

Exploring Autism Spectrum Disorder in Genetic Perspective Review

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Abstract. Autism in children is a common mental and behavioral disorder in pediatrics, and the incidence is increasing year by year, but the pathogenesis of autism has not been clear, and there is no specific drug. At present, the number of autistic groups in China is still growing, which brings great pressure to families and society. In recent years, public awareness of autism has significantly increased, thanks to the dissemination of knowledge in professional journals and the widespread use of social media. As a result, professionals in the fields of psychology and biology are increasingly using the term 'autism spectrum disorders' (ASDs) to describe this condition. This paper aims to explore the ASD in genetic perspective which include several ways to diagnose ASD, introduction of different type of symptoms such as Rett syndrome or Asperger's syndrome, also giving variety causes both in genetic and nurture factors and some conservative therapy recommendations such as some drugs therapy.

Keywords: Autism, diagnosis, influencing factors, treatment.

1. Introduction

ASD is a behaviorally defined disorder characterized by qualitative impairments in social communication, interaction, and imagination, as well as repetitive behaviors and habits of limited interest and stereotyping. Although hereditary factors can contribute to the disorder, it is still poorly understood [1, 2]. According to a short documentary posted by a news agency accredited by the Chinese government, individuals with autism often experience sensory overload due to the excessive processing of sensory information in the cortical column of their cerebral cortex. As a result, they may experience fear, panic, and other negative emotions when exposed to stimuli that most people would consider benign, such as soft light or quiet sounds.

2. Symptoms

Symptoms of autism can vary widely, as it is a neurodevelopmental disorder that typically emerges in infancy or childhood and follows a variable course. Individuals affected by autism may exhibit severe impairments in some areas while excelling in others, often surpassing the capabilities of neurotypical individuals. Diagnosing autism can be challenging for doctors as it encompasses a wide range of behaviors, leading to ongoing uncertainty about proper categorization [3]. This is because individuals with autism display abnormal sensory processing, the intensity of which varies from person to person, resulting in diverse responses to different stimuli.

Autism is not characterized by a simple symptom but rather by a triad of symptom features: impairment in social connection, and limited interests paired with repetitive behaviors.

Typically, developing infants display social capabilities, such as the ability to make eye contact, respond to sounds, and even smile. However, individuals with autism often exhibit avoidance of eye contact and face challenges in developing reciprocal interactions. According to research by Simon Baron-Cohen, children with autism commonly lack the trait known as 'theory of mind' [4]. This trait involves the ability to perceive the perspectives of others, a skill that typically emerges in humans around the age of five and in primates. By age five, neurotypical children can interpret gestures, facial

expressions, and social cues to understand others' knowledge, emotions, and intentions. Unfortunately, children with autism often struggle with this ability, making it difficult for them to comprehend and interpret the behaviors of others. Consequently, individuals with autism may exhibit the following symptoms (American Psychiatric Association Autism [5]. Limited use of body language or non-verbal communication skills, including avoiding eye contact. Difficulty forming appropriate peer relationships. Weaker interpersonal communication skills compared to neurotypical individuals. Limited motivation and ability to actively share interests and emotions during communication. Challenges in initiating social interactions. Struggles in maintaining two-way conversations.

Difficulty in establishing and maintaining friendships" is a common challenge faced by individuals with autism [6]. Many individuals with autism also experience difficulties in sensory processing. They may exhibit hypersensitivity or hyposensitivity to certain sounds, lights, tastes, smells, and touch. For instance, they may cover their ears to avoid loud noises or have an aversion to being touched or hugged. They may struggle to process multiple sensory inputs simultaneously, showing preferences for specific sensory stimuli such as glowing or spinning objects or engaging in repetitive behaviors like clapping hands or an inability to sit still. Additionally, young children with autism often demonstrate delayed motor development or poor motor coordination.

People with autism frequently experience heightened levels of anxiety. It is a kind of repetitive pattern of behavior. Routine activities or changes in their environment or the presence of unfamiliar individuals, such as classmates, family members, or colleagues, can trigger feelings of nervousness. In moments of anxiety, they may engage in self-harming behaviors, such as biting their hands or objects around them. Some individuals with autism may also exhibit negative emotional reactions, including tantrums or engaging in self-talk.

Different symptom and diagnosis

Diagnosis should be made by combining the results of, physical and neurological examination, psychiatric examination, and auxiliary examination. The main diagnostic points include onset within 36 months; the main manifestations are social interaction barriers, communication barriers, narrow interest and rigid and repetitive behavior; Excluding Rett syndrome, Heller syndrome, Asperger syndrome, speech and language development disorders and other diseases [7].

Rett syndrome, which exclusively affects girls, typically emerges between the children in 7 and 24 months. Children development progresses normally prior to onset, but after the onset, cranial development slows down, acquired speech and social communication abilities rapidly deteriorate, and cognitive functions are severely impaired. This condition often coexists with hyperpnea, gait instability, ataxia, scoliosis, and seizures.

Childhood disintegrative disorder, characterized by symptoms appearing mostly around ages 2 to 3 years, also exhibits typical development prior to onset. However, after onset, intelligence and other acquired abilities, such as speech, social communication, and self-care skills, rapidly decline or are completely lost.

Asperger's syndrome shares certain features with childhood autism and is more prevalent in boys. Symptoms typically become prominent during school age and primarily manifest as interpersonal communication difficulties, limitations, stereotypical patterns, and repetitive interests and behaviors.

Children with expressive or receptive language disorder demonstrate impaired ability to express or comprehend language, despite having normal or near-normal intelligence levels. They exhibit good nonverbal communication skills and do not display qualitative defects in social interaction, narrow interests, or rigid repetitive behaviors. In other words, these individuals solely have a faulty language system, as they can understand others' speech and express themselves through nonverbal means such as sign language or drawing [8].

Childhood schizophrenia typically emerges in early adolescence. Prior to onset, development follows a normal trajectory, but hallucinations, thought disorders, emotional indifference or disharmony, lack of volitional activity, and unusual behaviors may manifest after onset.

Children with intellectual disability do not exhibit qualitative defects in social communication. Their language abilities are consistent with their level of intellectual functioning, and they do not

demonstrate narrow interests or rigid repetitive behaviors. However, in cases where a child displays symptoms characteristic of both autism and intellectual disability, a diagnosis for both conditions may be warranted.

Differentiating among these six typical disorders requires a comprehensive evaluation involving a detailed medical history, physical and neurological examinations, psychiatric assessments, and auxiliary tests.

3. Cause of ASD

There is no single cause of autism, both environmental factor and genetic factor can affect the risk of having autism. Autism has a strong hereditary component, as evidenced by studies involving families and monozygotic twins. The risk of autism is around 50% in direct relatives and as high as 90% in monozygotic twins [9]. There is a clear association between autism and certain genes, as certain genetic disorders can directly cause autism. Examples include fragile X syndrome (FXS), tuberous sclerosis, and RASopathies. These genetic disorders are closely linked to the brain and often present with learning disabilities, intellectual impairments, and autism-like symptoms.

3.1. FXS

FXS is a common monogenetic risk factor of autism. A single gene mutation can cause FXS. FXS patient is often associated with ADHD, cognitive disability, anxiety, and ASD.

FXS is a disorder caused by a dominant gene on the X chromosome, and because males have just one X chromosome, they typically experience more severe symptoms, occasionally including seizures. Physically, individuals with FXS may exhibit characteristics such as abnormal ear and face, flattened feet, and soft skin. The mutation takes place in the regulatory area of the FMR1 (fragile X messenger ribonucleoprotein 1) gene. In individuals without the condition, the CGG trinucleotide repeat in this region typically ranges from 6 to 53 repeats. However, a mutation can cause an expansion of this repeat to a range of 55 to 230 repeats [10]. This expansion leads to the methylation of the CGG sequence and the silencing of the adjacent CPG island, ultimately resulting in the suppression of the FMRP gene [11]. FMRP is a regulatory protein that plays a role in synapse function, particularly in the process of negatively regulating the translation mediated by mGluR 1, a type of receptor involved in synaptic signalling. mGluR is a receptor located on the surface of synapses. When it is activated by the neurotransmitter glutamate, it sets off a series of reactions that result in the synthesis of Activity-regulated cytoskeleton-associated protein (ARC). ARC plays a role in clathrin-mediated endocytosis, a process involved in the removal of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) from the synaptic membrane. AMPA receptors are essential for synaptic plasticity, which is closely linked to processes like memory and social abilities. While the precise mechanisms are not yet fully understood, a reduction in the production of FMRP due to a mutation in the FMR1 gene disrupts the regulation of ARC production [12]. This disruption leads to an increased rate of AMPA endocytosis. Such dysregulation contributes to the development of conditions such as autism, social disabilities, and learning disorders (as depicted in Figure 1).

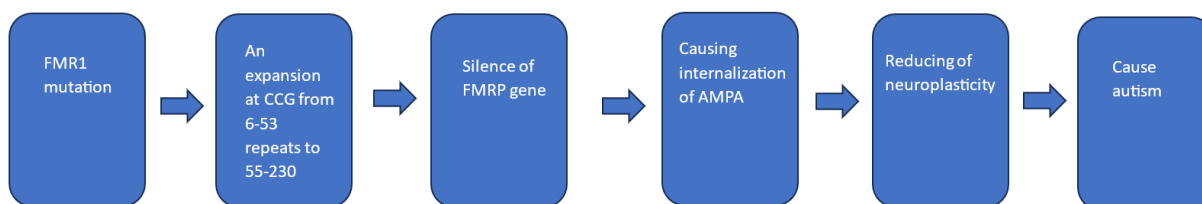


Figure 1. Caused by FMR1

3.2. Tuberous Sclerosis

Tuberous sclerosis is a genetic disorder characterized by the formation of non-cancerous tumours in the brain and various parts of the body. Approximately 40-50% of individuals with Tuberous

sclerosis develop ASD. This condition is caused by mutations in either the TSC1 or TSC2 genes located on chromosome nine. Any mutation in these genes can lead to abnormal development of body cells. TSC1 produces a protein called hamartin, while TSC2 produces a protein called tuberin. Both proteins act as tumour suppressors within cells, regulating cell growth through the mammalian target of rapamycin (mTOR) pathway and serving as negative feedback mechanisms. Mutations in the TSC1 or TSC2 gene result in reduced levels of hamartin or tuberin, leading to the growth of tumours. Neurobiological investigations have shown that abnormalities in the frontal and temporal regions of the brain can affect individuals and potentially contribute to the development of autism [13]. Tuberin, the protein produced by the TSC2 gene, is highly expressed in these brain areas. The presence of tubers (abnormal growths) in the temporal lobe, frontal lobe, posterior tuber, or cerebellum can lead to intellectual disabilities, seizures, and autism [14]. These generalized disruptions in brain function account for about 50% of individuals with tuberous sclerosis complex exhibiting autism as one of their symptoms. (as depicted in Figure 2).



Figure 2. TSC 1 or TSC 2 mutation

3.3. RASopathies

RASopathies are a group of syndromes that result from mutations in genes responsible for regulating signals along the Ras/mitogen-activated protein kinase pathway. While there are high numbers of individual with RASopathies who also have ASD, there is limited research available on this specific association. The Ras/mitogen-activated protein kinase pathway plays a crucial role in controlling growth factors and embryological development. In addition to ASD, RASopathies are associated with various other clinical features, including growth problems, heart disease, and an elevated risk of cancer. Some specific RASopathy syndromes, such as neurofibromatosis type 1, Noonan syndrome, Costello syndrome, and cardio-facial-cutaneous syndrome, exhibit traits that resemble autism. However, the precise mechanisms by which abnormalities in this pathway contribute to the risk of developing autism are not yet fully understood. (as depicted in Figure 3).

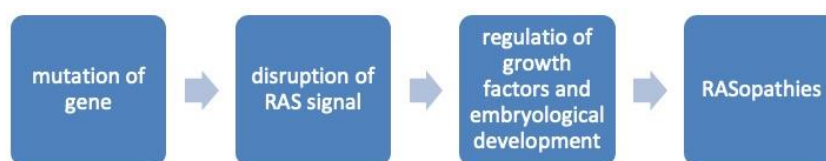


Figure 3. Caused by mutation of gene

3.4. Other Biomarkers

Some children with ASD exhibit mitochondrial dysfunction, characterized by impaired energy production [15]. Although most cases of mitochondrial dysfunction in individuals with both mitochondrial dysfunction and ASD may be acquired rather than inherited, there is a possibility that an abnormal pyruvate ratio could increase the risk of developing ASD.

Autoimmune autistic disorder is a specific subset ASD in which autoimmunity is believed to play a role in the abnormal language development observed in children with autism. In individuals with ASD, there have been discoveries of autoantibodies that target the nervous system [16]. These include antibodies against ganglioside M1, antineuronal antibodies, and serum anti-nuclear antibodies, all of which can contribute to the severity of autism symptoms. These antibodies are often found in the cerebellum and frontal lobe of the brain, and children with these antibodies may exhibit cognitive dysfunction compared to those who do not have them. It is likely that mutations in specific genes are responsible for the production of these antibodies.

Certain gene methylation patterns at specific sites are linked to the severity of autism. The methylation pathway plays a critical role in regulating gene activity by adding or removing methyl groups, which in turn influences gene expression. In individuals who are genetically predisposed, oxidative stress can disrupt methylation processes, leading to neurological deficits and potentially contributing to the development of autism [17]. A reduction in the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) in individuals with ASD may be a result of impaired methylation. Methylation of specific genes, such as the oxytocin receptor and MeCP2 in the frontal lobe, can serve as genetic markers for autism [18]. The oxytocin receptor is a type of G protein-coupled receptor that responds to the neurotransmitter oxytocin. It plays a significant role in the central nervous system and is believed to be crucial for social and emotional behaviour, as well as dopamine release. MeCP2 (methyl CpG binding protein 2) is a protein found in nerve cells and is essential for normal neuronal function. The MeCP2 gene is located on the X chromosome, and mutations in MeCP2 are the primary cause of Rett syndrome, a genetic disorder that primarily affects females. Symptoms of Rett syndrome include slowed growth, difficulty walking, microcephaly (abnormally small head), and impairments in language and coordination. Individuals with Rett syndrome often also exhibit varying degrees of ASD.

4. Treatment

It is challenging for professionals supporting patients with autism and their families to determine an optimal treatment approach due to the wide range of symptoms and the influence of internet information. Nowadays, individuals can easily access online resources and gather a wealth of information, even though much of it has not undergone a peer-reviewed process. This accessibility raises concerns as parents may question the relevance of established therapies and programs, leading to disagreements with professionals and delaying timely diagnosis and treatment.

ASD exhibit significant symptom variability and severity, making it difficult to determine an appropriate treatment. However, doctors can refer to the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association to confirm ASD diagnosis and involve specialists in the diagnostic process. Genetic testing is recommended to identify any underlying genetic disorders like Rett syndrome or FXS, which affect neurons and the brain. Additionally, the child's communication skills, behavioral changes, and developmental patterns should be observed, along with hearing and speech assessments.

There is currently no cure can 100% deal with ASD, but some medications can be used to address certain symptoms such as anxiety, self-injurious behavior, or sleep problems. Atypical antipsychotics, particularly risperidone, have shown effectiveness in managing challenging behaviors like aggression and self-injury in children with autism. Stimulants and alpha-Adrenergic agents can be used to address issues of hyperactivity, hyper-vigilance, inattention, and impulsivity commonly observed in children with autism. Although stimulants are widely used to treat attention deficit hyperactivity disorder (ADHD) which means the people who seem restless, may have trouble on concentration, their efficacy in ASD children is not extensively studied. Only limited research suggests some improvement in ADHD symptoms in children with autism. Melatonin is used to improve sleep problems, as pineal endocrine hypofunction has been observed in autistic patients [19]. Sleep disturbances can be challenging for the entire family, with difficulty falling asleep at night. While the use and efficacy of melatonin have not been extensively researched, studies have shown its usefulness in improving sleep induction [20]. Empirical trials of low-dose melatonin may be beneficial for children experiencing difficulty falling asleep at night. On the other hand, by doing some exercises and other physical activities do help the patients that have ASD to reduce autistic traits, and, in some cases, it is possible to provide a therapeutic intervention during the cure [21]. The 48-weeks experiment has shown a positive result by comparing the children who took the intervention programs and those who didn't, the group that receive the intervention shows a slightly higher increase in a height of 3.7cm and 2.4cm in control group. Furthermore, after the clinical trial, a questionnaire is

sent to the families of the participants, asking about the progress of the follow-up patients. Fortunately, most of the family members report that their children's behaviors and autistic reactions have reduced. Therefore, by collecting and analyzing those data, it proves that there is an increase, both for physical health score (13.3, 95% CI 7.7–18.9, effect size $1/4$ 1.05) and psychosocial health score (15.2, 95% CI 9.8–20.7, effect size $1/4$ 1.66)

5. Conclusion

ASD present significant challenges across various disciplines, including psychology, biology, and sociology. Despite advancements in understanding the disorder, autism remains a complex and challenging issue. One critical concern is the delayed diagnosis and inadequate intervention for children with autism. This problem is particularly prevalent in rural areas where parents may have limited awareness of mental health issues, and medical professionals may lack sufficient knowledge about autism. Autism has been found to have a strong hereditary component, with a higher risk observed among individuals with affected relatives. While the exact causes of autism vary, they range from specific single-gene mutations to a combination of genetic. Although some drugs can target specific genetic variations associated with autism, effective treatments are largely lacking.

In conclusion, ASD is a genetically inheritable condition influenced by various factors and interconnected with brain-related diseases. Common symptoms include difficulties in forming friendships, lack of motivation, and challenges in maintaining peer relationships. Treatment options are limited, and while certain medications can help manage specific autism symptoms such as anxiety and insomnia, unfortunately researchers still do not have a cure for ASD. Research focusing on the genomics of autism holds promise for the development of targeted drugs or treatments. Gene sequencing can also help identify autism risk factors and enable precautions to minimize the impact of the disorder. Overall, there has been a growing public awareness of autism in recent years, and ASD continues to be an area of significant research. A comprehensive understanding of the genetic aspects of autism contributes to unraveling the mysteries of this syndrome, bridging the fields of neurology and psychology.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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