

## GENETIC RISK FACTORS OF AUTISM SPECTRUM DISORDER

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Received: 27.02.2023, reviewed: 02.03.2023, accepted: 28.04.2023

**Keywords:** *autism spectrum disorder, epidemiology, risk factors, genetics.*

Autism Spectrum Disorder (ASD), according to the Centers for Disease Control and Prevention (CDC), is a condition of nervous system development that can result in substantial problems in the social, behavioral, and communication domains.

Leo Kanner, an Austrian-American psychiatrist, initially identified autism in 1943 as an underlying inability to establish genuine emotional contact with others [32].

The diagnosis of ASD is based on three key domains: communication difficulties (verbal and nonverbal), social interaction problems, and restricted, stereotyped repetitive behavior and interests.

Despite intensive research, not all etiologic factors for ASD have been adequately investigated. Significant progress has been made in figuring out the genetic and neurological underpinnings of this disorder [46]. ASD is heritable, but environmental factors also have a significant impact [48].

The main genetic risk factors for autism spectrum disorder are summarized in this review.

While ASD symptoms typically begin to develop by age three, recent research suggests that they can also appear as early as from 6 to 18 months of age and may not fully manifest until school age or later [52]. Compared to severe cases, milder cases have a lower likelihood of being discovered and properly diagnosed while they are younger [60]. Around four times as many men as women have ASD, while the sex ratio declines as severity rises [56].

Intellectual disability, existing in about 30% of cases [10] and attention deficits (occurring in 30-40% of cases), along with issues with sensory sensitivity, gastrointestinal tract, anxiety, sleep disorders, depression, immunologi-

cal deficits, etc., are typical impairments associated with ASD [12]. Genetic disorders, such as tuberous sclerosis, fragile X syndrome, Timothy syndrome, and others may be present in up to 15% of cases [15].

Clinical diagnosis of ASD is based on expert judgment referring to serious impairments in the main behavioral domains. The Diagnostic and Statistical Manual of Mental Disorders' fifth version (DSM-5), released in 2013, modified the diagnostic criteria for ASD [16]. Asperger's syndrome, autistic disorder, and pervasive developmental disabilities were among the diagnostic categories that were eliminated to establish the single category known as ASD. The DSM-5 combined the criteria for social and communication deficits into one domain and included a severity scale. Moreover, in addition to ASD, social communication disorder (SCD) has been included as a new diagnosis [16].

One of the most serious neurodevelopmental disorders in the world, ASD, places a heavy financial strain on caregivers and families. In the US, it has been calculated that the annual overall costs related to ASD will be close to \$250 billion. The estimated lifetime expenditures for each person with ASD were reported to be between \$1.5 and \$2.5 million (in US dollars, 2012) [8]. However, these expenditures may be underestimated because of a historically low diagnosis rate of ASD. Thus, it is anticipated that by 2025, the total costs associated with ASD will exceed \$450 billion [39]. ASD is unreasonably thought to be a childhood condition, whereas it has lifelong impairments. Psychiatric comorbidities are also present along with main deficits [33]. ASD has been linked to a high risk of non-behavioral health effects like injury [42] and elevated mortality risk [50]. As a result, research on ASD in adults has grown over the past ten years, and results related to lifelong quality of life for those with ASD have now been reported [28].

The aim of this review is to identify and describe the most significant genetic risk factors of autism spectrum disorder.

### EPIDEMIOLOGY

Around 1 in 59 children, according to the Centers for

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Disease Control and Prevention (CDC), have an ASD diagnosis. In 2012, the CDC reported that about 1.5% of 8-year-old children in the United States had ASD. This was established via active surveillance and professional evaluation of medical and academic records [10]. The estimates for 2012 were comparable to those for 2010. The initial CDC monitoring prevalence was 0.66% in 2002 [4]. Nevertheless, a large telephone survey conducted between 2011 and 2014 that relied on parents reporting the ASD diagnosis in their children (3 to 17 years old) produced a slightly higher US national prevalence figure (2.2%) [59]. The findings show that milder ASD cases have accounted for a large portion of the growth in CDC estimates over the past ten years, while changes in the prevalence of ASD combined with intellectual disability have been less pronounced [4]. The use of administrative data to separate fluctuation in ASD prevalence owing to change in real risk from variation due to other factors is hampered by the ongoing difficulties of changes in diagnostic technique, coding, as well as community awareness [29, 40].

Estimates of US prevalence are influenced by demographic variables. In particular, Hispanic ethnicity, non-White race, and poor socioeconomic status (SES) have been linked to lower ASD prevalence and delayed diagnosis [34]. Different US regions' disparities in prevalence have decreased over time, and they are less noticeable when there is an intellectual disability present [18]. In contrast, ASD diagnosis in Scandinavian countries tend to be associated with risk variables for lower SES [47].

In 2010, the World Health Organization reported that 0.76% of children worldwide have ASD [5], even though this data came from nations with only 16% of the world's children [21]. Several international systematic analyses of prevalence studies have reported similar summary figures of around 0.7% [5, 20], however, a Chinese assessment revealed lower estimates [55]. Yet, summary estimates mask geographic, methodological, and temporal variability. In South Korea between 2005 and 2009, the highest estimate of the most current global incidence was 2.64% for children of the age group from 7 to 12 years old. A two-stage screening-confirmation strategy was implemented for this measurement [38]. According to registration statistics, the estimated prevalence of ASD in 2011 was greater than 1% in Finland and Sweden and 1.5% in Denmark. These measurements reveal a consistent rise in the prevalence of age-specific ASD from 1990 to 2007 [3], which is similar to reports in the United States [10]. In Sweden, the increase was

explained by better documentation and the detection of milder ASD [30]. All of these attempts to estimate the frequency of ASD abroad [27, 43] nevertheless confront the same difficulties as those made in the United States. Ultimately, substantial prevalence data from developing countries are still very limited. Although there has been an increase in interest over the past 10 years, there has not been sufficient research on how cultural differences affect the understanding of and diagnosis of ASD globally [20, 53]. It is also important to note that almost all descriptive epidemiological research on ASD has focused on children. In England, only one proper study examining the prevalence of ASD in adults was carried out in 2007 [7]. To arrive at an estimate of 1%, this study used a community-based adult sample using a two-stage active screening-confirmation strategy.

### GENETIC RISK FACTORS

The evidence from twin and family studies is largely in favor of a genetic etiology for ASD. Currently, estimations on genetics in Europe and the United States range from 50% to 95% [26, 49]. Moreover, siblings of autistic children are more likely to repeat behaviors by 3% to 18% [11, 45]. In recent decade, genetic studies have been quite successful at identifying rare genetic variation, including inherited and de novo mutations, copy number variations (CNVs) linked to autistic features [25]. The cumulative effect of multiple common genetic variations is a significant indicator for ASD risk [6, 14]. Many reliable candidate genes have been identified, such as members of the neurexins family (e.g., CNTNAP2), contactin members (e.g., CNTN4), postsynaptic scaffolding members (e.g., SHANK3), and members of the chromatin remodeling family (e.g., CHD2) (see Table 1). There is more and more evidence to support the idea that genetic risk variations seen in people with ASD combine on shared hereditary pathways. It is also believed that common variations causing ASD's polygenic origin are shared by other neurodevelopmental and psychiatric disorders. Large-scale genome-wide ASD and cross-disorder association studies with enough statistical power are necessary to estimate small effects from common genetic variants.

### Gene-by-Environment Interaction

The high phenotypic and genetic variation indicates a complex etiology for ASD, despite the strong hereditary component. There are conflicting findings about the significance of environmental factors in the development of ASD. Some samples exhibit a dominant additive genetic

**Table 1***Summary of main genetic risk factors associated with ASD*

Inherited and de-novo mutations
Copy number variations
Multiple genetic variations
Neurexin family genes (e.g., CNTNAP2)
Contactin genes (e.g., CNTN4)
Postsynaptic scaffolding genes (e.g., SHANK3)
Chromatin remodeling genes (e.g., CHD2)

effect, whereas others demonstrate about equal contributions from heritable and non-heritable components [53].

It was first suggested that perinatal complications could be a result of interactions of genetic and environmental factors. In fact, the epidemiological study including a comparison group of siblings presented healthy siblings had less prenatal and perinatal complications than their autistic siblings, but more than controls [24]. According to this, people with ASD may react differently to the same environmental factors and may be less resilient to the prenatal adverse experience compared to their siblings. Moreover, research using animal models has demonstrated that genetic abnormalities in synaptic function may alter susceptibility to environmental influences [22]. Also, animal models have shown that the premature brain's the most serious pathology is the disruption of synaptic development [13]. It was therefore proposed that environmental variables and gene abnormalities in synaptic function would interact to increase the risk of ASD. Another hypothesis suggested is the interaction between melatonin pathway genetic variations and oxidative stress [54, 58]. Additionally, it was hypothesized that genetic variations result in deficit in enzymes [44]. Furthermore, a number of prenatal and neonatal risk factors may be linked to a higher risk of hypoxia [23, 57]. It was hypothesized that a deficit of melatonin could be considered in the consequences of perinatal distress [9].

Apart from these conclusions, some animal models bring evidence supporting the contribution of gene-by-environment (GxE) to ASD risk [19]. Ehninger et al. concluded that mice which were haploinsufficient for the TSC2 gene showed a lack of normal social behavior only when experienced maternal immune activation exposure. According to the authors, the immune activation may be more prominent in mutants due to the role of TSC/mTOR signaling in the adaptive immune response regulation. Another animal model [1] described prenatal maternal immune activation and expression of a mutant DISC1

protein interaction which resulted in changed sociability.

Despite these interesting results, family and population-based association studies in ASD have not been done for GxE interaction yet. The major problem related to this kind of study is that the power to detect GxE interactions is even lower than the one to detect genetic or environmental effects. In addition, GxE research in other psychiatric disorders has recently shown the absence of many positive results [17]. However, these studies are essential and might support to disclosure of the inconsistency in results found in classical association studies and provide useful hints for prevention. There have been launched two large prospective epidemiological studies investigating environmental factors and GxE interaction. The first study is "The National Children's study" following 100000 children in the US from conception to age 21 [37]. Biological samples are taken both from a mother and the child. The second one is "The Autism Birth Cohort" which will follow 100000 children from conception to age 7 [51]. Biological samples are collected from children and both parents.

Another challenge in family and population-based association studies is that study of the interaction of rare variants associated with ASD and environmental factors in populations carrying identical mutations would be helpful but will be difficult to implement due to the small number of carriers.

To meet these challenges and to develop research in this area, several investigations have been started to collect convenient data sets. In addition, work to develop novel tools to enable meta-GxE analyses across studies and application of recently established well-powered GxE methods is in the process.

### Epigenetics

Epigenetics describes a broad range of molecular information that locates on top of the DNA sequence and regulates a wide set of cellular processes, involving gene expression, imprinting. Lately, there has been an increased interest in investigating epigenetics in ASD due to their potential mechanistic involvement in etiology, or to serve as biomarkers of previous exposure or disease [34]. Studies have reported that DNA in particular to explain the effects of environmental exposure or GxE associations with ASD methylation, a type of epigenetic change, can be controlled by genetic variation [40] and can change due to environmental factors [2, 31, 36] (See Table 1).

What's more, Rett syndrome, Angelman syndrome,

and fragile X syndrome are all caused by epigenetic deregulation [1, 17, 19], and each has phenotypic overlap with ASD. Epigenetic changes have been described in the brains of individuals with ASD, including hypo- and hyper-methylation and spreading of histone 3 lysine 4 trimethylation marks, as well as in DNA derived from a range of other tissues. These findings show the future potential for epigenetics to serve as a biomarker of disease. What is more, rare genetic variants for ASD affect chromatin remodeling, another aspect of epigenetic regulation. Chromatin structure has not been investigated in ASD yet as well.

### Genomics

There has been considerable focus recently on leveraging genomics to define common biological processes implicated across genetic discoveries in ASD. Investigation of rare variants linked to ASD has reported three common biological pathways—chromatin remodeling, synaptic cell adhesion and scaffolding, and neuronal signaling and development [25, 37]. The results of transcriptomics studies, considering ASD-associated co-ex-

pression patterns in postmortem brain, have identified networks of brain development genes [51] implicated in ASD and specified mid-fetal development as a critical period for initiation of ASD neuropathology [35]. What is more, these studies have revealed networks of genes related to immune response [41, 51] and activation of M2 microglia to be differentially co-activated in ASD brains, however questions remain trying to find whether this has etiologic implications or is a downstream consequence of other events.

### Conclusion

Contrary to the common claim that we know very little about the risk of autism, significant progress has been achieved in this area over the past ten years. Particularly, recent developments in genetics have enabled a novel view of the pathology's molecular and cellular underpinnings. Other issues are also brought up, such as the function of common variations and the connection between genotype and phenotype. More focused research is required to determine whether environmental influences have an additive or multiplicative effect.

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ԱՄՓՈՓՈՒՄ

ԱՌԻՏԻՉՄԻ ՄՊԵԿՏՐԻ ԽԱՆԳԱՐՄԱՆ ԺԱՌԱՆԳԱԿԱՆ ՌԻՍԿԻ ԳՈՐԾՈՆՆԵՐԸ

Մխիթարյան Մ.

ԵՊԲՀ, Նեյրոգիտության լաբորատորիա

**Քանալի բառեր` աուտիզմի սպեկտրի խանգարում, համաճարակաբանություն, ռիսկի գործոններ, գենետիկա:**

Հոդվածի նպատակն է նկարագրել աուտիզմի սպեկտրի խանգարման (ԱՍԽ) հիմնական ժառանգական ռիսկի գործոնները: Ըստ տարբեր գենետիկական ուսումնասիրությունների տվյալների` պարզվել են մի քանի հազվադեպ de novo մուտացիաներ, ինչպես նաև էպիգենետիկա, պոլիգենային ռիսկ և գեների միջև փոխազդեցությունը: Վերջին տասը տարիների ընթացքում հայտնաբերվել են հայտնաբերվել, որոնք դեր ունեն ծանր վարքագծային, սոցիալական և հաղորդակցական այն խնդիրներում, որոնք հաճախ

խաղեպ են ԱՍԽ ունեցող մարդկանց շրջանում: Աուտիզմի սպեկտր առաջացնող առանձին պելևերի հայտնաբերումը կարևոր դեր է ունեցել ԱՍԽ-ն ըմբռնելու համար: Այնուամենայնիվ, դեռ շատ անպատասխան հարցեր կան: Ակնհայտ է դառնում, որ շրջակա միջավայրի գործոնները, և թե ինչպես են դրանք փոխազդում ժառանգական գործոնների հետ, պետք է հաշվի առնել ԱՍԽ պատճառագիտության մեջ:

Այսպիսով ավելի նպատակաուղղված հետազոտություններ են անհրաժեշտ ԱՍԽ-ի ժառանգական ռիսկի հատուկ գործոնները հստակեցնելու համար:

РЕЗЮМЕ

ГЕНЕТИЧЕСКИЕ ФАКТОРЫ РИСКА РАССТРОЙСТВ АУТИСТИЧЕСКОГО СПЕКТРА

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**Ключевые слова:** расстройство аутистического спектра, эпидемиология, факторы риска, генетика.

Цель этого обзора — описать основные генетические факторы риска расстройств аутистического спектра (РАС). Данные различных генетических исследований выявили несколько редких мутаций de novo, а также эпигенетику, полигенный риск и взаимодействие генов с окружающей средой. За последние десять лет было обнаружено, что сотни генов играют роль в серьезных поведенческих, социальных и коммуникативных проблемах, с которыми часто сталкиваются

люди с РАС. Открытие определенных аллелей, вызывающих спектр аутизма, внесло решающий вклад в понимание РАС. Однако, есть еще много вопросов без ответов. Становится очевидным, что факторы окружающей среды и то, как они взаимодействуют с наследственными факторами, следует учитывать при определении этиологии РАС. Тем не менее, необходимы более целенаправленные исследования, чтобы точно определить специфические наследственные факторы риска РАС.