

The Environment Affects Autism Spectrum Disorder by Moderating Gene Expression and Mutation

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Abstract: Autism spectrum disorder (ASD) is a kind of developmental condition that is brought on by flaws in the brain. The "exclusive environment" approach of the Bettelheim period has given way to the "exclusive genetic" approach, and a significant amount of study has been concentrated on the causes of ASD, especially variables related to genetics. The question of whether or not ASD is influenced by one's surroundings is still being discussed. The purpose of this paper is to explore how the environment affects ASD and to argue, based on the publications that were evaluated, that genes are important variables that directly impact ASD, especially gene mutation, and that the environment factors are an influence that affects ASD indirectly. Through its regulation of gene expression and gene mutations, the environment factors have an indirect impact on the pathophysiology of ASD. It is more advantageous for the prevention and treatment of ASD to study the environmental and genetic variables that contribute to autism, which needs to be further explored and verified by future research.

Keywords: Autism spectrum disorder, Gene, Environment

1. Introduction

Autism spectrum disorder (ASD) is a developmental condition resulting from brain abnormalities [1]. People with ASD may behave, speak, engage, and learn differently than the majority of individuals. People with ASD often struggle with social communication and engagement, and exhibit hobbies or activities that are confined or repetitive. For example; repeatedly repeats words or phrases (called echolalia); must adhere to certain regimens. However, social skills differ widely among individuals with ASD. Some individuals with ASD may have good conversational abilities, whilst others may lack articulation. Some individuals with ASD need substantial assistance with everyday tasks, while others may work and live with little or no assistance.

The incidence of ASD is very high, with 1 in 44 children suffering from ASD. The onset of ASD is not age-restricted; preschoolers can also have ASD, and ASD can last a lifetime. People who suffer from ASD may have difficulty communicating with others to the best of their ability, making their social life more difficult. Therefore, it is important to understand the causes of ASD in order to reduce the incidence of ASD at the root.

Regarding the causes of ASD, experts argued that there are several reasons, including environmental, biochemical, and genetic aspects [1,2]. The question of whether ASD is environmentally influenced has long been debated. ASD has oscillated between the "exclusively

environment" approach of the Bettelheim era and the "exclusively genetic" perspective of more recent eras. Now, it is widely accepted that a combination of genetic and environmental factors influence ASD. There is a great deal of study on how genetic variables, or genes, influence ASD, but less on how environmental factors influence ASD. This article will provide a brief explanation of how genes influence ASD, describe the environmental factors that have been identified in relation to ASD, and then establish the link between environmental and genes factors, suggesting that the environment moderately influences the development of ASD through genes.

2. The Effect of Gene

2.1. Heritability

Due to the high heritability of the disorder, a lot of people think that autism spectrum disorder is caused by genes. The heritability of ASD was found to be approximately 90% in some studies, including those involving twins. For instance, in order to carry out a meta-analysis, Tick et al. [1] chose seven important twin studies. A further study by Deng et al. [2] reviewed 37 sets of twins, in each of which there was at least one twin with ASD. They found that ASD is caused by major genetic factors and is a highly heritable disorder with estimates ranging from 64-91%. The concordance rate for monozygotic twins (MZ) was found to be 80%, while the rate for dizygotic twins (DZ) was found to be 13.6%.

In addition, the high concordance rate for MZ and the low concordance rate for DZ in the ASD trial provide further support for the genetic pathology of ASD. As an illustration, the concordance rate for MZ in the British twin research project led by Bailey et al. [3] was sixty percent, whereas it was zero percent for DZ. According to the findings of one study, there was a probability of sixty percent that the other child in a group of MZ twins would also have ASD if the first child in the group had ASD. In contrast, there was no correlation between whether both DZ twins had ASD or not. The concordance between MZ and DZ was significantly different in the other two trials, with 95.2% and 90% concordance for MZ, respectively, compared to 0% and 4.3% concordance for DZ [4]. When it comes to the possible modes of transmission of ASD, researchers can only agree on one thing, and that is the fact that Mendelian inheritance does not account for the vast majority of cases.

2.2. Gene Mutation

ASD is associated with low rates of marriage and reproduction, despite the fact that it has a high heritability. Because of this, there has been an increased amount of selective pressure placed on the gene for ASD. Despite this, there is still a significant prevalence of autism spectrum disorder. It's possible that de novo mutations are what led to this condition in the first place. If mutations that cause ASD continue to emerge in the non-ASD population, they might be able to counteract the gradual removal of ASD genes from the population that is caused by the low average fertility of ASD patients [5]. This would be the case if mutations that cause ASD continued to emerge in the population of people who did not have ASD. This would be the case if mutations that cause ASD continue to emerge in the population of people who do not have ASD. In a similar vein, mutation may be able to help explain why MZ twins have a significantly higher rate of ASD concordance compared to DZ twins. This is due to the fact that an exclusive mutation is more frequently inherited by both children born to MZ twins than it is by either child born to DZ twins [5]. The reason for this difference is that it is statistically more likely for MZ twins to have identical offspring than it is for DZ twins.

Individuals who have autism spectrum disorder have been found to have a significant amount of genetic variation, which may include both locus and allelic heterogeneity. According to studies that

sequenced DNA, the newly predicted contribution to the risk of ASD of up to 234 loci may be further undervalued than previously thought. Alterations in synapses are one of the many gene variants that have been linked to ASD, and they have garnered a lot of attention as a result. Children who had been diagnosed with ASD had an abnormally high number of synapses in their brains, according to the findings of a study that was carried out at Columbia University [6]. Despite the significant genetic and clinical variability that is associated with ASD, a significant number of cases of the disorder are caused by mutations in genes that inhibit mammalian rapamycin (mTOR) kinase [7]. One example of a protein complex is the Tuberous Sclerosis Proteins 1 and 2, also known as hamartin and tuberin, respectively. Together, these two proteins form the Tuberous Sclerosis Complex. There is a possibility that tuberous sclerosis complex will develop as a direct consequence of these gene alterations. Neurofibromatosis type 1, also referred to as NF1 and commonly abbreviated as NF1, is a form of neurofibromatosis that is passed down through families and is characterized by the growth of tumours along nerves. In addition, the Phosphatase and Tensin Homolog that was lost on Chromosome 10 (PTEN) not only possesses the ability to phosphatase proteins and lipids, but it also functions as a tumour suppressor and regulates both cell growth and cell survival. In addition to the glutamate receptor mGluR1/5, synaptic mTOR is responsible for combining the signalling of multiple ASD synapses and regulatory proteins [7]. Mutations that take place in TSC1/TSC2, NF1, or PTEN lead to the activation of the mTOR pathway. An overactive mTOR signalling pathway has been linked to both ASD and excessive synaptic protein synthesis [6,7].

ASD has been linked to a number of genetic conditions. To be more specific, nearly sixty percent of individuals diagnosed with fragile X syndrome and seven percent of patients diagnosed with Down syndrome are afflicted by ASD in some capacity.

3. The Effect of Environment

3.1. Shared Environment

Despite twin studies have shown a high degree of concordance, this does not mean that MZ twins have perfect concordance, which demonstrates that other factors, such as environmental effects and changes in gene expression as a result of expressive genetic factors, are at play as well. Numerous studies are focusing on the role that environmental factors play in ASD, and this trend is expected to continue. Shared environment also has a degree of contribution to the prevalence of ASD. This idea was drawn from a large number of twins who were diagnosed with ASD. The range of shared environmental impact was found to be anywhere from 64 to 78 percent, according to the data that was obtained from the Social Communication Questionnaire and the Social Response Scale, which were used to quantify the symptoms of ASD [8]. In another study, ASD had a medium heritability (38%) and a large shared twin environmental component (58%) [6].

3.2. General Environment

According to the findings of the twin research, ASD is affected not only by the twins' shared environment but also by a number of other environmental factors. Researchers [9] discovered a wide variety of pollutants that were linked with an increased prevalence of ASD. Children who were subjected to larger concentrations of mercury, cadmium, nickel, trichloroethylene, and vinyl chloride had significantly higher occurrences of ASD [9] compared to those who were subjected to lower numbers. In addition to this, the occurrence of ASD is much more common in areas that are located farther north. According to research carried out by the Centers for Disease Control, New Jersey had an ASD incidence rate that was much higher than that of nine other states located at comparably low latitudes. In the second research, Alabama had a much lower prevalence of ASD

than the other three states that are located at a higher latitude. Also, a higher incidence rate of ASD was also significantly connected to live in regions that received a larger amount of precipitation. According to Waldman et al. [10] 's research, the prevalence of ASD was shown to be significantly higher in regions that had a greater availability to cable television. In addition, the findings of Waldman et al. [10] are in line with the hypothesis that there is a connection between the incidence of ASD and the fact that individuals spend more time indoors watching television and, as a consequence, less time outside in the sun.

4. Environment as Moderating Effect

There is a possibility that differences in gene expression are brought about by environmental impacts, which also helps to illustrate the fact that the MZ twin concordance rate in the twin experiment is not perfect one hundred percent. The hypothesis presented in this research is that ASD is caused by interactions between genes and the environment. And the environment may have an effect on gene expression and can also induce gene mutation that are relative to ASD.

First, Tick et al. [1] came to the conclusion from their meta-analysis that the strong shared environmental effects might be an incidental occurrence, and that the excessive environmental effects might be a statistical artifact caused by the over-inclusion of concordant DZ twins. Both of these ideas are related to the possibility that the strong shared environmental effects might be a statistical mistake. In a similar vein, the assertion made by Frazier et al. [8] that a shared environment is responsible for more than fifty percent of ASD's effects is inconsistent with the findings of the vast majority of studies. This is because a large number of DZ twins are raised in the same environment, despite the fact that the consistency of DZ remains unchanged in the vast majority of experiments [3,4].

Second, environmental variables that cause genetic alterations associated to ASD may provide an explanation for the correlation between high levels of heavy metals and the incidence of ASD. In the same category as vinyl chloride and trichloroethylene, the elements mercury, nickel, and cadmium are categorized as mutagens. First, they result in oxidative stress, which induces the production of free radicals and may cause oxidative damage to DNA [11]. Second, they prevent the machinery that repair DNA from working [5]. The development of ASD may also be influenced by abnormalities in the repair of oxidative DNA damage, oxidative stress, and oxidative DNA lesions [5]. 3) The amounts of reducing agents found in cells may be decreased by mercury, cadmium, and nickel. Cells create reducing agents such as glutathione in order to maintain redox equilibrium in a stable state. By lowering the quantities of glutathione found inside cells and attaching to sulfhydryl groups on proteins, mercury, cadmium, and nickel render DNA more sensitive to the mutagenesis effects that are caused by reactive oxygen species (ROS) [11]. For instance, subjects with ASD had a low ratio of reduced glutathione (GSH) to its oxidized form glutathione disulfide (GSSG), which indicated the presence of oxidative stress [5]. Additionally, these subjects had a decrease in total GSH levels, which suggested that the subject's redox homeostasis system and antioxidant defense mechanisms were impaired. In addition, abnormalities in oxidative DNA damage and antioxidant capacity were discovered in the plasma of children with ASD, in comparison to children who did not have the disease.

Third, mutations that lead to ASD-related genes might potentially explain the relationship between a higher frequency of ASD and higher latitudes, more precipitation, and greater availability of cable television. The most efficient and all-natural approach to absorb vitamin D is to expose one's skin to ultraviolet radiation from the sun. Additionally, decreasing one's time spent in the sun substantially raises the risk of developing vitamin D insufficiency. Because of the decreased amount of time spent in the sun caused by increased rates of precipitation, vitamin D insufficiency is frequent in those who live at high latitudes [12]. In addition, those who watch more television spend

less time outside, which limits their exposure to sunshine and further increases the likelihood that they are deficient in vitamin D. Vitamin D's primary effects on the CNS include nerve cell growth, neurotransmission, oxidative stress, and immunological function [13]. Therefore, a lack of vitamin D during development may reduce the ability to repair new DNA mutations and oxidative DNA damage, which in turn raises the risk of ASD [14].

5. Conclusions

In spite of the significant progress made in the field of study on autism spectrum disorders over the course of the last half-century, the root causes and underlying pathology of the illness are still not fully understood. This paper aims to discuss the ways in which environmental factors contribute to the development of ASD in the hope of establishing a connection between environmental and genetic factors, which would prove that environmental factors have more of an indirect influence on ASD than a direct one. The start of autism, like the onset of a great number of other illnesses, is impacted by both heredity and environment, with genes playing a significant part in both variables. Twin studies give evidence that the condition is inherited, but they also represent that Environmental factors are likely to be involved in its development. Environmental factors of risk can comprise advanced age of the parents, problems in pregnancy and maternal illness. Other environmental risk factors include organic contaminants, air pollution, and drug exposure during pregnancy. This research asserts that environmental variables impact the emergence of ASD via the expression of moderate genes with induced gene variations. This is based on an assessment of how these environmental factors influence the development of ASD. Studying the effect that environmental and genetic variables have on one another will assist to understand the nature of the pathogenesis of ASD, which will in turn help to better avoid the development of ASD. However, it is more persuasive to research the heredity of the condition by watching the occurrence of the sickness in a full family, and this is a subject that might be explored further in the future. In the past, the majority of the studies were carried out on twins. In addition, based on the hypothesis that environmental factors have an indirect effect on ASD by having an effect on genes, the environmental factors that influence gene expression or gene mutations that cause ASD can be deduced through further research, which will promote better prevent the onset of ASD.

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