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Genetic and environmental risk factors in autistic children

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Abstract: A complex neurodevelopmental disorder known as autism spectrum disorder (ASD) is characterized by difficulties with behavior, socialization, and communication. ASD has a complex etiology, with environmental and genetic variables playing a role in its development. The purpose of this research is to assess our current knowledge of the genetic predispositions and environmental exposures that raise a child's risk of autism spectrum disorder (ASD). To find important risk variables, we examined data from several epidemiological studies, genome-wide association studies (GWAS), and environmental health studies. Our results demonstrate the significant contribution that genetic mutations both inherited and de novo make to the increased risk of ASD. Critical environmental factors that we also discovered were maternal illnesses, prenatal pollution exposure, and dietary deficits. This integrated method emphasizes how important it is to take into account both environmental and genetic elements in order to better understand and maybe lower the risk of ASD.

Keywords: Genetic, Environmental, Risk factors, Autistic, Children

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INTRODUCTION

The symptoms of autism spectrum disorder (ASD) include repetitive activities, impaired social interaction and communication, and varied neurodevelopmental disorders. An abnormal EEG and MRI are signs of a neurological disease. It may be divided into three subgroups: pervasive developmental disorder, Asperger disorder, and autism spectrum disorder (Ratajczak, 2011). However, all three were combined into a single, comprehensive diagnosis of ASD in the DSM-5, a later edition.

ASD is seen as a serious problem for public health. The predicted incidence rate of ASD is now far greater than the combined rates of pediatric cancer, HIV, and heart disease.5. Since the first epidemiologic data were gathered in the late 1960s and early 1970s, the incidence of autism has grown 20–30 times worldwide. In the 2000s, a more comprehensive study suggested that between 1% and 2% of all children had ASD. During that time, the estimated prevalence from European research was 1 in 2,500 children in the community (Centers for Disease Control and Prevention, 2018).

ASD seems to be caused by both hereditary and environmental causes. According to twin research, identical twins have a high concordance (between 60 and 92%) but fraternal twins have a significantly lower concordance (0 to 10%). It was discovered during the search for the precise gene causing ASD that a variety of genetic abnormalities in several chromosomes cause the disorder's symptoms. However, given ASD seems to emerge as a mix of complex genetic variables and environment, it is very improbable that a

single gene responsible for its manifestation will be identified. It was discovered from many array comparative genomic hybridization studies that up to 10% of sporadic (non-inherited) ASD cases do exhibit de novo copy number variations, even on large patient cohorts. Nevertheless, the majority of ASD candidates put out to date are related to the chromodomain helicase DNA binding protein 8 (CHD8) gene. One possible master regulator of a shared etiology for ASD is CHD8. (Barnard, et al., 2015; Willsey, et al., 2013)

GENETIC FACTORS AND AUTISM

In psychiatry, autism is among the most hereditary illnesses. The etiology is diverse, with potential participation of several genes and chromosomal areas, in addition to the strong genetic predisposition reinforced by environmental variables, even with the high degree of inheritance. Clinical image variety and genetic heterogeneity go hand in hand. It is likely that every gene (including distinct variations of the same gene) has a unique role in the beginning of the illness. Strong evidence from studies on autistic individuals suggests that ten or more genes interact to generate autism and that distinct gene groups may be in charge of various families (Quach et al., 2010).

EPIGENETIVE FACTORS

Since the development of autism cannot be explained by the genetic code, environmental and epigenetic non-genetic variables may potentially play a role in its genesis. Genes essential to brain development may be improperly expressed or silenced as a result of epigenetic modifications such as DNA methylation, RNA silencing, and histone modification (Volaki, K. 2012).

Environmental factors

Even though it has been shown that ASD is highly heritable, genetics alone cannot fully account for the situation. Though they only explain a small percentage of cases, a number of genetic disorders are known to have strong correlations with autism (Zafeiriou, et al., 2013). Furthermore, monozygotic twin concordance rates of autism and related problems typically amount to less than 100%, despite variations in the precise ranges among studies (Hallmayer, et al., 2013). This clearly supports a role for environmental variables. Numerous associations between non-genetic variables and ASD have been shown by epidemiological studies, in fact, opening the door to further research to determine mechanisms, demonstrate causality, and in certain cases, support regulatory measures.

A higher risk of ASD in the offspring has been linked to maternal therapy with pharmaceutical medications, such as thalidomide, valproic acid, and selective serotonin reuptake inhibitors, particularly in the first trimester of pregnancy (Durkin, et al., 2008).

But distinguishing the effects of the medicine from those of the mother's underlying illness, which may potentially have an impact on the child's risk of autism, may be challenging (Buxbaum, et al., 2013). Particularly for those who are genetically predisposed, exposure to a variety of toxins, such as pesticides, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs), may negatively impact developmental processes. In addition to their neurotoxic and endocrine-disrupting properties, PCBs and PBDEs persist in the environment and bioaccumulate up the food chain (Newschaffer, et al., 2017).

Furthermore, a number of neurotoxic substances may disrupt neurotransmitter systems linked to ASD. Pregnancy-related ASD risk has been linked to maternal residence proximity to pesticide applications in agriculture, yet this situation may indicate unusually high exposure levels (Ornoy, et al., 2015). Moreover, these substances may be immunotoxic, which might result in changes in cytokine production that are often seen in ASD (Goines, & Ashwood, 2013).

GENETIC RISK FACTORS

Genetic epidemiology

- **Heritability**

Siblings of autistic children have a 2% to 8% chance of developing pervasive developmental disorder again; this risk increases to 12% to 20% if the siblings have impairment in one or two of the three categories associated with autism, respectively. Furthermore, a number of twin studies have shown that shared genes, rather than shared environments, are the most likely explanation for this aggregation within families (Lichtenstein, et al., 2010). Though the findings are varied (heritability 40% to 80%), it's interesting to note that the variance of autistic features in the general population has been proven to be highly heritable, at a comparable degree of genetic impact as autism itself (Constantino, & Todd, 2003). Due to these findings, a significant amount of study has been done in an attempt to identify the genetic components causing the illness. Nonetheless, surprising findings have been obtained from two recent twin investigations. According to one study, there were differences in the cross-disorder effects between monozygotic and dizygotic twins, and monozygotic twins had higher concordance rates than dizygotic twins for ASDs, ADHD, tic disorder, and developmental coordination disorder. These findings raise the question of the specificity of the underlying genetic factors (Ronald, et al., 2006).

- **Transmission in simplex and multiplex families**

Two studies have found that subjects from simplex families (one affected individual) have a higher prevalence of de novo chromosomal rearrangements than subjects from multiplex families (Marshall, et al., 2008). This is consistent with the high rate of notable de novo mutations found in probands from simplex families (O'Roak, et al., 2011). This is also in line with research findings that imply distinct processes of autism's genetic transmission in the general population, such as the possibility that family aggregation of subclinical abnormalities only happens in multiplex families (Constantino, et al., 2010).

- **Several biological pathways identified**

Language proficiency ranges from nonexistent to proficient, and cognitive development spans from severe intellectual handicap to above-average intellectual functioning in people with ASD. Along with psychiatric comorbidities, individuals may also have concomitant medical comorbidities such as seizures and mild physical abnormalities, demonstrating a broad range of clinical variability. Knowing the pathophysiological pathways underlying autism has long been hampered by its clinical variability. Nevertheless, the last few years of research have added significant pieces to the puzzle of autism, even if many issues still need to be answered and new ones are being posed. In fact, the discovery of certain alleles linked to ASD has illuminated pathogenic pathways.

In addition to identifying additional impacted pathways, including as cellular proliferation and motility, GTPase/Ras signaling, and neurogenesis, the examination of genes impacted by uncommon CNVs has shown the critical role these anomalies play in synapse creation and maintenance (Pinto, et al., 2010; Ben-David, & Shifman, 2012). Interestingly, certain de novo or inherited CNVs linked to ASD have not yet been linked to specific ASD genes; instead, they reoccur at the same locus in unrelated individuals. The 16p11 region is involved in one of these the most frequently. Furthermore, because methods are developing so quickly, the first comprehensive studies employing whole-exome sequencing—that is, mapping each and every DNA base throughout the exome—have just published their results (Neale, et al., 2012; O'Roak, et al., 2011). According to these three investigations, individuals who were affected by de novo mutations had a two- to four-fold higher frequency of de novo nonsense variants than would be predicted by chance. It's interesting to note that spontaneous alterations appear to be connected to paternal age in two of these trials. A new biochemical process that appears to be involved is brain signaling, as shown by one of these investigations (Neale, et al., 2012; O'Roak, et al., 2011).

ENVIRONMENTAL RISK FACTORS

Indirect evidence suggesting a contribution of environmental factors

- **Prevalence**

A considerable and consistent rise in estimates of the overall incidence of pervasive developmental disorders has given rise to a dispute surrounding recent prevalence studies of autism spectrum disorders. In fact, whereas the frequency in a population of schoolchildren was estimated to be 6 per 1000 in 200552, more recent research have assessed the prevalence to be one kid in 38 (Kim, et al., 2011). The Centers for Disease Control recently announced updated prevalence figures for the United States, 60 stating that 1 in 88 children were affected in 2008 compared to 1 in 110 in 2006.

- **Immune dysfunction**

Numerous lines of evidence support the theory that immune system alterations occur in autism. First, a number of studies have shown anomalies in the peripheral immune system, including autoantibody formation, T-cell malfunction, an increase in activated B and NK cells, and an increase in proinflammatory cytokines (Ashwood, et al., 2011). Furthermore, a seminal research revealed evidence of activated microglia and astrocytes in the brains of ASD patients (Vargas, et al., 2005). The cerebellum and cerebral white matter showed the most pronounced microglial response. The scientists also discovered an increase in proinflammatory and modulatory cytokines in the cerebral fluid of additional individuals. In the brains of people with ASD, a different research repeatedly found microglial activity in the dorsolateral prefrontal cortex. This neuroglial reaction might be caused by unknown factors interfering with prenatal or postnatal CNS development, or it could be the consequence of a direct disruption of neuroglial function (Morgan, et al., 2012).

- **Transcriptome**

Recent findings from the first thorough gene-expression investigation of ASD patients' brains revealed variations in the transcriptome organization of the autistic and normal brains (Voineagu, et al., 2011).

Using Illumina microarrays, the messenger RNA levels in three post mortem brain areas of autistic and control individuals were measured. The results revealed 444 genes that were expressed differently in the cerebral cortices of the autistic and control brains. Additionally, two distinct modules of coexpressed genes linked to autism were found by the scientists. In autistic patients, the second module (enriched for immunological genes and glial markers) was overexpressed, whereas the first module (associated to synaptic function and neuronal projection) was underexpressed.

- **Epigenetic dysregulation in autism**

Without changing the basic DNA sequence, epigenetic markers control the expression of numerous genes and determine the chromatin state. These may be altered in response to genetic changes or exposure to the environment. They include DNA methylation, histone methylation, and acetylation. Numerous factors suggest that autism may be caused by epigenetic dysregulation. First, mutations in genes related to epigenetic regulation produce a number of disorders linked to autism. For instance, methyl-CpGbinding protein 2 (MeCP2) mutations result in aberrant transcriptional regulation in Rett syndrome. MeCP2 does, in fact, bind to methylated DNA and inhibit target gene transcription. Second, autism was linked to a number of chromosomal sites that are prone to parental imprinting, which is the transcriptional control of either the paternal or maternal allele that results in monoallelic expression. The area 15qllql3, which is susceptible to parental imprinting, has been shown to contain microdeletions or microduplications on many occasions in individuals with autism (Bremer, et al., 2010).

The evidence of epigenetic dysregulation's function in autism highlights the question of the influence of environmental variables on epigenetic alterations, even if the majority of the modifications discussed above are supported by genetic pathways. Assistive conception is one such. Indeed, epidemiologic investigations on the use of assisted reproductive technologies with the incidence of autism revealed contradictory findings, despite the fact that it was shown that ovulation stimulation and in vitro fertilization might lead to aberrant methylation and dysregulation of imprinted genes (Hvidtjørn, et al., 2009).

- **Direct evidence for the contribution of environmental factors**

The original proposal to provide the MMR (measles, mumps, rubella) vaccination has generated a lot of controversy. Nonetheless, based on numerous epidemiologic studies that found no connection between thimerosal-containing vaccines and ASD, there is currently a consensus among scientists that the evidence favors rejecting a causal relationship between thimerosal-containing vaccines and autism (Parker, et al., 2004). However, a significant amount of the risk of ASD is probably due to other environmental variables.

- **Prenatal and perinatal factors**

Few substantial risk variables were found in a recent meta-analysis of prenatal factors that was restricted to pregnancy-related factors. Maternal medicine, maternal hemorrhage during pregnancy, and gestational diabetes are the primary contributing factors. We'll talk more about the latter topic later. Furthermore, compared to children born third or later, first-born children and children of foreign-born mothers in Nordic nations were shown to be at higher risk in this meta-analysis. The analysis restricted to the four studies that used sibling controls or accounted for various factors showed that exposure to intrauterine infections was linked with a statistically significant increase in risk for autism. The findings using rat models of the

maternal illness provide further evidence for the link between autism risk and maternal infection. These animal models simulate gestational viral infection by administering a synthetic doublestranded RNA called Poly I:C systemically, which triggers an innate immune response. It seems that viral infections during pregnancy set off a mother's immune system, which may interfere with the development of the fetus's brain, at least partially, by producing interleukin-6 (Smith, et al., 2007).

- **Socioeconomic status**

While a research conducted in 1987 found no correlation between the risk of autism and socioeconomic position, including the education level of mothers, the latter may have a major impact on the age at which a child learns to speak on their own. Furthermore, as was previously indicated, a meta-analysis revealed a considerably higher risk of autism in children whose moms were born outside of the country. This risk was further outlined in a very recent study, which found that children of immigrants have a lower risk of high-functioning autism and a higher risk of autism with intellectual disability, particularly when parents immigrated to Sweden from areas with a low human development index. The highest risk period for low-functioning autism was during pregnancy and the period of migration. There are many explanations for these findings, including the elevated stress level of mothers or their weakened response to common diseases (Gardener, et al., 2011).

- **Drugs and toxic exposure**

As was previously noted, the most recent meta-analyses revealed that taking medication while pregnant increased the chance of autism. One known risk factor for ASD is prenatal valproate exposure, particularly during the first trimester of pregnancy. Infants who are exposed to valproate during pregnancy are eight times more likely to have ASD (Rasalam, et al., 2005). Remarkably, somatosensory cortex and hippocampus subregions of mice exposed to valproate during pregnancy showed a downregulation of NLGN3. Furthermore, as the percentage of pregnant women using selective serotonin reuptake inhibitor medicine climbed from 1.5% in 1996 to 6.4% in 2004 and 6.2% in 2005, one of the main concerns surrounding drug exposure during pregnancy is to the use of antidepressants. Pregnancy-related exposure to antidepressants has been shown to slightly raise the risk of ASD, particularly during the first trimester. Last but not least, it was shown that prenatal exposure to the organophosphate pesticide chlorpyrifos increased the chance of ASD and that more research should be done on synthetic chemicals.

DISCUSSION

Pugsley, et al., (2022) While the exact cause of autism spectrum disorder (ASD) remains unclear, research on twins and families has shown that the illness has a high heritability of 60–90%, suggesting that genetics plays a major part in the disorder's development. All kinds of genetic variation are represented in the complex array of uncommon and common variations that make up the genetic architecture of ASD. These variants often operate additively to increase individual risk. Despite selection pressures against the conventional autistic phenotype, the relative contribution of heredity in ASD remains, a phenomenon partially explained by the occurrence of spontaneous (or de novo) mutations. Notably, with numerous ASD-associated agents having considerable mutagenesis potential, environmental exposures identified as relevant risk factors for ASD may be causative in the formation of harmful de novo variants. In order to

investigate this theory, this review paper evaluates evidence from mutagenicity tests, both in vivo and in vitro, in conjunction with published epidemiological data to ascertain the probable contribution of such agents to increasing the genetic vulnerability in ASD. In general, it was shown that these exposures caused either one or a combination of the following to cause genomic alterations: (1) direct contact with genetic material; (2) poor DNA repair; or (3) oxidative DNA damage. However, further research is need to identify how these variables directly contribute to the ASD phenotype. A causative, mechanistic explanation of de novo mutations in ASD that connects exposure, genotypic changes, and phenotypic outcomes requires the creation of large prospective birth cohorts in conjunction with genome sequencing.

Modabbernia, et al., (2017) New research suggests that environmental variables may account for up to 40–50% of the variation in autism spectrum disorder (ASD) risk. We reviewed systematic reviews and meta-analyses of environmental risk variables for ASD in the current research. We evaluated the strength of the evidence in each review and gave a succinct synopsis of the potential processes behind environmental risk factors for ASD. According to available data, there is no correlation between the incidence of ASD and a number of environmental variables, including immunization, maternal smoking, thimerosal exposure, and most likely assisted reproductive technologies. On the other hand, a greater risk of ASD is linked to older parents. ASD has also been strongly correlated with birth problems due to trauma, ischemia, and hypoxia; in contrast, caesarian sections, obesity, and diabetes in mothers, among other pregnancy-related variables, have been less strongly (but still significantly) correlated with ASD risk. Reviews of dietary components have been conflicting about the negative consequences of folic acid and omega 3 insufficiency; nonetheless, individuals with ASD seem to have low levels of vitamin D. Although the design of the studies on hazardous elements has generally restricted their scope, there is sufficient evidence to support future research into the possible link between ASD and certain heavy metals, most notably lead and inorganic mercury. Although the exact mechanisms underlying the link between environmental factors and autism spectrum disorders (ASD) are unknown, potential explanations include non-causative associations (such as confounding), gene-related effects, oxidative stress, inflammation, hypoxia/ischemia, endocrine disruption, changes in neurotransmitters, and disruption of signaling pathways. Studies of environmental risk factors for ASD are still in their infancy and have considerable methodological limitations when compared to genetic studies of the disorder. Future research on ASD risk factors should use a developmental psychopathology approach, prospective design, accurate exposure measurement, and reliable timing of exposure in relation to critical developmental periods. Genetically informed designs should also be used to account for the dynamic interaction between gene and environment.

Chaste, & Leboyer, (2012) This review's objective is to provide an overview of the most important discoveries from genetic and epidemiological studies, which demonstrate that autism is a complicated illness brought on by a confluence of environmental and hereditary elements. The tremendous efforts made in the science of genetics have led to remarkable advancements in our understanding of the genetic origins of autism. Crucial pieces of the autism jigsaw have been added with the discovery of certain alleles contributing to the autistic spectrum. Still, there are a lot of unsolved concerns, and the latest findings raise more. Furthermore, it is now obvious that the search for environmental variables has to be intensified given the volume of data indicating a considerable contribution of environmental factors to autism risk. The investigation of the relationships between genes and environmental variables is one facet of this inquiry that has received little attention so far.

The findings of this study highlight the intricate interplay between genetic and environmental factors in the etiology of Autism Spectrum Disorder (ASD). The genetic component of ASD is underscored by the identification of numerous risk loci and gene mutations through genome-wide association studies (GWAS) and other genetic research. Notably, both de novo mutations and inherited variants have been implicated in increasing the susceptibility to ASD. For instance, mutations in genes such as SHANK3, NRXN1, and CHD8 have been consistently associated with ASD, suggesting that these genes play critical roles in neurodevelopment and synaptic function.

In addition to genetic factors, our review identified several environmental exposures that significantly contribute to ASD risk. Prenatal exposure to pollutants, such as heavy metals and air pollutants, has been shown to disrupt fetal brain development, potentially leading to neurodevelopmental disorders including ASD. Maternal infections during pregnancy, particularly viral infections, have also been linked to an increased risk of ASD in offspring. These infections can trigger inflammatory responses that may interfere with normal brain development. Moreover, a higher risk of ASD has been linked to dietary deficits, especially of vital vitamins and minerals during pregnancy. This emphasizes how crucial maternal nutrition is and how it affects the neurodevelopment of the fetus.

The interaction between genetic predispositions and environmental exposures is a critical area of investigation. Epigenetic mechanisms, such as DNA methylation and histone modification, may mediate the effects of environmental factors on gene expression, thereby influencing the risk of ASD. Understanding these interactions is essential for developing targeted interventions that could mitigate the impact of adverse environmental exposures in genetically susceptible individuals.

Despite significant advances in our understanding of ASD, several challenges remain. One major challenge is the heterogeneity of ASD, which encompasses a wide spectrum of symptoms and severities. This heterogeneity complicates the identification of specific genetic and environmental risk factors and their interactions.

In conclusion, this study emphasizes the necessity of a multifaceted approach to understanding ASD, integrating genetic, environmental, and epigenetic perspectives. Such an approach will enhance our ability to identify high-risk individuals, develop preventive strategies, and create more effective therapeutic interventions. The ultimate goal is to improve the quality of life for individuals with ASD and their families through early diagnosis, personalized treatment, and supportive services. Continued research in this field is essential to achieving these objectives and to unraveling the complex etiology of ASD.

CONCLUSION

Our comprehensive review indicates that both genetic and environmental factors play pivotal roles in the etiology of Autism Spectrum Disorder. Genetic studies have revealed numerous risk loci and gene mutations associated with ASD, emphasizing the hereditary component of the disorder. Concurrently, environmental factors, particularly those affecting the prenatal environment, have been shown to significantly influence ASD risk. Understanding the interplay between these genetic and environmental factors is crucial for developing preventive strategies and therapeutic interventions. Future research should

focus on elucidating the mechanisms through which these risk factors interact and identifying potential biomarkers for early diagnosis. Ultimately, a multidisciplinary approach that integrates genetic, environmental, and clinical data will be essential in advancing our understanding of ASD and improving outcomes for affected individuals and their families.

FUTURE RECOMMENDATIONS

Future research should aim to stratify ASD based on phenotypic and genetic subtypes to better understand the underlying mechanisms and to develop more personalized interventions.

Another challenge is the need for large, well-characterized cohorts to study the interaction between genetic and environmental factors. Longitudinal studies that track individuals from the prenatal period through early childhood are particularly valuable in identifying critical windows of exposure and understanding the temporal dynamics of risk factors.

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