptic dysfunction and impairments in motor and cognitive functions. In mice, knockdown of the Chd8 gene downregulates canonical Wnt-β-catenin signaling, thus causing abnormal behaviors. Nevertheless, the activation of a stable form of β-catenin expression can partially restore these defects [10].

3.2. Protein synthesis and gene regulation in ASD

Disrupted protein synthesis is recognized as a fundamental driver of synaptic dysfunction in ASD, thus positioning its restoration as a promising therapeutic strategy. The loss of fragile X mental retardation protein (FMRP) triggers the expansion of CGG repeats in the FMR1 gene's promoter region, leading to excessive DNA methylation and transcriptional silencing, which further disrupts mRNA transport and translational regulation [11]. The mammalian target of rapamycin (mTOR) signaling pathway serves as a key regulator of local protein synthesis, playing an vital role in diverse neurophysiological processes. Mutations in mTOR-associated genes including TSC1/2, PTEN, and CNTNAP2 have been strongly linked to ASD. And studies using animal models have demonstrated that early inhibition of the mTOR pathway can significantly ameliorate neuroanatomical and behavioral phenotypes, whereas its efficacy is markedly reduced in adulthood. This finding underscores the critical importance of early intervention in mitigating core ASD symptoms.

Beyond the mTOR pathway, dysregulated branched-chain amino acid (BCAA) metabolism has also been implicated in ASD pathogenesis. Loss-of-function (LoF) mutations in SLC7A5 and BCKDK are strongly associated with ASD. Studies have demonstrated that increasing BCAA levels in the brain, via intracerebroventricular injection or dietary supplementation, can restore neurological function. Also, dietary interventions have been shown to improve neurological symptoms in patients carrying BCKDK mutations, supporting the concept of personalized treatment strategies based on precise molecular mechanisms [10].

3.3. Epigenetic modifications and genetic regulation in ASD

Epigenetic mechanisms regulate chromatin structure and gene expression without modifying the DNA sequence [3]. The research has shown that DNA methylation changes and microRNAs (miRNAs) play a crucial role in the development of ASD, with analyses of lymphoblastoid cell lines and whole-blood DNA from monozygotic twins identifying differentially methylated regions (DMRs) and variations in their expression levels [3]. Regions located in CYP2E1 and IRS2, which control the methylation levels, are associated with the genotype of autism and prenatal vitamin use. However, blood-DNA analysis of CpG sites reveals no methylation differences, suggesting its potential as a biomarker for adult ASD [12]. Symptoms such as sensory impairments and motor coordination deficits in ASD patients have been linked to DNA methylation. The methylation levels of candidate genes are also analyzed using hypermethylated genes like APOE, HTR2A, and HTR4 [3]. In addition, miRNA expression in ASD individuals is different from the controls. In the blood sample, down-regulation of miR-6126 has been detected in adult ASD individuals. Furthermore, both blood and serum samples have been utilized to identify three miRNAs (miR-130-3p, miR-181b-5p, and miR-320a), with the area under the curve (AUC) exceeding 0.85 in ASD patients compared to controls [3]. miRNA-based therapies hold great promise, as miRNAs can be delivered into cells without

DOI: 10.54254/2753-8818/2025.24079

integrating into the host genome. Consequently, therapeutic approaches like miRNA inhibition can be used by down-regulating miRNA antagonists [3].

4. Related clinical approaches and therapeutic strategies

4.1. Non-pharmacological interventions in ASD

Targeting neural circuit molecules may aid in ASD treatment. While both pharmacological and non-pharmacological approaches exist, the latter has indicated promising therapeutic effects, particularly behavioral and psychological interventions such as music therapy, cognitive behavioral therapy (CBT), and social behavioral therapy (SBT), all of which have demonstrated positive outcomes. Prior studies showed that music therapy alters the structural and functional connectivity of the cortex, thus boosting multisensory integration during early development. CBT not only addresses core symptoms but also helps manage comorbid anxiety and depression in ASD. SBT focuses more on emotional regulation, social skills, and functional communication. The combination of these three therapies can markedly improve the independence and quality of life of individuals with autism [13].

Brain stimulation therapy is another treatment option for ASD. Non-invasive techniques such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) enhance regional cortical excitability and are well tolerated by both children and adults [13]. However, these treatments may yield the best results only when administered at an early age. Also, the availability and implementation of non-pharmacological interventions vary across regions, thereby posing challenges to clinical practice [13]. Currently, the evidence supporting the efficacy of non-pharmacological therapies remains insufficient.

4.2. Pharmacological treatments for ASD

In pharmacological therapy, no drug has proven effective in treating the core deficits of autism. Instead, medications are primarily used to manage maladaptive behaviors and comorbid conditions, such as sleep disturbances, anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD). Only two drugs, aripiprazole and risperidone, have been officially approved for managing irritability in children with ASD [14]. However, no medication has been proven effective in addressing the core deficits of autism. Medications used in ADHD and depression treatment are also used in treating ASD. For example, α-Adrenergic drugs such as guanfacine used in ADHD are used to reduce disruptive behavior in ASD [13]. SSRI, a class of antidepressants, are used to alleviate emotional instability, anxiety, and stereotyped repetitive behaviors in ASD [13]. Besides, melatonin has been proven effective in reducing sleep-related issues in ASD children [14]. However, only limited results are observed. Medications like SSRIs are not suitable for every patient, especially autism patients with anxiety or obsessive should be careful when taking the medications. Moreover, all medications come with side effects that vary among individuals. Common adverse effects include increased appetite, fatigue, tremors, dizziness, drowsiness, constipation, and vomiting [14]. Therefore, diet treatment is also used as a complementary approach to manage ASD. Regulating nutrition intake, such as increasing multivitamins, minerals, magnesium, and folic acid in the diet, can help alleviate ASD symptoms to some extent [14].

5. Conclusion

ASD is a complex disorder with genetic and molecular underpinnings, influenced by genetic mutations, epigenetic modifications, and environmental factors. Research has identified several candidate genes, including FOXP2, RELN, and POU3F2, along with chromosomal variations associated with ASD. In addition, molecular mechanisms such as mTOR signaling dysregulation and

DOI: 10.54254/2753-8818/2025.24079

synaptic dysfunction have been extensively studied, offering valuable insights into ASD pathology. Despite research progress, the ASD still has many limitations. The interaction between genetic and environmental factors remains unclear, and universal genetic markers have yet to be identified. Besides, current animal models fail to replicate the complexity of human ASD. Despite some effectiveness, core ASD symptoms remain hard to improve. Given that the causative genes are linked to other neurological disorders, further research and integrated behavioral-molecular therapies may enhance treatment efficacy. Future research should refine the understanding of gene-environment interactions in ASD, identify molecular targets for early diagnosis and intervention, and investigate targeted gene therapy and personalized pharmacological approaches. Exploring the reversibility of epigenetic modifications may offer new therapeutic strategies.

References

[1] *Miles, J.H. (2021) Autism spectrum disorders - A genetics review. Genetics in Medicine, 13(4): 278-294*

[2] *Masini, E., et al. (2020) An Overview of the Main Genetic, Epigenetic and Environmental Factors Involved in Autism Spectrum Disorder Focusing on Synaptic Activity. International Journal of Molecular Sciences, 21(21): 8290.*

[3] *Yoon, S.H., et al. (2020) Genetic and Epigenetic Etiology Underlying Autism Spectrum Disorder. Journal of Clinical Medicine, 9(4): 966.*

[4] *Gill, P.S., et al. (2021) Molecular Dysregulation in Autism Spectrum Disorder. Journal of Personalized Medicine, 11(9): 848.*

[5] *Wang, L., et al. (2023) Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. International Journal of Molecular Sciences, 24(3): 1819.*

[6] *Ergaz, Z., Weinstein-Fudim, L. and Ornoy, A. (2016) Genetic and non-genetic animal models for autism spectrum disorders (ASD). Reproductive Toxicology, 64: 116-140.*

[7] *Stewart, A.M., et al. (2014) Developing zebrafish models of autism spectrum disorder (ASD). Progress in Neuro-Psychopharmacology and Biological Psychiatry, 50,: 27-36.*

[8] *Najm, D., Alame, S. and Chamoun, W. (2024) Unraveling the Role of Wnt Signaling Pathway in the Pathogenesis of Autism Spectrum Disorder (ASD): A Systematic Review. Mol Neurobiol.*

[9] *Thomas, S., et al. (2023) mTOR Signaling Disruption and Its Association with the Development of Autism Spectrum Disorder. Molecules, 28(4): 1889.*

[10] *Bonsi, P., et al .(2022) Postsynaptic autism spectrum disorder genes and synaptic dysfunction. Neurobiology of Disease, 162: 105564.*

[11] *Lo, L. and Lai, K.O. (2020) Dysregulation of protein synthesis and dendritic spine morphogenesis in ASD: studies in human pluripotent stem cells. Molecular Autism, 11: 40.*

[12] *Bhandari, R., Paliwal, J.K. and Kuhad, A. (2020) Neuropsychopathology of Autism Spectrum Disorder: Complex Interplay of Genetic, Epigenetic, and Environmental Factors. In: Essa, M., Qoronfleh, M. (eds) Personalized Food Intervention and Therapy for Autism Spectrum Disorder Management. Advances in Neurobiology.*

[13] *Jiang, C.C., Lin, L.S. and Long, S. (2022) Signalling pathways in autism spectrum disorder: mechanisms and therapeutic implications. Sig Transduct Target Ther, 7: 229.*

[14] *Pistollato, F., et al. (2020) Pharmacological, non-pharmacological and stem cell therapies for the management of autism spectrum disorders: A focus on human studies. Pharmacological Research, 152: 104579.*