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■ REVIEW ARTICLE

Understanding Genetic & Environmental Factors Associated with Autism Spectrum Disorder to Create a Better Diagnosis

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ABSTRACT: Autism was first named in 1911, and then redefined to fit the symptoms of patients in the mid-1960s to 1970s. Today, autism spectrum disorder (ASD) has been more commonly described as a neurodevelopmental disease with common symptoms that include repetitive behaviors and restricted interests. Progress in understanding ASD has brought scientists closer to finding factors that may affect the onset of ASD in children or the cause of autism. These factors can include either genetic or environmental factors. One genetic factor is gender and environmental factors include drugs and smoking during pregnancy. These factors can be combined to create a quantitative diagnostic test or a more accurate diagnostic test to diagnose autism earlier in childhood. Currently, autism doesn't have many quantitative diagnostic tests. Some diagnostic tests are available; however, these tests have limitations which can lead to incorrect diagnosis. The lack of both diagnosis and proper treatment, can lead to ethical concerns, as parents may abandon their child due to a misdiagnosis or cost of treatment. This review hopes to elucidate the current genetic and environmental associations with ASD to provide alternative ways for quantitative diagnosis in the future as advances in science are made.

KEYWORDS: Behavioral and Social Sciences; Neuroscience; Genetics; Autism; Diagnosis.

■ Introduction

Autism was first defined by Leo Kanner in 1948. He described it as an innate inability to create normal, biologically determined, emotional contact with others.[1] Autism spectrum disorder (ASD) has since been more commonly described as a neurodevelopmental disease with common symptoms that include repetitive behaviors and restricted interests. Progress in understanding ASD has brought scientists closer to finding factors that may affect the onset of ASD in children. These factors range from environmental to genetic. For example, males are three times as likely to get ASD as females, which is likely a product of X-linked mutations that possibly cause the uneven ratio of autism between males and females.[2,3] Other genetic causes include mutations in various genes associated with ASD, such as SHANK 3, TSC1, TSC2, and FMRP.[4] Despite there being an array of genetic factors associated with ASD, there are also several environmental factors known to contribute to an increased prevalence of ASD. These factors are typically centered around complications in fetal development during pregnancy such as exposure to pollutants, fever, the use of drugs, or smoking.[5,8] Other environmental factors that can increase the chance of ASD include older parents at the time of conception, maternal obesity, and complications during birth in which the baby is deprived of oxygen for extended periods of time.[9] The combination of these factors can increase our insight into the causes of autism and how we can better treat and/or diagnose it (Figure 1).

Currently, autism does not have a quantitative diagnostic test. Instead, diagnosis occurs through a qualitative test in which the behavior of a patient is observed. The lack of quantitative testing for ASD can lead to misdiagnoses in patients, resulting in insufficient treatment plans.[10] A patient who does not get the appropriate treatment for ASD may lack the ability to speak, behave in normal ways, and be unable to develop effective social skills. This is significantly detrimental since there are treatment options for patients with ASD. Current treatments of autism include behavior/communication approaches, dietary approaches, and medication.[11] A review article about ASD can be useful for comparing different environmental and genetic factors and their effects on the diagnosis of ASD. Understanding these factors and causes and combining this knowledge with autism symptoms can aid in creating a more accurate diagnostic test.

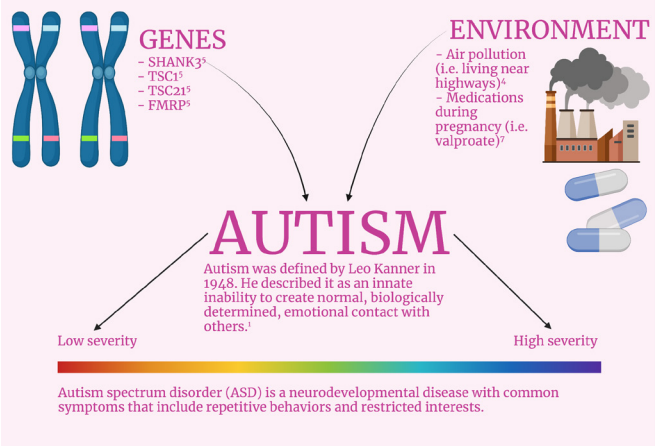

Figure 1: Overview of autism and it's genetic and environmental factors. The figure depicts common genes and environmental factors that have high association with autism. Autism is defined as a complex developmental condition where the effects of ASD and the severity of symptoms are different in each person, leading to a spectrum of severity.

DOI: 10.36838/v4i2.9

History of Autism :

Autism was first named and introduced in 1911 by Eugen Bleuler, a German psychiatrist, but not as its own disorder but as a symptom of some cases of schizophrenia.[12] It wasn't until 1943 that Leo Kanner was the first clinician to identify autism as a disorder in his patients. He defined it as partially due to "genuine lack of maternal warmth".[13] However, in the 1950s, the definition of autism was changed again to be more of a symptom that consisted of excessive hallucinations and fantasy in infants. Then later, in the mid-1960s and 1970s, autism was redefined to be a complete lack of fantasizing, contradicting the previous definition of autism.[12] As new definitions of autism were created, the process of diagnosis became more accurate, which led to a rise in the prevalence of autism. Since then, autism has always been diagnosed with a qualitative test and is now defined by the CDC as behavioral deficits in social or emotional reciprocity, a lack of nonverbal communication, and difficulty in developing, maintaining, or keeping relationships.[14] These criteria have helped create better diagnostic methods and we can see an increase in the prevalence of autism since the 2000s (Figure 2). Throughout history, our understanding of autism and how it is diagnosed has consistently been changing and it is currently diagnosed through observing the behavior of a patient. Unfortunately, the use of these diagnostic methods may not be fully accurate, which can result in patients left undiagnosed or being misdiagnosed with autism. Consequently, these patients may not have access to treatment, and this would negatively affect the development of their social skills.[15] Alternative ways to test for autism, such as screening through genetics, may help to create a more quantitative test. Quantitative measurements may help enhance diagnosis and therefore leading to proper treatment for patients with autism.

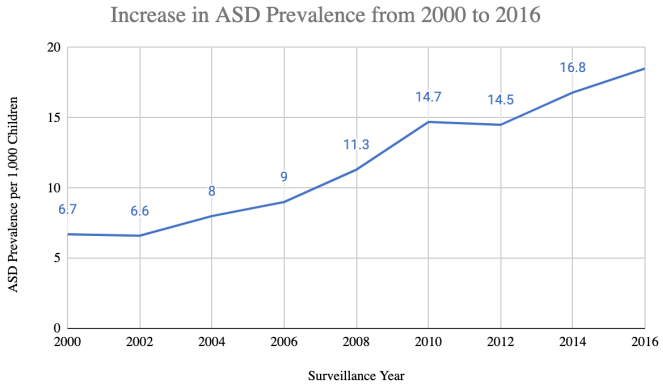

Figure 2: Increase in ASD Prevalence from 2000 to 2016. In the graph above, the prevalence of ASD is shown to be Increasing. The prevalence of ASD was steady from 2000 to 2002, however it started to increase in 2004 and more than doubled by 2010. From 2010 to 2012 we see the prevalence of ASD plateaus again, but then continues to increase in the following years.

Genetics of Autism :

Genetics are known to play a role in the onset, severity, and the symptoms of autism.[2] These genetic factors may also help to determine the underlying cause of autism. One of the most relevant genetic mutations that may lead to autism is related to the uneven ratio of males compared to females diagnosed with autism. Currently, this ratio is 3:1, male: female.[2] This ratio indicates that there may be genes on the X chromosome that affect or cause ASD. One example of this is fragile X mental retardation 1 (FMR1, also known as FMRP) that causes the fragile X syndrome. It was found that 30 % of patients with FMR1 will also be diagnosed with ASD (Figure 3).[3,5] MECP2 is another X-linked gene associated with autism. A mutation in the MECP2 gene is also known to cause an X-linked disorder called Rett's syndrome.[3] Rett's syndrome is a neurodevelopmental disorder that can lead to a progressive loss of motor skills and speech. While Rett's syndrome is more common in females with ASD than males with ASD, it is important to note that males with a full or partial mutation in MECP2 have significantly more severe forms of Rett's syndrome and ASD and have a lower life expectancy.[16] Other X chromosome linked disorders, such as Turner's syndrome and Klinefelter's syndrome, have also shown to be associated with patients diagnosed with autism. Turner's syndrome is characterized by a missing or incomplete X chromosome in females and Klinefelter's syndrome is characterized by an extra X chromosome in males. In fact, more than 25 % of the patients with Turner's syndrome are diagnosed with ASD and in Klinefelter's syndrome, almost 30 % of patients are diagnosed with ASD (Table 1).[2] This shows that there are various genes on the X chromosome alone that are associated with the expression of ASD phenotypes and possibly ASD itself. Since men have only one X chromosome, any mutations in the X chromosome affects all their cells, while females may require significantly more mutations to see similar effects or symptoms of ASD.

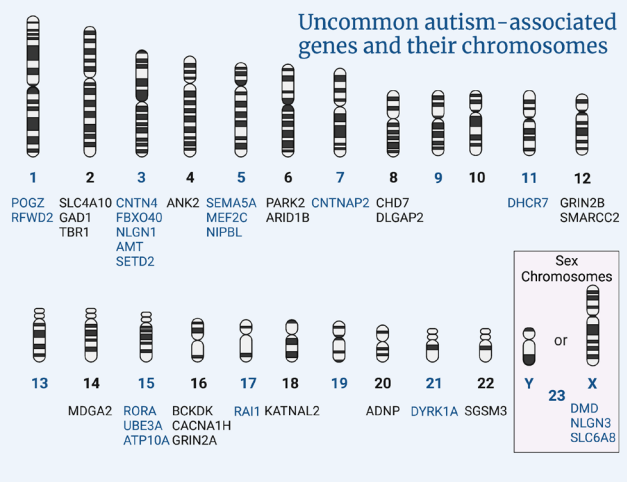

Figure 3: Uncommon autism-associated genes and their chromosomes. This figure shows uncommon genes that have been associated with ASD and their respective chromosomes. As depicted, no one chromosome is solely responsible for autism.

Other genes associated with Autism are SHANK 3, TSC1, and TSC2. Mutations in these genes are some of the most prevalent in patients with ASD.5 TSC1 and TSC2 are both part of the Tuberous Sclerosis Complex (TSC).[34] TSC1 and TSC2 function as tumor suppressor genes. Along with this, TSC1 codes for production of hamartin, while TSC2 codes for productions of tuberin. Tuberin and hamartin interact to suppress unneeded cell growth.[35] Mutations in either, or both,

DOI: 10.36838/v4i2.9

of these genes leads to the development of the disease TSC. Patients with TSC often have symptoms of psychotic disorders such as schizophrenia, and anywhere from 17 % to 60 % have been reported to show additional symptoms of ASD.[34] These mutations can have a high variability in severity of ASD within patients.[34] Furthermore, post-mortem studies in ASD patients show that Purkinje cell loss, which are inhibitory neurons in the cerebellum, has been associated with the TSC complex. Therefore, the loss of Purkinje cells can lead to autism-like characteristics in patients.[36] From this, it can be concluded that the cerebrum may be where patients with ASD may see a deficit based on the skills that autistic patients are lacking. Since mutations in either TSC1 or TSC2 have shown high correlation with the expression of ASD symptoms, it is likely that the function of these genes plays a critical role in the maintenance of Purkinje cells and understanding the pathology of ASD.

Table 1: Linear regressions models of COVID-19 case frequency. The cells in the table below contain regressions coefficients for each variable. The legend explaining the meaning of the colors is located in the bottom row.

Gene Abbreviation	Gene Name	Prevalence	Function
TSC1	Tuberous Sclerosis 1	40.5% of patients with TSC1 or TSC2 mutations can be diagnosed with ASD.[3]	encodes for hamartin, tumor suppressor.[21]
TSC2	Tuberous Sclerosis 2		encodes for tuberin, tumor suppressor.[21]
FMRP	Fragile X Mental Retardation 1	30%. [5]	causes fragile X syndrome.[3]
MECP2	Methyl CpG Binding Protein 2	2.8% of females.[5]	Plays a role in gene silencing and RNA splicing.[5]
NRXN1	Neurexin 1	8.7% of ASD patients have a mutation in this gene.[18]	associated with the synaptic cell adhesion and synaptic function.[18]
PTEN	Phosphatase and Tensin Homolog	Prevalence of 8.3% and 12.2% in developmental delay and mental retardation respectively.[17]	tumor suppressor gene.[17]
CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C	N/A	Provides instructions for making calcium channels.[33]
SCN2A	Sodium Voltage-Gated Channel Alpha Subunit 2	50%.[19]	encodes a neuronal voltage gated sodium channel, NaV1.2.[19]
SYNGAP1	Synaptic Ras GTPase-activating Protein 1	0.5–1.0% of ID cases.[20]	integrate signaling through NMDA receptors with structural and functional synapse plasticity.[20]
CHD8	Chromodomain Helicase DNA Binding Protein 8	N/A	Acts as a chromatin remodeling factor and regulates transcription.[32]
SHANK3	SH3 and Multiple Ankyrin Repeat Domains 3	1%.[22]	encodes a protein that helps in the functioning of an excitatory synapse.[21]
SLC6A4	Solute Carrier Family 6 Member 4	2.1% in males with X-linked mental retardation and 1% of males with unspecified mental retardation.[6]	codes for the serotonin transporter.[21]
NLGN4X	Neuroligin-4	N/A	Encodes for cell adhesion protein.[24]
PAH	Phenylalanine Hydroxylase	N/A	Provides instructions for making phenylalanine hydroxylase, which is responsible for the first step in processing phenylalanine.[25]
PEX7	Peroxisomal biogenesis factor 7	N/A	Binds to the N-terminal PTS2-type peroxisomal targeting signal and helps with peroxisomal protein import.[26]
POMGNT1	Protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-)	N/A	Participates in O-mannosyl glycosylation by catalyzing the addition of N-acetylglucosamine to O-linked mannose on glycoproteins.27
SYNE1	Spectrin Repeat Containing Nuclear Envelope Protein 1	N/A	Encodes for a linking network between organelles and the actin cytoskeleton to maintain the cellular organization.[28]
VPS13B	Vacuolar Protein Sorting-Associated Protein 13B	N/A	Codes for a protein that is associated with the Golgi apparatus.[29]
NF1	Neurofibromatosis 1	N/A	Stimulates the GTPase activity of Ras GAP, which accelerates GTP hydrolysis.[30]
BDNF	Brain-derived Neurotrophic Factor	N/A	Signaling molecule that activates the signaling of NTRK2. Promotes differentiation of selected neuronal populations. Participates in axonal growth.[31]
SHANK2	SH3 And Multiple Ankyrin Repeat Domains 2	0.17%.[23]	Scaffold proteins located at glutamatergic synapses.[23]
RPL10	Ribosomal Protein L10	N/A	Transcriptional repressor.[21]
RELN	Reelin	N/A	Codes for a protein with a role in migration of cells.[21]
ITGB3	Integrin Beta-3	30%.[21]	Ligand for members of the frizzled family of seven transmembrane receptors.[21]
DYX1C1	Dynein Axonemal Assembly Factor 4	N/A	Expressed in a subgroup of human neuronal and glial cells.[21]
DISC1	Disrupted-in-Schizophrenia 1	N/A	Codes for a protein that plays a role in neuronal growth and migration.[21]
AVPR1a	Arginine Vasopressin Receptor 1A	N/A	Encodes the arginine-vasopressin receptor (AVPR).[21]

SHANK 3 is another gene that is heavily associated with autism. It encodes for a protein that plays a role in the formation and maintenance of synapses. Synapses are junctions between different neurons, and SHANK 3 specifically affects the synapses of excitatory neurons, which are a type of neuron that releases excitatory neurotransmitters to produce an action potential in the next neuron.[37] The deletion in SHANK3, which is on chromosome 22, results in a disorder called 22q13.[3] deletion syndrome or Phelan-McDermid syndrome. Phelan-McDermid syndrome is typically characterized by speech delay and other autistic phenotypes.[37] SHANK3 is also heavily implicated in other intellectual disabilities, such as Down syndrome.[3] SHANK3 can also lead to defects in motor coordination, another symptom of ASD. Scientists have narrowed down the mutation of SHANK 3 that is heavily associated with ASD patients to occur on the SHANK 3 CpG islands, which are numerous repeats of cytosine and guanine bases.[37] SHANK3 mutations are particularly implicated in patients with ASD and several of its mutations lead to autistic phenotypes.

Some other critical, but less studied genes, associated with ASD include SCN1A, SCN2A, and SCN3A. SCN2A is the most prevalent of these genes and encodes for a voltage gated sodium channel, called NaV1.2, that is primarily found in excitatory neurons. These sodium channels are seen to have familial inheritance of autism.[38] Furthermore, SCN2A is suspected to be inherited in an autosomal dominant manner, meaning that it is expressed regardless of the other allele. SCN2A can also have single nucleotide polymorphisms (SNVs), mutations of a single nucleotide such as A to C, that have also been associated with intellectual disabilities like schizophrenia, epilepsy, and episodic ataxia.[5] In conclusion, mutations in SNC2A as well as SCN1A and SCN3A, have been implicated in patients with ASD.

Many other genes have been linked with autism, but the aforementioned genes are the most prevalent in people diagnosed with ASD. As previously mentioned, these genes can be related to the X chromosomes,[2] while other genes are found elsewhere, such as FMR1, MECP2, TSC1, and TSC2. Additionally, the similarities in cognitive symptoms in most of these mutations lends to the belief that these genes which, when mutated, may lead to autism, are likely responsible for imperative neurological functions, such as development or continual maintenance. Understanding the mechanism and prevalence of these genes can better increase the chance of creating new quantitative ways to diagnose, as well as understand, autism.

Autism and Environmental Factors :

Like genetics, many environmental factors have also been linked with autism. The majority of these environmental factors are specific to periods involving fetal development. Some of these factors are related to maternal diseases. For example, fever and infections during pregnancy, including influenza, have been associated with ASD or other neurodevelopmental disorders/delays.[6] A case control study of children with neurodevelopmental disorders or ASD looked at maternal influenza as a cause and found that there was an association between the two.[6] Another maternal disease that can increase

the child developing autism is diabetes. Type 1 diabetes and type 2 diabetes should be explored separately, as type 1 diabetes in the mother has been found to have no correlation with autism.[39] On the other hand, type 2 diabetes has been associated with autism in a retrospective longitudinal cohort study.[40] Gestational diabetes, diabetes that specifically occurs during pregnancy, has also been associated with autism.[40] These are only some of the diseases known to be associated with the development of autism during pregnancy.

Another environmental factor associated with the development of ASD is the use of drugs during pregnancy. Studies have specifically shown that antidepressant exposure during pregnancy can moderately increase the risk for autism. Another drug, valproate that is used to treat seizures, has been found to significantly increase the risk for ASD if taken during pregnancy in a population-based study.[41] Similarly, smoking during pregnancy after the first trimester is also associated with ASD or other neurodevelopmental disorders.[8] Interestingly, smoking during the first trimester of pregnancy does not have a huge effect on the probability of ASD occurring in the baby.[8] Certain trimesters or time periods during pregnancy can have different effects on the onset, or severity, of autism. Brain development occurs mainly during the third trimester.[42] Smoking during pregnancy (especially during the third trimester) can have detrimental effects on the brain.[43] This can be explained by considering our understanding that specific neurological development occurs at various trimesters of pregnancy, and multiple genes are responsible for various aspects of neurological function.

Despite there being an array of environmental exposures associated with developing ASD, the common denominator they all share is time. Autism is known to have various associations to multiple environmental factors, so long as a person was exposed during their fetal development. This is a key takeaway for progressing towards the understanding of the pathology of ASD and creating more accurate quantitative diagnosis.

Discussion

Both genetic and environmental factors can affect the onset of autism. An accurate, or quantitative, diagnostic test for autism has not yet been developed. However, it can be concluded that both the genetic and environmental factors associated with autism are necessary for creating such a test. As previously discussed, many different factors can lead to the onset or severity of autism in a child. Mutations in a myriad of genes have been found to have high associations to autism. These range from those found on the X chromosome, such as FMR1 and MECP2, to others that are more prevalent in patients with autism, like TSC1 and SHANK3. Additionally, environmental factors have also been linked with autism. These include things such as exposure to drugs, smoking, and influenza, specifically during certain trimesters of pregnancy. This specificity of the timing of each environmental exposure helps us understand that there is likely a link between genetics and environmental factors. However, most of these factors have yet to be directly correlated together, which is likely one the biggest reason that there is no current quantitative diagnostic test for autism.

As the understanding of genetics and environmental factors grow, it is likely that the development of a diagnostic test will be established. However, as with the discovery of all new medical techniques, so too comes questions of ethics. Currently, the genetic tests for diagnosis of autism are performed before birth and therefore before current CDC standards of autism diagnosis. While many parents have opted to perform such testing, several studies have shown that anywhere from 33 % to over 50 % of mothers surveyed would terminate their pregnancy if results showed positive for autism.[44,45] Unfortunately, these tests do not guarantee 100 % accuracy or even an understanding of the severity of autism one's child may have. This is because, as mentioned, very few people with autism opt for genetic testing, and no singular gene has been linked to being responsible for causing autism.[44] Despite the noninvasive nature of the tests, their inaccuracy lies in the fact that they look only at the largest genetic contributors of autism. Therefore, the disease may be missed. As previously mentioned, most autism cases are polygenic, meaning that there are many genes involved and some genes, even when mutated, do not guarantee the diagnosis of autism. Another issue that arises is that sometimes the maternal genetic samples can be interpreted instead of the baby's, as these tests look at the genetics of the fetus from blood that is taken from the mother.[46,47] As such, any improved diagnosis of autism would need to be highly accurate and discussions around ethics should be considered in order to best understand the implications such testing may have on the autistic community.

Conclusion

Autism is a neurodevelopmental disease that can be described by repetitive behaviors and restricted interests. Despite the increase in ASD over the years and continual research, the ability to diagnose ASD and the understanding of autism is lacking. Many factors, such as environmental and genetic, have been linked with autism. Some specific genetic factors are associated with one's gender, as more males are diagnosed with autism than females. Therefore, genes on the X chromosomes were explored and mutations on many of them have been found to be linked with autism. These genes include MECP2 and FMR1. Other genes also associated with autism include the tumor suppressor TSC1 and TSC2, and SHANK3 and SCN2A. There are a great deal of other genes that have also been discovered to have associations with ASD, however, their exact roles are still being studied. Similarly, exposure to specific environmental factors during pregnancy have been seen to have a high correlation to ASD. These include drugs, smoking, gestational diabetes, and influenza. The timing of exposure to these environmental factors may help scientists better understand how these factors can be linked to the aforementioned genes associated with autism. As such it is likely that both genetics and environmental factors will be necessary for the development of a more accurate and quantitative diagnosis of ASD in the future

DOI: 10.36838/v4i2.9

Acknowledgements

I would like to thank Mrs. Katrina Wilson for being my mentor. I also wish to show my appreciation to Biorender.com, with which I generated two of my figures.

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DOI: 10.36838/v4i2.9