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Review Paper

Unraveling the Genetic Architecture of Autism Spectrum Disorder: A Review of Twin, Family, and Genome Sequencing Studies

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder affecting social interaction, communication, and behavior. Its etiology includes both genetic and environmental factors. Existing literature indicates that genetics plays a supreme role, with heritability of 60-90%, in which most ASD risk is genetically inherited. Key genes always implicated in ASD include CHD8, SHANK3, SCN2A, and SYNGAP1, which regulate brain development, formation of synapses, neural communication, and chromatin remodeling. Mutations in these genes have been shown to disrupt neural connectivity, leading to the characteristic social and behavioral symptoms of ASD. Genetic mutations in ASD are rare or common. Rare variants exert strong effects to cause large developmental changes, while common variants exert weak individual effects that sum up to contribute to risk. Polygenic risk models have been developed to estimate the combined effect of these variants and to explain variation in symptoms among individuals and families. De novo mutations, which arise spontaneously and are not transmitted, also play a significant role in some cases. Environmental insults like maternal infection, prenatal stress, and exposure to toxins may have the capability to intersect with genetic predisposition, often by epigenetic change like DNA methylation. Advances in sequencing technology like whole-exome sequencing and whole-genome sequencing have allowed identification of these genes and their functional significance. Overall, ASD is the result of the intricate interplay among genetic, epigenetic, and environmental factors. This explanation facilitates early detection, individualized treatments, and the incorporation of genetic information with behavioral and clinical research to enhance overall knowledge of ASD.

Keywords: *Autism Spectrum Disorder, Genetics, Heritability, Neurodevelopment, Gene Mutation*

Autism Spectrum Disorder (ASD) is a complex brain disorder that is causing us to talk and behave improperly with people as well as to repeat some of our actions that we may not otherwise repeat. It manifests itself in various forms with some individuals being more afflicted than the others and it is usually accompanied by other conditions such as learning discrepancies, seizures and ADHD. The big book of mental stuff (DSM-5-TR) and global statistics estimated that approximately one or two % of the entire

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population has ASD, which also increases due to easy detection of ASD (APA, 2022). The cause of ASD is yet unknown, but according to science, genes contribute an enormous portion to it, influencing the functioning of the brain and its appearance.

In 1900s, everyone believed that the causes of autism were due to stressful social factors such as parental lifestyles or childhood stress. They were mistaken since twins researches indicated a large genetic streak. Within the past three decades, research in gene stuff, biology and computer genetics has made ASD a brain-based combination of genes and environment. Currently, we all hold the opinion that autism is the result of a pool of various genetic risks, some inherited, some just eventual, and external factors that modify the manifestation of genes in the body (Devlin & Scherer, 2012; Geschwind & State, 2015).

We are aware of family genes since twin studies are hyper convincing. The probability of an individual with ASD getting a same-size twin with the condition is 60-90 and the probability of getting a different-size twin is 20-30 (Hallmayer et al., 2011). It translates to between 70-90% hereditability of ASD, equivalent to the highest of any mental health problem. Even the identical twins differ indicating that the external factors such as environment or epigenetics also play a role. This proves that autism is a complex issue: genes precondition it, but an environment makes a significant contribution.

The angle of the gene is supported by family and sibling researches. The risk of ASD is 15-20 % among a sibling of a person with ASD and 1-2% among the general population (Ozonoff et al., 2011). The risk has been identified as decreasing in direct proportion to the genetic distance between full siblings, half-siblings, cousins, and Scandinavian big studies determined that there are numerous genes involved (Gronborg et al., 2013; Sandin et al., 2014). It is not a single gene that is the culprit but there are many variants of genes that combine to influence the development of the brain.

The breakthrough of genes discovery was especially significant with the advent of fast sequencing and genome-wide research (GWAS). These were useful in discovering the rare and potent mutations and also common and subtle mutations accumulating to create a significant risk. To illustrate, the ASD spontaneous gene mutations in sperm or eggs lead to a large proportion of single incidences. These mutations were indicated in big studies of brain-important genes, such as CHD8, SHANK3, SCN2A, and NRXN1 by Iossifov et al. (2014) and De Rubeis et al. (2014). This proved both brain wiring and cell connection pathways are important and the fact that we can now categorize autism into molecular subtypes to make it a more targeted treatment.

Although rare mutations have huge effects, the vast majority of the risk is associated with lots of common gene variations, which do little things individually, although when combined have a massive effect. According to Gaugler et al. (2014), common variants contribute over fifty % of genetic risk. So ASD appears to have a lot of genes that individually alter the development of the brain, the work of synapses or chemical signals.

The explanation of everything is not limited to genes. They interrelate with the environment and epigenetic material which influences the development of the brain. To illustrate, older dads, prenatal exposure to toxins, immune problems of moms, and birth complications are slightly associated with ASD risk (Bai et al., 2019; Huguet et al., 2016). They may accomplish this probably by altering gene activity by the action of DNA methylation or

histone modification that modify the growth and formation of brain cells. The research on gene and environment interactions is a big frontier in the study of autism.

Such gene discoveries provide us with actual clinical advantages. Genetic testing and counseling are becoming increasingly popular particularly in families that have a history of ASD or any other disorder of the brain. The awareness of certain gene variations can warn about other possible issues, inform the treatment decisions or allow families to make reproductive decisions. In addition, through the determination of genetic subtypes, the doctors could possibly devise drugs that correct the molecular defects rather than controlling behaviors.

In a nutshell, autism is not only something, but a combination of bizarre DNA stuff that have not quite fit the normal rules. These are these inherited and random genetic bits which all combine and determine the way the brain develops and how people behave. This bizarre genetic history is a nice foundation on which to start understanding why people are different, identifying it early in life, and modifying interventions to suit an individual.

There has been incredible advancement in science, however, inconsistent aspects such as the presence of certain genes not appearing in all people, and the occurrence of traits everywhere, and difficulties in matching genetics with the functioning of the brain in real life continue. Some more team projects that combine genetics and brain science and behavior studies will be required in case we would like to chart out how all this DNA stuff connects to autism and translate that into useful assistance to patients.

METHODOLOGY

The research adopted a literature based review in databases like PubMed, ScienceDirect and Nature Genetics. Articles that are published in 2014-2024 were also included, and were mainly on genome-wide association, exome sequencing, and the heritability studies.

Data Collection

- The keywords were searched in the terms: autism genetics, ASD heritability, and polygenic risk. The choice of the peer-reviewed journal articles, reviews, and meta-analyses was made according to the quality of the methodology and size of the sample.
- Results of individual studies were summarized to find out similar genetic relationships, biological pathways, and heritability patterns.
- The literature looking into the impact of genetic mutations, chromosomal changes, and epigenetic alterations on ASD was considered. Articles that are not in English and peer reviewed articles were disqualified.

Objectives

1. To review and summarize recent research identifying genes linked to ASD.
2. To test the estimate of heritability and polygenic risk factors in ASD.
3. To talk about the relationship between genetic and environmental factors in ASD development.

DISCUSSION

Genetic Heritability of ASD

1.Twin and Heritability.

It is a fact that twin research is one of the most interesting in the behavioral genetics as it helps us to clarify the proportion of genetics and the proportion of environment in complex qualities. Comparisons of MZ (identical) with DZ (fraternal) twins are made via the observation of prevalence of shared traits in twins. Autism Spectrum Disorder remains a disorder that has the highest rates of heritability estimates.

The first massive intervention was Hallmayer et al. (2011) which was carried out on over 2,700 pairs of twins in California. They found out that MZ twins were around 70-90% probable of acquiring ASD both whereas DZ twins were only around 20-30% probable of acquiring ASD. Such a huge difference shows the sheer power of genetics, and the fact that not all MZ twins are identical shows the presence of the non-shared environment.

Colvert et al. (2015) then proceeded to carry out a standard interviews study using the UK as the setting. It was found that the heritability was about 74-84 and the shared environmental effect was very minimal. The fined statistics enabled them to decompose additive genetic effects and unique environment effects, and this was what led to the fact that environment affects things only at individual level and not at family level.

One of the meta-analyses by Tick et al. (2016) has over 20 studies, which were conducted by various populations, such as twins. They possessed a joint heritability of about 80 and were relatively uniformly reproducible between methods, culture and diagnostic criteria. The authors suggested that the decreased heritability reports were usually due to sampling bias, or shift in diagnostic practice, rather than due to the actual population difference.

In the real-life scenario, Sandin et al. (2017) employed the massive twin registry in Sweden to test heritability. Their results confirmed decades of consistent heritability in spite of the rise in autism diagnosis. This means that it to a large extent is not determined by newborn genetic risks but by the improved capacity of identifying and generate awareness about the problem.

2. Strengths and limitations.

Twin studies give the impression of a natural experiment although they are not the best. The diagnostic differences can confound interpretation, selection bias and finding common environment and not an easy task of identifying common environment and correlated genetics. In addition, the same twins share equal numbers of prenatal factors hence, it is hard to isolate the pure genetic effects. However, the ability to reproduce the findings in other samples of individuals adds to the fact that ASD is extremely hereditary.

All these studies give strong evidence that the ASD variability can be best discussed as a variant of genetics where the heritability of the ASD is always in the range of 70-90%. The alternate one is explained by the accidental developmental circumstances, genetic environmental interaction and epigenetics. It is worth noting that these discoveries represent a contradiction of the previous myths of the past that autism is a simple parenting/ psychosocial phenomenon. Their work has given the grounds of molecular and genomic research that is uncovering the secrets regarding the actual genes involved. Therefore,

having family history with reference to a particular disease predisposes one to chronic diseases.

Genetic loading and Familial Aggregation

1. Family and Sibling Studies

Therefore, family and sibling study are all to monitor the risk of autism among its children. They in the most general terms study the likelihood of children in the same family developing autism and the relationship with the degree of relatedness of the family members.

Ozonoff and crew (2011) -infants followed who had an older brother or sister with an ASD diagnosis. About 18 % of those younger siblings were getting ASD and it is significantly high as compared to the 1-2 % of the general population. And 30 % of them had some of the wider autism phenotype materials i.e. showed some of the characteristics, not the complete ASD, but only partial genetic carrier-over.Gronborg et al. (2013) analyzed information in the Danish registries and determined a risk-effect in distancing yourself as much as possible out of the first sibling with autism. The most hazardous of all the family ties are the siblings (seven times higher) who are followed by half-siblings and then cousins. Such trend promotes the belief that autism is caused by many genes, each of which is contributing a little.

The study by Sandin et al. (2014) is also based in Sweden; the authors also managed to demonstrate the same rule: the closer the genetic correlation, the higher the probability of being influenced by ASD. It is therefore the combination of genetics and not the environment.

A twist was made by Bai and group (2019) though parents were considered in this. Older fathers were its risk factor by its own because older fathers are more likely to provide their children with new mutations during the production of sperm that can increase ASD risk and other brain-development issues.

2. Implication to Genetic Counseling

This research might suggest the use of clinical interviews as a beginning point in counseling in order to establish genetic predispositions that will help in diagnosis of autism. Genetic counseling is the use of the knowledge of the genetics to determine those individuals who are prone to the occurrence of diseases or disorders in a particular population group of individuals. One should be aware that families with one autistic child possess far greater opportunities to have other children with ASD. The doctors will be in a position to train the parents on the need to be watchful and not create a panic by conducting early screenings and keeping up with the screening of the unborn children. The genetic counseling is logical to the families of the numbers and the way genetics is not a set-in-set trap, the way people cannot make their choices.

Combined together, the sibling and family studies allow one to conclude in favor of the hypothesis that autism is inherited immensely. They also portray new mutations particularly in old fathers, which have made significant contributions towards cases of sporadic cases. Of course, there is influence of the environment which may include health of mom or financial status but genes are first of all.

Major Genes Implicated in ASD

Exome-wide sequencing has revealed a number of high risk genes with large confidence. CHD8 controls the chromatin remodeling, and mutations cause macrocephaly and social malfunction (Bernier et al., 2014). SHANK2 and SHANK3 are scaffolding proteins that are vital in the formation of synapses; their impairments contribute to the poor neural connection (Berkel et al., 2010; Durand et al., 2007). Mutations in the SCN2A change the function of sodium channels, influencing the neural excitability (Sanders et al., 2018). Recurrently implicated other genes are SYNGAP1, DYRK1A, and PTEN that have effects on neuronal growth and signaling (De Rubeis et al., 2014; Iossifov et al., 2014).

Table 1. Chosen genes and biological functions related to ASD.

Gene	Biological Role	Functional Impact in ASD
CHD8	Chromatin remodeling	Stuttered transcription and macrocephaly.
SHANK3	Synaptic scaffolding	Hampered connectivity and communication impairments.
SCN2A	Sodium channel regulation	Neural excitability is one of the changes.
SYNGAP1	Synaptic plasticity	Ineffective learning and memory.
PTEN	Neuronal growth regulation	Abnormal brain structure and functioning.

The majority of the genetic risk that occurs is due to many small-effect variants that are common (Gaugler et al., 2014). Grove et al. (2019) and Feliciano et al. (2019) conducted genome-wide association studies that showed over one hundred additively acting risk loci of ASD. Polygenic models assist in the explanation of why ASD characteristics are present on a continuum and why they are not clearly present in family members who are not thoroughly diagnosed (Anney et al., 2017).

Gene-Environment Interactions

Although genetics provides a good basis of risk of ASD, the environment influences the expression of genes and phenotypes through the action of epigenetics. The study of the interaction of genes and environments (gene-environment interaction, or GxE) involves the examination of how environmental exposures that are not genetic adapt the phenotype of genetically inherited or de novo variants.

Huguet et al. (2016) conducted a summary of the evidence related to the prenatal conditions such as maternal immune activation, exposure to air pollution, and nutritional deficiency that decrease vulnerability to ASD. They can influence DNA methylation or histone acetylation and hence neural gene expression during important development stages.

The advanced paternal age was also identified by Bai et al. (2019) as a reliable risk factor that was mediated by the accumulation of de novo mutations. Motherly metabolic disease, infection and exposure to valproic acid have been added. More importantly, these exposures rarely lead to ASD alone but rather in combination with underlying genetic factors can push development in the direction of aberrant results.

Recent studies in epigenomics e.g. of DNA methylation in postmortem brain are demonstrating that genes associated with ASD have dissimilar epigenetic marking. It means

that environmental factors may have an impact via transcriptional dysregulation of genetically sensitive pathways. The understanding of GxE interactions is the most important to prevent and even to intervene early. It allows the recognition of risk factors that can be modified to reduce the phenotypic expression of genetic liability and opens the path to the use of precision public health interventions.

Neural Pathways and Molecular Pathways.

In the cells, numerous genes related to ASD intersect on pathways of synaptic signalling and cortical development (Bourgeron, 2021; Deisseroth & Huguenard, 2022). Functional MRI analyses demonstrate the changed connection in frontal and temporal systems, which may be caused by such genetic variants (Ecker et al., 2015). Transcriptional findings also indicate that the genes of ASD are over-expressed in mid-fetal neurons of the cortex, which indicate that it disrupts brain development during early stages (Willsey et al., 2013).

Ethical and Social Implications

The potential in diagnosing genetic discoveries, produces ethical issues concerning the privacy and neurodiversity. Genetic testing is becoming more commonly available, which may bring misunderstanding or abuse of the findings (Bourgeron, 2021). This then has to make genetic knowledge be utilized in order to give support and inclusion but not stigma.
Researchers discovered that not all autism genes were one. Many genes are involved in complicated networks. These sort into brain development pathways such as connection between the neurons and regulation of brain signals. Other brain disorders are also associated with the same genes and hence autism is just the tip of the iceberg.

Nonetheless, there are still major issues. First, the known variants can only account (partly) for the genetic risk and there is a puzzle of the missing heritability, perhaps since genes interact and interplay with the environment. Second, mutation of a similar mutation may produce various symptoms altering its manifestation. Third, human beings must consider ethics, including testing, telling the truth, and stigma, in particular, since autism is so varied, and individuals appreciate their identity.

CONCLUSION

Genetic studies indicate that Autism Spectrum Disorder develops out of complicated interactions of uncommon mutations and moderate variants concerning the brain formation. The estimates of hereditability are usually over 60 % and the genes like CHD8, SHANK3, and SCN2A have been associated on numerous occasions with ASD. Even though genes can be affected by environmental factors to produce increased symptoms, the genetic factor still dominates. Further studies of how genomics, neuroscience, and behavioral research can be combined in the future are going to yield a better comprehension and bring about more customized diagnosis and treatment. Gene data, combined with brain imaging, behavior tests, and long-term studies will aid in the association of genes with brain behavior and functionality. The research should also consider diversity in future since majority of the information is of European descent and thus could not be applicable worldwide. In summary, Autism, according to the studies, appears to be largely genetic with numerous factors being involved. Approximately 80 % of the danger is predetermined by genes, yet the surroundings and chance materials determine how it is manifested and how intense it is.

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Conflict of Interest

There is no conflict of interest associated with this research.

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