

# The pathogenesis and differences in molecule of autism

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**Abstract.** With the deepening of the understanding of autism, the scope of autism spectrum disorder (ASD) continues to expand. The prevalence rate of ASD has arrived over 1% around the world. Language and social communication issues, as well as recurrent stereotyped interests and behaviors, are the main signs of autism. To find out the pathogenesis of autism, scientists have found a lot, which show that autism is a complex disorder resulting from many factors, but many questions remain unanswered. Numerous theses have been written about the causes and symptoms of autism, but frequently only a few of these perspectives have received attention. This review is to sum up the causative factors of autism, including genes and environmental, and lists how autism different from normal people in terms of genes, proteins, and cells. This review will introduce these factors with some examples.

**Keywords:** Autism, SHANK3, ADNP, WDFY3, IgG

## 1. Introduction

With its high occurrence, autism may significantly affect a patient's life. Researchers have looked at autism in a variety of methods to try and understand what changes in individuals with autism make them abnormal. Numerous domains, including genes, proteins, cell architecture, brain regions, environmental influences, and more, are involved in the research of autism. This review aims to provide an overview of the causes and variations of autism. Numerous studies have been conducted on the causes of autism. The goal of this paper is to provide an overview of some of the key findings in a few of the more significant areas.

Autism is a representative disorder of pervasive developmental disorder (PDD). It is a condition characterized by developmental abnormalities of the central nervous system brought on by a combination of hereditary and environmental factors. It is a congenital mental illness which usually onset before the age of 3. The cause of autism is diverse, and the severity of symptoms varies widely from patient to patient. Heredity is an important factor in causing autism.

The topical autism has three core symptoms: 1. Social communication disorders. Manifested by a lack of interest in communication and social skills. 2. Communication barriers. They have obvious barriers to language communication, including impaired language comprehension, abnormal speech form and content, and impaired speech use ability. 3. Narrow interests and stereotyped, repetitive behaviors. They always exhibit stereotyped, repetitive movements and bizarre behavior. However, lots of patients with autism present with atypical autism, and they have varying degrees degrees of deficits in only one or two of these symptoms. So, people have proposed ASD based on these three core

symptoms. In addition to the core symptoms, autism also show peripheral symptoms such as low intellectual development, uneven ability development, and distraction.

Autism was first reported in 1943 when Kanner described the strange behaviors of 11 children. One of these behaviors is the serious problem of social interaction, and the other is the repetition of stereotypical behavior. Subsequently, through continuous research and in-depth discussion of autism, the understanding of autism has been deepened, and people have gradually realized that autism is a unique disease. In DSM-III, autism is classified as “pervasive developmental disorder” (PDD) as “infantile autism.” However, there are many patients who do not show typical PDD, and extensive atypical PDD has attracted attention. After a long period of research and constant revision, ASD was proposed. There was also the introduction of the DSM-V and ICD-11, which include autism as a single classification of core symptoms. DSM-V and ICD-11 consider the severity of patients with similar core symptoms to be different, making diagnosis difficult and providing limited reliability across subcategories. DSM-V and ICD-11 remove subcategories of autism, such as Asperger’s syndrome, and classify the diagnosis by severity [1].

Even though the mechanism of autism has been investigated for many years, specific related molecules, cell behaviors and environmental factors still need to be clarified.

This review firstly discussed the genetic etiology of autism mechanism. Then the downstream protein expression profile and corresponding cellular response were also discussed, respectively. Finally, the environmental factors influence on autism were also demonstrated.

## 2. Genetic etiology

Studies on families and twins have demonstrated that there is a hereditary component to autism and that environmental factors are not major contributors. The genes that cause the disease vary greatly from person to person with autism, and large-scale studies using whole genome sequencing have identified multiple high-risk genes, many of which coincide with other diseases [2]. These high-risk genes fall into two main categories: genes involved in transcriptional regulation and genes associated with synaptic proteins. I will introduce ADNP, SHANK3, and fragile X syndrome as examples.

### 2.1. ADNP

ADNP has a variety of functions and is a transcription factor associated with the SWI/SNF family of chromosomal remodeling complexes (Gene transcription can be inhibited and activated by SWI/SNF, which has a significant impact on the development of various tissues, particularly the nervous system). In addition to this, it is also related to cytoskeletal proteins, as well as some additional functions. The eukaryotic translation initiation factor 4E and ADNP’s numerous WD-repeat proteins 5, which facilitate the formation of histone modification complexes, were both shown to interact with one another by immunoprecipitation. The study found that ADNP can interact with related proteins of autophagy initiation protein microtubules, and also with SHANK3. The effects of SHANK3 and autophagy on ASD will be introduced later. The ADNP gene has five exons, and most of the ADNPs observed in ASD patients are C-terminal truncations caused by mutations. ADNP acts as a transcription factor in the SWI/SNF family chromatin remodeling complex, which interacts with SWI/SNF via the C-terminus. The C-terminal truncation prevents it from functioning properly, resulting in ASD [3].

### 2.2. SHANK3

SHANK3 is a synaptic protein-related gene that encodes for a scaffold protein. SHANK3 is associated with the formation of PSD, binds to neuroligins, promotes the maturation of dendritic spines, and plays a crucial part in the healthy formation of neural connections. PSD is a postsynaptic membrane structure of glutamatergic energy. When the SHANK3 gene is mutated, it is found that the expression of several scaffold proteins and glutamate receptors of PSD is reduced, glutamatergic signalling is affected, and the morphology of neurons is also affected. In the region of the striatum, where it is closely connected with the caudate nucleus, SHANK3 mRNA is strongly expressed. The volume of the caudate nucleus increases in SHANK3 mutants, which leads to repetitive stereotyped behaviour of ASD [4, 5].

### 3. Changes at the protein level

Protein is the main substance that performs life functions in an organism. Therefore, mutations in genes lead to variations in protein structure, quantity, and function. Protein differences are also the direct cause of neuronal abnormalities, further leading to autism. These include those described earlier that are synapses-related or associated with gene transcriptional regulation, such as voltage-gated ion channels that regulate action potential propagation, pacing, and excitability-transcription coupling, and proteins associated with histone modification and chromatin remodeling [6].

#### 3.1. *WDFY3*

The autophagy process is complex and involves multiple genes and proteins, so excessive or insufficient autophagy by abnormal proteins in it will affect the survival of neurons. Autophagy disease is one of the important causes of neurodegenerative diseases, and of course, it can also cause ASD. Defects in the autophagy gene *WDFY3* have been shown to hinder nerve development, and the loss of the *WDFY3* protein is one of the causes of ASD. *WDFY3* can act in aggregates, removing aggregate proteins through autophagy. *WDFY3* may be able to modulate Wnt signalling by removing *DVL3* aggregates to regulate brain size. Scientists have also observed early brain overdevelopment and primary microcephaly in *WDFY3* mutants [7].

### 4. Changes in the cells

Although the ASD gene has been well studied, not much is known about the changes in specific cell types. ASD is associated with the connection of neurons, which mainly involve excitatory neurons, interneurons, and astrocytes. Scientists analyze changes in the expression of specific cells and find that some genes are expressed in altered amounts in specific cell types. Dysregulation of differential expression of these genes (DEGs) mostly relates to GABA ( $\gamma$ -aminobutyric acid) signaling, axon guidance, chemical synaptic transmission, and neuronal migration these DEG leads to dysregulation of upper cortical circuit components, as well as synaptic signaling and changes in microglial and protoplasmic astrocytes status. In addition, through studies of ASD severity and DEGs in different cells, it was found: Microglia and L2/3 neurons were the most accurate indicators of clinical severity [8].

### 5. Pathogenic factors of the environment

Among the causes of autism, environmental factors have been always overlooked. Although hereditary factors are the primary cause of autism, environmental variables also contribute. Medication, hazardous exposures, parental age, diet, and the environment of the fetus are only a few examples of these environmental influences [9]. Numerous pieces of evidence point to a link between parental age and the beginning of conditions like ASD, bipolar illness, schizophrenia, and other conditions. Studies have connected sperm's age-related methylation changes to an increased prevalence of ASD [10]. Among the most researched risk variables for ASD are perinatal risk factors. Two comprehensive meta-analyses mentioned 60 obstetric factors, all of which were difficult to predict. In addition, ASD may be related to hormone levels, maternal nutrition during pregnancy, and trace element levels [9].

Through the study of the prenatal environment of the foetus, the effect of maternal immunoglobulin G (IgG) antibodies on ASD has been discovered. The researchers gave the pregnant monkeys IgG taken from the mothers of children with ASD and children without ASD, respectively to examine the newborn rhesus monkeys. They found that baby monkeys born to rhesus monkeys which injected with IgG extracted from the mothers of ASD-affected children showed symptoms of ASD. This is because normal maternal IgG can enter the foetus through the placenta during pregnancy to protect the foetus, but IgG antibodies extracted in the mother of children with ASD can produce an immune response with the foetal brain protein, resulting in brain nerve development problems [11].

### 6. Conclusions

Around the globe, the prevalence of autism is rising. Although there is some knowledge of the pathophysiology of autism, the primary method of treatment at this stage is still intervention through

guiding and instruction because autism is a complicated condition. Even though the pathophysiology of autism has been studied and its risk genes are somewhat understood, it is still difficult to predict autism through gene sequencing and it cannot be effectively treated. In order to better predict, diagnose and treat autism, people need to focus more on the pathogenesis related to autism, not only genetic factors, but also environmental factors, as well as some epigenetic and environmental gene interaction mechanisms not mentioned in this article.

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