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Autism spectrum disorder: An integrative review of etiology, risk stratification and future directions

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent challenges in social communication and the presence of restricted, repetitive patterns of behavior, interests, or activities. The etiology of ASD is multifactorial, involving a combination of genetic, epigenetic, and environmental influences that affect early brain development. Increasing prevalence rates worldwide have highlighted the importance of understanding underlying mechanisms, identifying risk factors, and improving early diagnosis and intervention strategies.

Objective: To evaluate current research on the etiology of autism spectrum disorder, identify key risk factors for effective risk stratification, and explore emerging directions for diagnosis, management, and future research.

Discussion: The development of ASD is strongly associated with genetic susceptibility, including rare mutations and common genetic variants that influence neurodevelopmental pathways. Environmental factors such as prenatal exposures, maternal health conditions, and perinatal complications also contribute to ASD risk. Advances in neuroimaging and molecular biology have improved understanding of atypical brain connectivity and synaptic function in individuals with ASD. Risk stratification approaches, including genetic screening and early behavioral markers, play a crucial role in early detection and personalized intervention. Additionally, interdisciplinary approaches integrating behavioral therapy, educational support, and emerging biomedical interventions are shaping future management strategies. Ongoing research is also focusing on biomarkers and precision medicine to enhance individualized care.

Conclusion: Autism Spectrum Disorder arises from a complex interplay of genetic and environmental factors. Improved risk stratification and early identification are essential for optimizing outcomes. Future research should prioritize integrative approaches that combine biological, clinical, and technological advancements to enhance diagnosis, treatment, and long-term support for individuals with ASD.

Keywords: Autism Spectrum Disorder; Etiology; Risk Stratification; Early Diagnosis; Neurodevelopment

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1. Introduction

Autism Spectrum Disorder (ASD) is a neuro-developmental condition, whose global prevalence over many years is increasing and at present is approximated between 1% and 2% of the pediatric population [1]. This rising prevalence reflects not only improved awareness and expanded diagnostic criteria but also underscores the urgent need to better understand the underlying causes and mechanisms of the disorder. ASD exhibits marked clinical heterogeneity, with considerable variation in symptom severity, cognitive function, and associated comorbidities among affected individuals. This variability is largely attributed to its multifactorial etiology, involving intricate interactions between genetic susceptibility, environmental exposures, and perinatal influences. Consequently, the traditional paradigm of identifying a single causative factor has shifted toward a more integrative framework that emphasizes the convergence of genetic vulnerabilities and environmental triggers, particularly during critical periods of prenatal and early postnatal brain development [2,3].

Recent advances in genomics, neuroimaging, and molecular biology have further expanded our understanding of ASD pathophysiology, highlighting the role of gene–environment interactions and epigenetic regulation in shaping neurodevelopmental outcomes. These insights have paved the way for a paradigm shift from symptom-based management to precision medicine approaches, which aim to identify biologically distinct subgroups and tailor interventions accordingly.

In this context, risk stratification has emerged as a key concept, enabling the early identification of high-risk individuals through the integration of genetic, biological, and behavioral markers. Early detection is particularly critical given the heightened neuroplasticity during early childhood, which provides a valuable window for intervention and improved long-term outcomes [4].

This integrative review aims to synthesize current evidence on the etiological factors contributing to ASD, including genetic architecture, environmental and perinatal risks, and epigenetic mechanisms. Furthermore, it explores advances in risk stratification, emerging diagnostic biomarkers, and future directions toward personalized and precision-based intervention strategies.

2. Genetic Architecture And Heritability

ASD is one of the most heritable neuropsychiatric condition. Large studies show that this genetic influence may vary from rare but powerful gene changes to common genes but their combined effects. Scientists believe that more than 200 genes are linked to ASD risks. These genes may impact important brain functions like connection and communication of neurons e.g *SHANK3*, *SYNGAP1* or how genes are regulated and packaged e.g *CHD8*[5]. Rare genetic changes like deletion and duplication of DNA or single-letter spelling errors have more significant risk on development of ASD than other genetic changes. These rare genetic risk are often linked to older paternal age[6]. For example, the *16p11.2* deletion has shown that it leads to imbalance in brain signals by disrupting development of key brain cells. This imbalance is major theory of causation of ASD symptoms[7]. Many researchers suggest that the females have some kind of biological protection which means they often need stronger magnitude of genetic risk factors to show signs of ASD. So the biology of women sets a higher bar for symptoms to appear[8].

3. Environmental And Perinatal Risk Factors

There is substantial evidence for environmental factors to play significant role in causation of ASD. Prenatal and early post-natal events are directly or indirectly related to ASD.

3.1. Prenatal exposure

Many researches show that various factors during pregnancy are linked to higher chance of the child having ASD and those factors include:

- Very highly active immune system of the mother
- Various medical condition of the mother during pregnancy like diabetes, obesity, high blood pressure (pre-eclampsia)
- Exposure of the mother to harmful substances in the environment like air pollution, pesticides or chemicals found in plastics.

There is growing evidence that the children's gene can interact with these environmental factors which increases the risk of ASD [9,10]. Some medicine like Sodium valproate has definite association with ASD but for other medicine like SSRI (Selective Serotonin Re-uptake Inhibitor) the connection is less clear. It is difficult to establish what is the cause of ASD either it is effect from the medication or mother's underlying mental health condition which led to its use [11].

However, certain nutrients during pregnancy may help protect enough the developing brain. Getting enough Vitamin D and folic acid during pregnancy appears to strengthen the baby's developing brain and nervous system against potential harms and may help to counterattack some environmental risks [12,13].

3.2. Perinatal and Neonatal Insults

Preterm birth (being born too early) is one of the significant and independent risk factors for ASD. This risk is especially highest for babies born extremely early, specifically before 30 weeks of gestation [14]. Babies who are born this early often have a distinct pattern of behaviors, which can make it difficult to spot the signs of ASD in their first few years complicating early diagnosis.

Apart from preterm birth other complications during pregnancy and birth increases the risk of ASD. These are as follows:

- Fetal distress: It indicates that baby is not getting enough oxygen before or during birth.
- Low birth weight: Babies born with very low weight is often linked to prematurity or growth problems in mother's womb.
- Congenital Anomalies: Health problem either physical or biochemical conditions present before birth [15].

Another factor includes how a baby is born either by normal process or by Cesarean section which play a role, but the link is not specific. Research show that baby born by cesarean section under General Anesthesia (GA) is associated with higher risk of ASD but if c-section is done under regional (spinal anesthesia or epidural) where the mother is not awake does not show same link than c-section done under GA where mother is not awake. This suggests exposure of anesthetic drugs used in General Anesthesia might affect baby's developing brain leading to increased risk of ASD [16].

3.3. Gene-Environment and Epigenetic Interactions

Scientists all over the world agree that ASD risk does not come from single cause but usually occurs through "multiple-hit" model which includes:

- Genetic susceptibility (First Hit): A person who inherits specific gene has their developing brain more vulnerable and susceptible.
- Environmental Trigger (Second Hit): Exposure to environmental risk factors like those mentioned above increases the existing vulnerability which further amplifies the risk of ASD [17].

Epigenetics is the study of how experiences and environment can change our genes work without altering the DNA sequence itself. DNA methylation is the most important epigenetics study used in autism which explains how this might work. DNA methylation has the ability to turn genes "on" and "off" which acts as dynamic interface, translating environmental exposures (like diet or toxins) into long-lasting biological changes. Since these epigenetics markers are measurable, researchers are studying these markers which provide great promise as biomarkers to help identify individuals at higher risk of autism [18]. The complex interaction underlying ASD etiology is illustrated in Figure 1

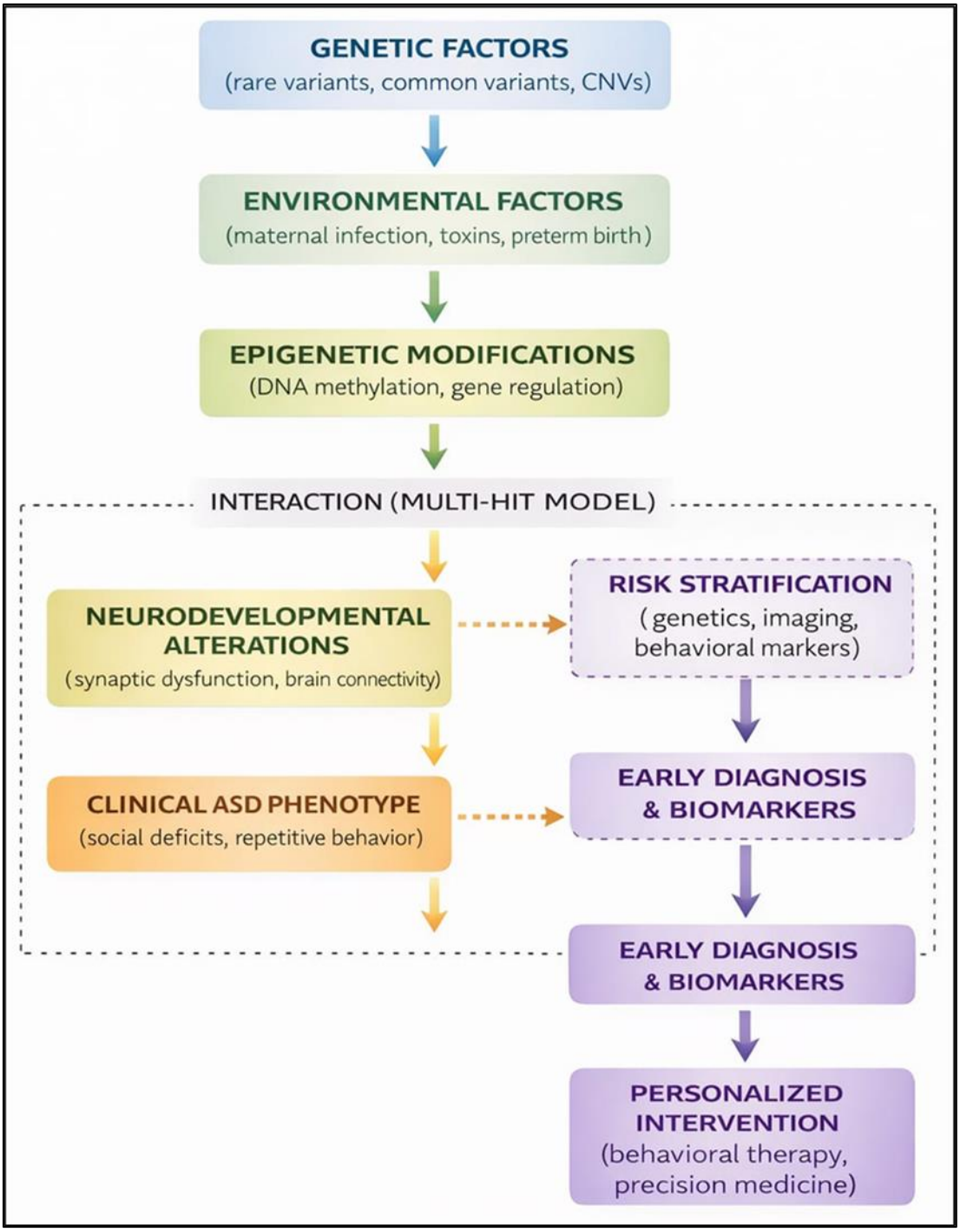

Figure 1 Integrated model showing etiology and risk stratification of Autism Spectrum Disorder

3.4. The Preterm Infant: A High Risk Phenotype

Babies that are born prematurely, especially those born very early, form a unique high-risk group for brain and nervous system disorders including autism spectrum disorder (ASD) . Early diagnosis of ASD is very challenging and difficult in preterm babies because these infants have early behaviors that are similar with that of signs of ASD. For example, they might be very sensitive to sounds or touch or have difficulties with social cues like eye contact. Since these traits are also very common in many premies it can be very hard for doctors to tell if they are temporary effects of prematurity or early signs of autism [19]. In preterm infants, advanced neuroimaging has shown positive hope for finding detecting early warning signs or biomarkers. The key finding is:

- Altered Cerebral growth which shows altered difficulty in coordination & learning

- Changed white matter connectivity

These specific brain differences are associated with higher likelihood of developing ASD in the childhood [20].

There are significant differences in risk of ASD based on the gender of baby.

- Females: The risk of Autism increases exponentially the earlier they are born.
- Males: They show generally elevated risk in all preterm births regardless of exactly how early they are born.

This contrasting fact clarifies one thing that underlying biological vulnerabilities which may lead to ASD may be different in males and females [21].

4. Diagnostic Challenges And Advances

The problem with current diagnosis is that for getting a diagnosis of autism spectrum disorder it still depends on a clinician observing a child's behavior. Clinicians use gold-standard tools like ADOS-2 (Autism Diagnostic observation Schedule, Second edition) which is a play-based observation and ADI-R (Autism Diagnostic Interview, Revised) which is a detailed parent interview. However, a key challenge is that these behavioral tools can sometimes suggest autism in children who don't have it, particularly in groups like preterm infants. These children often have general developmental delays and behaviors related to those delays (like limited eye contact) which can look similar to autism, leading to potential false positives leading to diagnostic challenges [19, 22].

Because of these challenges many research are now focusing on finding objective biomarkers which can be measured and so that it can lead to correctly identity risk without any difficulty. Some of them includes:

- Eye-tracking: This is one of the promising fields where technology is used to precisely measure where a baby or child looks. Any abnormal patterns like constantly looking for objects rather than people's faces can be an early signal [19].
- Neuroimaging: Using brain scans like MRI can be used to identify patterns in brain structure and how different regions communicate with each other. And by using this technique we can detect these pattern as early as in infancy [20].
- Genetic testing: In order to find known genetic changes that are linked to autism, the best way is to use genetic tests like chromosomal microarray and whole-exome sequencing. These easily helps us to identify specific genetic subtypes of ASD [23].

Multi-omics: This is an advanced approach that tries to combine many layers of data which mainly looks on:

- Epigenetic marks: how environment has affected gene activity
- Proteomic profile: patterns of proteins in blood or saliva
- Metabolomic signatures: patterns of small molecules produced by the body's metabolism.

The goal of multi-omics is to find comprehensive biological fingerprint of risk [24].

The main goal of this research is early detection which can range from few weeks to few months of onset of disease. Identifying children at high risk ideally before 18-24 months of age is very critical because this period is when the brain is most adaptable as known as brain plasticity. So, it is best to apply intervention with therapies during this time and we can hope for having greatest positive impact on child's long-term growth and development [25].

5. Co-Morbidities And Behavioral Outcome

Autism spectrum disorder (ASD) very often exists with other challenges. These co-morbidities affect a person's development, mental health and physical health. Common examples include other neuro-developmental conditions like intellectual disability, attention deficit hyperactivity disorder (ADHD), psychiatric condition like anxiety and depression and medical issues such as epilepsy, sleep disorders. Research show that for predicting serious long-term behavioral challenges, having co-occurring conditions like conduct problems and attention problems is more significant than the core symptoms of autism alone. These specific conditions are strongly linked to future difficulties with behavior, managing emotions and having higher risk of trouble with law [26].

With regards to physical health, in individuals with ASD there are irregularities in the immune system. It is important to note that this does not mean that common allergic diseases like asthma are more frequent in the autistic population. However, a family history of allergic disease (known as familial atopy) might play a role in shaping a specific type of immune system in subgroups of autistic individuals [27].

6. Intervention And Management

There is no medication that can cure the core social and communication deficits of autism spectrum disorder, that's why the treatment and management must be focused on support, skill building and education. Treatment is focused on early behavioral and educational strategies. And the best time to start intervention is early in life so that it can offer greatest benefit. Programs known as Early Intensive Behavioral Interventions (EIBI) such as the Early Start Denver Model (ESDM) uses play based, relationship focused teaching to engage young children. When started early (often before age 3 or 4), these evidence-based interventions allow for more personalized treatment that improves thinking, language, and everyday living abilities [28].

Emerging research is exploring more personalized treatments based on biological profile of specific individuals. These are not cures but may help in management of associated challenges. For example, in cases of ASD where there is evidence of neuro-inflammation, a natural compound 'luteolin' is being studied. Luteolin acts as a mast cell stabilizer which regulates overactive immune cells in the brain and early trials shows that it may help reduce irritability and improve focus in this subgroup [29].

A complete lifelong management plan extends beyond direct therapy for the individuals, and it includes following components:

- Family-centered care: Providing training and supports to parents and caregivers which empowers them for better care.
- School-based supports: Individualized Education Programs (IEP) and classroom accommodations are invaluable for learning.
- Treating co-occurring conditions: Active treatment of other conditions like anxiety, epilepsy, sleep disorders, and attention difficulties is a vital part of care as these conditions significantly affect daily functioning and well-being [2].

7. Future Directions and Research Imperatives

7.1. Precision phenotyping & biomarkers

The main goal is to stop grouping autism only by using observed behaviors like social difficulty or repetitive actions but by using new ideas to create subgroups using typical causes (e.g. sensing biological cause. Researchers are aiming to do so by combining data based on neuro-imaging, genetics and molecular tests and hope to identify measurable "biological markers" that allows for accurate classification and personalized care [30].

7.2. Longitudinal Lifespan studies

To clearly understand how autism unfolds, we need to track individuals from infancy to all the way into adulthood. This is important especially in high-risk groups like babies born prematurely and younger siblings of autistic children. By studying these groups over longer period of time usually decades, we can map different developmental pathway, identify early prognostic factors and we can see how needs change across a lifetime [25].

7.3. Mechanistic and Translational Research

This priority focuses on understanding the precise chains of event that leads to autism. Scientists use advanced tools like Human cell models, animal models to know how a genetic risk factor or environmental exposure actually alters brain development which leads to behavioral differences The main aim here is to translate findings from lab into real-world understanding and therapies [31].

7.4. Intervention trials

The main goal is to treat sooner and with more precision. Future treatment research can work on two fronts. First one is very early intervention which means testing new therapies before symptoms appear in the first year of life which Include neuro-protective agents that safeguard brain development in high-risk infants like preterm baby. And second

one is targeted therapies like developing and testing specific drugs for individuals with identified genetic subtypes rather than for all groups as a single and common entity [32].

7.5. Global Health and Equity

The goal is to ensure fair access for all. This includes fixing the unequal access to autism diagnosis, support and services which includes addressing disparities that affect racial and ethnic minority groups, people with low socioeconomic background, communities in low-resource setting and countries. New research must focus on creating accessible, affordable, and culturally appropriate tools and services to achieve global health equity [33].

8. Conclusion

Autism Spectrum Disorder is a multifactorial condition driven by the interaction of genetic and environmental influences. Advancing early detection and individualized care through biomarker discovery and precision-based approaches is essential to improve outcomes and quality of life for individuals with ASD.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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