

Genetic and Environmental Predisposing Factors of Autism Spectrum Disorders

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In 1943, Dr. Leo Kanner introduced the terminology of medicine to the word autism.^[1] Autism spectrum disorder (ASD) is a complex developmental condition with persistent difficulties in social interaction, speech, nonverbal communication and repetitive behavior. The effects of ASD and the severity of symptoms vary in every person. Most symptoms of ASD usually occur in children aged about 2 to 3 years and are usually diagnosed at these ages. Until they start to walk, some children with ASD will normally stop developing skills and lose what they have previously gained. According to a worldwide study by the US Department of Health, one in 59 children has autism spectrum disorder. Autism spectrum disorder is three to four times more common in boys than in girls, and many girls with ASD show less prominent signs than boys.^[2]

Symptoms of Asperger syndrome, one of the autism spectrum disorders described by Doctor Hans Asperger, are usually manifested at older ages, unlike other autism spectrum disorders, and, unlike the general indicators of autism, there is no developmental retardation in speech and language skills. As it can be understood, ASD is two-way. Such that; a number of recent studies have reported a positive genetic correlation between autism and

ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental situation with persistent difficulties in social interaction, speech, nonverbal communication and repetitive behavior that can be diagnosed at an early age. In recent years, the increasing number of ASD cases has shifted the interest of science in this direction. According to a worldwide survey, one in every 59 children has autism spectrum disorder. In this article, environmental and genetic factors that cause autism spectrum disorders are discussed.

Keywords: Autism spectrum disorder, autistic, biomarkers, serotonin.

measures of mental ability. These findings show that the alleles of ASD are broadly overlapping with the paradoxical seemingly high-intelligence alleles, which are generally characterized by below-average intelligence quotient (IQ).^[3] This paradox can be solved under the hypothesis that the etiology of ASD generally includes components of advanced but unbalanced intelligence. This hypothesis is supported by evidence that autism and high IQ share various convergent correlations such as large brain size, rapid brain growth, increased sensory and visual-spatial abilities, improved synaptic functions, increased attention focus, and high socioeconomic status.^[4]

Autism spectrum disorder is known to be a multifactorial syndrome. In addition to environmental causes, genetic causes have recently been found (Table 1, 2).^[4]

ETIOLOGICAL FACTORS AND GENETIC DISEASES WITH AUTISM SPECTRUM DISORDER^[5]

Are there any ASD Genes?

The increased prevalence of genetic testing has allowed exploration of relationships between

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Table 1. Etiological factors

Genetic diseases
Natal factors
Neuroanatomic factors
Neurochemical factors
Immune factors
Genetic factors
Environmental factors

Table 2. Genetic diseases with autism

Fragile X syndrome
Tuberous sclerosis
Phenylketonuria
Williams syndrome
Cornelia de Lange syndrome
Joubert syndrome
Moebius syndrome
Smith-Lemli-Opitz syndrome
Neurofibromatosis
Sotos syndrome
Hypomelanosis ito
Aarskog syndrome

multiple genes and various neurological disorders. There are 1007 genes identified in the SFARI Gene database for susceptibility to ASD. Several genes have been identified, including the MECP2 and CHD8 genes, which are specific to autism alone.^[6] It has been reported that some genes that are found to undergo changes with ASD play an important role in hormonal pathways.^[7] The RORA gene, which plays an important role in immunity and neurodevelopment, has been shown to be associated with the level of transcription such as NLGN1 and NTRK2 genes. These genes are also those that encode the catalytic receptors of neurotrophins. In addition, the effect of ITPR1 gene on calcium channels has been shown to play an important role in neurodegenerative diseases. The RBF0X1 gene encodes insertions to provide membrane stimulation and synaptic transmission.^[8] Studies have shown that there is a relationship between autism and various variants of the OXTR gene.^[9]

Methylation of the OXTR promoter gene has been found to be associated with the etiology of autism, albeit in small studies.^[10] At the same time, transcriptional differences related to hypermethylation of the OXTR gene in the

temporal lobe of autistic individuals have been observed.^[11] One of the biomarkers investigated in ASD is high serotonin level.^[12] The relationship between polymorphism in the serotonin regulator SLC6A4 gene and psychiatric diseases has been reported.^[13] SLC6A4 gene expression was found to be lower in individuals with autism. Therefore it is thought that there is a lack of serotonin reuptake.^[14] Mutations in the RELN gene in ASD may result in decreased expression of the reel. It is thought that expression changes resulting from hypermethylation of the promoter region of the RELN gene or mutations by an unknown mechanism may be associated with neuropsychiatric diseases.^[15] When RELN polymorphism was compared to healthy controls in individuals with ASD, it was reported that rs1270519 polymorphism was found to be statistically significant compared to healthy controls, whereas no significant difference was found between rs362691 in the two groups.^[16]

The methylenetetrahydrofolatreductase (MTHFR) enzyme is an important enzyme in folate metabolism. The MTHFR gene is localized on chromosome 1p36.3. MTHFR converts 5,10 methylenetetrahydrofolate (5,10-methylene THF) irreversibly to 5-methyl tetrahydrofolate (5-methyl THF).^[17]

Since the enzyme will be inactive when the MTHFR gene is mutated, it causes hyperhomocysteinemia and homocysteinuria, which is an important risk factor for cardiovascular and cerebrovascular diseases.^[18]

Two polymorphisms have been reported in the MTHFR gene, C677T (rs1801133) and A1298C (rs1801131).^[19]

Based on this information, it has been reported that MTHFR gene may play an important role in the pathophysiology of autism.^[20]

SHANK3 is a member of the family of structural proteins located at the center of the postsynaptic density of the excitatory glutamergic neurons. It acts as the main regulator of glutamergic synapses.^[21] The incorporation of SHANK3 into actin nucleation and the association of variant S685I with OSB shows that actin nucleation plays a critical role in the pathogenesis of SHANK3 deficiency.^[22]

Nowadays, although genetics of autism is widely discussed and researched, it opens the door to new research. In the context of autism and genetics, many genes are suspected to be associated with autism. Especially according to candidate gene studies, hundreds of genes are responsible for autism, especially NRXN1, SHANK3, NLGN3, NLGN4, MeCP2,

Table 3. List of genes associated with ASD^[23]

Chromosome	Known genes
2	NRXN1, SCN7A
3	GAT1, OXTR, CNTN3, SLC9A9, D1A1
7	FOXP2, WNT2, RELN, HOXA1, HOXB1, MET, EN2
11	HRAS
15	GABRB3, GABRA5, GABRG3, UBE3A, ATP10C
17	5-HTT
22	SHANK3
X	MeCP2, NLGN3, NLGN4, SLC9A6, FMR1

EN2, CNTNAP2, OXTR, RELN, GABRB3, GABRA5, GABRG3 (Table 3).^[23]

ENVIRONMENTAL FACTORS CAUSING ASD

Although genetics play a major role in the pathophysiology of ASD, the impact of environmental factors is considerable.^[24]

Abnormal melatonin synthesis

Melatonin is an endogenous neurohormone produced predominantly in the pineal gland in the dark and levels of melatonin or melatonin derivatives in individuals with ASD are generally found to be below average.^[24] Circadian abnormalities in autism may be the result of genetic abnormalities related to melatonin synthesis. Deletions of the ASMT (acetylserotonin O-methyltransferase) gene encoding the last enzyme of melatonin synthesis have been found in several individuals with ASD.^[25] In addition, environmental factors may affect melatonin synthesis. For example, maternal stress has been shown to cause lower melatonin levels.^[26]

Zinc deficiency

The balance of metal ions in our bodies is essential for the brain to function correctly and when this balance is broken, neurological symptoms are inevitable. Since zinc, which is one of these ions, plays a major role in cell division and differentiation, its deficiency will make significant changes in neurological functions.^[27] It is so clear that zinc supplements are used in nutritional therapy in autistic patients.^[28]

Maternal diabetes

Meta-analysis studies showing that exposure of the embryo/fetus to pregnancy complications may

increase the risk of autism has shown that maternal diabetes during pregnancy increases the risk of autism twice.^[29] The pathophysiology of this process; maternal-hyperglycemia, fetal hyperinsulinemia and increased maternal-placenta-fetus insulin-like growth factors have been identified in recent years.^[30]

Foods and intestines

The main problem with autism is in the brain, but some other organs may also have some effect on autism. The most important representative of these organs is the intestine. The reasons for the recent focus on the brain-intestinal-behavior axis are; Two-way partnership showing intestinal and behavioral findings, possible relationship between diet-GIS-autism, and bowel microbiota collection related to autism. For now, information on this subject is limited, but scientific studies are ongoing.^[31]

PRENATAL AND PERINATAL STRESS FACTORS

Occurring in the mother; Immune changes such as lymphocyte proliferation, natural killer cell activity, and decrease in cytokines may reduce viral resistance. It was thought that pathological mechanisms that may arise with this decrease may increase the risk of autism.^[32] The effect of prenatal stress on postnatal HPA (hypothalamus, pituitary, adrenocortical system), ACS (acute coronary syndrome) reactivity and stress hypersensitivity have been reported to be associated with autism in some studies.^[33] It has been reported that autism is more common in men than in women. Therefore it is thought that high levels of testosterone exposure during critical periods of pregnancy may increase the risk of autism.^[34]

PARENT AGE

In a meta-analysis study involving 25,687 ASD cases and 8,655,576 control groups, advanced maternal age was considered to be among the factors increasing the risk of autism. Studies related to father age are ongoing. The mechanisms of advanced maternal and paternal age being risk factors are different. Small-scale de-novo mutations accumulate mostly in fathers. These are associated with advanced parental age.^[35] In addition, advanced maternal age may be a risk factor for autism with increasing pregnancy complications.^[36] However as shown in the tables, there is no statistically significant difference (Table 4).^[29]

Tablo 4. OSB ve ebeveyn yaşı değerlendirilmesi^[38]

	Evaluation of mothers' age		p
	Severe ASD	Average-mild	
	Mean±SD	Mean±SD	
Maternal age	34.1±3.9	33.6±5.8	0.682

	Evaluation of father' age		p
	Severe ASD	Average-mild	
	Mean±SD	Mean±SD	
Father age	36.5±3.5	36.7±5.40	0.888

SD: Standard deviation.

Prenatal infections

Maternal immunoglobulin G (IgG) antibodies that occur during infections during pregnancy and targeted to the brain of the fetus are claimed to be pathogenic in some ASD cases. Studies have reported that Rubella infection of the mother during pregnancy may cause ASD in the baby. Congenital Rubella infection has been reported to occur in approximately 4 to 7% of ASD cases. In a study comparing brain tissues of individuals with autism and brain tissues of control groups, Epstein-Barr virus, Herpes Simplex type 1 and type 2 virus, JC virus, citomegalovirus, BK virus, Herpes Simplex type 6 viruses were reported to be more common in individuals with autism.^[37]

In conclusion, although autism spectrum disorders have many genetic and environmental predisposing factors, it would not be correct to conclude that one or more of these disorders are strictly related.

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