HISTORY, EPIDEMIOLOGY, AND PUTATIVE MOLECULAR BASIS OF AUTISM SPECTRUM DISORDER

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Abstract. Autism spectrum disorder (ASD) is a human behavioral disorder related to neurology and development with a global health concern that affects nearly 1-2% of the population. The term "spectrum" denotes a broad range of ASD symptoms, widely starts in childhood, and often develops within the first year of development. ASD is characterized by repetitive behavior along with impairment in social communication jointly with restricted interest. Based on the available wealth of literature, ASD is considered a complex disorder that is associated with a range of defects and disorders such as epilepsy, cognitive impairment, immune diseases, and sleep problems. Although there is no cure for ASD, some medicines can alleviate ASD-related symptoms like depression, trouble focusing, seizures, and insomnia. However, studies have revealed that these medications are more effective when they are combined with other behavioral therapies. More recently, there has been extensive research on establishing the etiology of ASD through genetic mutation, and epigenetic dysregulation caused by environmental factors. The specific role of causative factors and their impact on autistic individuals are still unclear. Moreover, the diagnosis of ASD still relies on behavioral observation at the clinic. Hence, this review aimed to provide a concise overview of the current research on the epidemiology and molecular basis of ASD, as well as a potential strategy for the improvement of ASD diagnosis strategies and potential therapy.
Keywords: *ASD, epigenetic biomarker, DNA methylation, childhood behavior, epigenetic dysregulation*

Abbreviations

ASD	Autism spectrum disorder	HDAC2	Histone deacetylase 2
ADDM	The Autism and Developmental Disabilities Monitoring	HpaII	Haemophilus parainfluenzae
ANK3	Ankyrin 3	miRNA	MicroRNA
ADIR	Autism Diagnostic Interview-Revised	miR	MicroRNA
ADOS	Autism Diagnostic Observation Schedule	*MECP2*	Methyl binding protein 2
ADHD	Attention-deficient hyperactivity disorder	*NRXN3*	Neurexin 3
AD	Alzheimer's disease	*OXTR*	oxytocin receptor
CDC	The Centers for Disease Control and Prevention	OR2L13	Olfactory receptor family 2 subfamily L member 13
CACNA2D1	Calcium Voltage-Gated Channel Auxiliary Subunit Alpha2delta 1	PD	Parkinson's disease
CAST	Childhood Autism Spectrum Test	PRRT1	Proline-rich transmembrane protein
CNVs	Copy number variants	PTEN	Phosphatase and tensin homolog
CNS	Central nervous system	PDD	Pervasive developmental disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders	*PCDH9*	Protocadherin 9
DNA	Deoxyribonucleic acid	RNA	Ribonucleic acid
DBT	Dihydrolipoamide branched chain transacylase E2	*SHANK3*	SH3 And Multiple Ankyrin Repeat Domains 3
ERMN	*ERMN* gene	*RORA*	RAR-related orphan receptor A
FDA	Food and Drug Administration	USA	The United States
GCC	The Gulf Cooperation Council	UAE	The United Arab Emirates
HLA	Human leukocyte antigen	WHO	World Health Organization
HD	Huntington's disease	ZFP52	Zinc finger protein 52
H3	Histone 3		

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Introduction

Autism spectrum disorder (ASD) is a common neurological disorder that is associated with constant deficits in social communication with restricted and repetitive behaviors (Murphy et al., 2016; Baio et al., 2018; Lo and Lai, 2020). The term "spectrum" refers to broader symptoms and phenotypes, which differ in severity; some phenotypes are simple, while others are complex and manifest as significant impairments (Ardhanareeswaran and Volkmar, 2015). ASD is clinically characterized as a complex neurodevelopmental condition with different impairments including epilepsy, attention problems, and motor impairment (Geschwind, 2009; Voineagu and Eapen, 2013). ASD is believed to be one of the most neurological disorders that gained scholarly attention in recent years due to its prevalence. The first epidemiological studies of ASD were between the 1960s and 1970s with two to four ASD cases identified per 1,000 children in Europe and the United States. According to the latest reports published by the Centers for Disease Control and Prevention (CDC), the prevalence of ASD has rapidly elevated to 1 out of 68 children worldwide (Sanchack and Thomas, 2016; Nadeem et al., 2020). The rise in the prevalence of ASD in the past decade could be attributed to the evolution and advancements in the diagnostic criteria, as many overlapping phenotypes and conditions, like depression, schizophrenia, and hyperactivity, have become integrated with ASD syndrome (Grabrucker, 2013; Kim, 2015). Previous studies have shown that clinical features and behavior observation of the patient and the family history estimation are critical to facilitate diagnosis. Although a clinical examination is needed for a more practical assessment of ASD, diagnosis using DSM-5 criteria, which include three core features - impairment in social interaction, repetitive behavior or interests, and speech impairment - has successfully confirmed ASD diagnosis. Consequently, the use of both diagnoses by DSM-5 criteria and clinical observation is considered important for optimal diagnostic classification. Moreover, the complexity of ASD etiology is attributed to the interaction between genes and environmental factors that may lead to genetic or epigenetic alteration (Forsberg et al., 2018). This view is further supported by recent ASD etiology studies where 40-50% of ASD symptoms are shown to be caused by environmental factors, which equally influence epigenetic dysregulation (Onaolapo and Onaolapo, 2017). However, the amount of available evidence that describes the impact of these factors on autistic individuals is still scarce (Murphy et al., 2016). As there are many etiologies of ASD, the key to explaining the complex neurobiology leading to the development of ASD is to focus on the molecular mechanisms that affect the phenotype and alter gene expression in children with autism (Lo and Lai, 2020). This may provide insight into a more effective diagnosis and treatment for ASD.

Definition and Symptoms of ASD

According to recent epidemiological surveys, ASD has received considerable attention from investigators because of its high prevalence (Wiśniowiecka-Kowalnik and Nowakowska, 2019). ASD is a multiplex neurodevelopmental disorder that affects the nervous system, characterized by restricted and repetitive behaviors, and impairment in the social communication of the affected individuals, which makes them unable to interact with others (Murphy et al., 2016; Eshraghi et al., 2018; Baio et al., 2018; Lo and Lai, 2020). ASD relates to some phenotypic features such as gastrointestinal, cognitive, attention trouble and motor impairments, depression, anxiety, immune system aberration, mitochondrial impairments, and epilepsy (Geschwind, 2009; Voineagu and Eapen, 2013).

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Studies have further reported epilepsy observed in 15-47% of children with autism causing more social disability (Clarke et al., 2005). Furthermore, sleep troubles and wakefulness associated with severe ASD symptoms have been indicated in 50-80% of cases with ASD (Tyagi et al., 2019). Sleeping problems not only have a negative influence on ASD children but also on their families and augment the severity of ASD-related symptoms.

The Impact of ASD

Masi et al. (2017) reported in their study the considerable impact that ASD has on the community, spanning over a diverse range of sectors such as health, education, employment, and domestic economic and other unknown sections. It is predicted that in the USA alone the direct medical and non-medical expenses and related productivity loss related to ASD and managing practices could reach about $461 billion by the year 2025 (Leigh and Du, 2015).

The History and Diagnostic Criteria of ASD

Year	Author	ASD Criteria Description
1911	Eugen Bleuler	Bleuler used the term "autism" for the first time, which was derived from the Greek word "autos", meaning "self". He described “autism” based on the specific characteristics of schizophrenia (Scherbaum, 1992).
1943	Leo Kanner	Kanner characterized autism as a neurodevelopmental condition that impairs social communication in the early stages of development of children and persists throughout childhood (Kanner, 1943). Children with ASD have language defects, repetitive behaviors learning difficulty, even in nursery rhymes, along with being highly sensitive. The conclusion of the study, which involved eleven children aged 2 to 11 years old, was reported under the title “Autistic disturbances of affective contact”. He also described autism as one of the peculiar characteristics of schizophrenia (Kanner, 1943).
1944	Hans Asperger	Asperger’s described autism symptoms like those of Kanner's group, however, with advanced stages of cognitive skills and social communication. Consequently, they called conditions Asperger’s syndrome. Although these observations were reported during the Second World War period, they were not widely published and read in the English-speaking medical community during that time until 1970 (Geschwind, 2009).
1981	Lorna Wing	The author renamed "Autistic Psychopathy" to "Asperger syndrome" and amalgamated the similarities between Kanner's definition of autism and Asperger syndrome. Wing also the Asperger criteria for infantile autism or Kanner's autism (Wing, 1981).
1986	DSM-III	It diagnoses autism as a subgroup of pervasive developmental disorder (PDD) (Wing, 1981). PDD is characterized by aberrant or developmental impairment, difficulties in contact with other people, and language difficulties with no response to stimuli. However, most of these symptoms appear within 30 months of birth before they can be considered under the criteria of infantile autism (Masi et al., 2017).
1987	DSM-III-R	Broader criteria were recognized to include high-functioning individuals who showed no symptoms in their early life. Whilst DSM-III-R criteria extension allows a broad age range – from infancy to early childhood (after 36 months) - to be diagnosed, DSM-III excludes early childhood diagnoses, and it was only included in Infantile Autism (Murphy et al., 2016).
1994	DSM-IV	It contained specific criteria for Asperger syndrome, which includes the impairment in social communication, however, it did not include the difficulty in language and speech (Hohenshil, 1992).
2013	DSM-5	It replaced the old manual (DSM-IV), published by the American Psychiatric Association. DSM-IV explained autism spectrum disorder as different subdivisions: autistic disorder, childhood disintegrative disorder, and Asperger disorder. These terms replaced the joint term ASD. ASD diagnostic criteria have been further updated in DSM-5 to two-domain ASD symptom models based on the severity of social communication impairments, and restricted and repetitive patterns of behaviors (Huerta et al., 2012).

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Epidemiology of ASD

Earlier epidemiological studies reported in the 1960s and 1970s have shown that ASD incidence rapidly increased from 2 to 4 autistic children per 1,000 in Europe and the United States (Evans, 2013; Ciernia and LaSalle, 2016). Between 2000 and 2002, the Autism and Developmental Disabilities Monitoring (ADDM) network were established to define the worldwide prevalence of ASD and reported the prevalence rate of ASD among children (in the range of 8 years old) approximately about 6.6 per 1000 (Rice et al., 2007). However, between 2005-2009, the highest international prevalence rate of 2.64% was reported in South Korea for 7 to 12 years-old children (Kim et al., 2011). Also, ASD prevalence was estimated to be exceeded by 1% in Finland and Sweden in 2011, and 1.5% in Denmark (Murphy et al., 2016). To date, there are few studies on the epidemiology, prevalence, and risk of ASD in the Gulf Cooperation Council (GCC) countries. The incidence rate of ASD was reported as 1.4% per 10,000 among 0-14 years old children in Oman, in 2011 (Al-Farsi et al., 2011), 29 per 10,000 in UAE, in 2007 (Eapen et al., 2007), and 4.3 per 10,000 in Bahrain, in 2013 (AM and MM, 2013). Previous studies conducted on Swedish children revealed an elevated risk of autism among children who have older siblings with ASD (Elsabbagh et al., 2012; Sandin et al., 2014). The recurrence risk in siblings of children affected with ASD was estimated to be between 33 to 50% and about 20% in cases with a family history of autism, which is greater than the prevalence rate in the general populations (Elsabbagh et al., 2012; Sandin et al., 2014).

However, the accuracy of the prevalence rate reported for these countries was limited due to poor understanding and recognition of all cases of autism which inadvertently affected the diagnosis of all cases of autism, especially mild cases among children. The lack of awareness among autistic children's families and the health care provider may be the major reason for the decrease in the reported incidence of autism in the GCC countries. This view was further supported by the recent incidence trend estimated by the 2017 World Health Organization (WHO) where it was reported that 1 in 160 children is affected by autism (Sahana et al., 2018).

Furthermore, autism occurs more commonly in males than females, based on the prevalence ratio of about 4 males for every 1 female diagnosed with ASD (Wiśniowiecka-Kowalnik and Nowakowska, 2019; Tremblay and Jiang, 2019). Some studies have explained the gender bias of causatives in ASD and their prevalence, in which, the protective nature of females, which is of potential in protection from *de-novo* ASD risk variants that reduce the incidence of ASD; however, the reason for male dominance is not fully understood (Dong et al., 2014). Besides, several studies have also revealed that female requirement is more environmental. However, genetic risk factors play a crucial role in developing autism in females when compared to males (Jacquemont et al., 2014). Moreover, it was found that the gender ratio may be changed by hormonal factors which have the main role in the etiology of ASD. Nonetheless, male stereotyped behaviors were more frequent than females probably due to gender hormones such as testosterone, which modify the phenotypic presentation of ASD (Werling and Geschwind, 2013).

Diagnostic Criteria and Treatment Options for ASD

Previous studies have established the characteristic features for the diagnosis of ASD symptoms, which begin to manifest in early childhood (around two years old) (Martinez et al., 2018). Given the absence of diagnostic biomarkers for autism, like many other

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psychiatric disorders, the clinical diagnoses of ASD rely on the manifestation of the symptoms according to DSM-5. The symptoms include a continuous defect in social communication, restricted interests, and repetitive behavior (Grove et al., 2019). These features begin in early childhood and cause functional defects (Al-Zaalah et al., 2015). Different assessment tools can be used to diagnose ASD; including Autism Diagnostic Interview-Revised (ADIR), Autism Diagnostic Observation Schedule (ADOS), and Childhood Autism Spectrum Test (CAST) (Williams et al., 2008; Falkmer et al., 2013).

Although there are currently no medications to treat the core symptoms of autism (Lenroot and Yeung, 2013), there are limited medicines approved by the US Food and Drug Administration (FDA) to treat autism-related symptoms. Prominent examples of drugs approved include aripiprazole, and risperidone as a remedy for aggression and self-injury (Lo and Lai, 2020). Risperidone was shown to reduce symptoms of hyperactivity and stereotypic behavior in 5 to 17 years old children with autism (McCracken et al., 2002). The combination of early recognition and diagnosis as apparently influences a more positive outcome. This can be incorporated into the guidelines to ensure better treatment and diagnosis strategies and the reduced widespread of ASD.

Environmental Risk Factors

The increased interest in research into the prevalence of ASD has greatly contributed to the elucidation of major factors that contribute to its development, including prenatal, perinatal, and postnatal risk factors (Loke et al., 2015). Their literature review (Grabrucker, 2013) highlighted the role of environmental risk factors in autism (*Figure 1*). Prenatal viral infections of influenza and rubella have been shown to increase the risk of ASD development as they have a direct effect on fetal brain development and the immune system dysfunction of both the mother and the fetus (Pardo et al., 2005). These risks are further increased by many factors such as the viral load and strain of the virus, the maternal immune system, the stage of the fetus development, and the presence of pathogenic factors that are associated with ASD (Fox et al., 2012; Grabrucker, 2013). In addition, some medications taken during pregnancy such as histone deacetylase inhibitors (e.g., valproic acid) could alter fetal brain development. These medications have been shown to significantly raise the risk of ASD in children (Christensen et al., 2013).

Moreover, zinc deficiency has been considered a risk factor for ASD due to its critical role in brain development, cell division, and differentiation (Lo and Lai, 2020). Studies of Zinc disruption in infants showed a correlation between Zinc deficiency and neurodevelopmental disorder and reported cases of ASD and attention-deficient hyperactivity disorder (ADHD) (Yasuda et al., 2011; Hawari et al., 2020). Several studies have also found a relationship between maternal folic acid supplementation and reduced risk of having children with autism. Maternal metabolic diseases (such as diabetes), obesity (Krakowiak et al., 2012), prenatal alcohol consumption, and maternal smoking during pregnancy were linked to increased risk of ASD and/or the produced adverse effects in neuropsychiatric conditions and language performance in children with autism (Miles et al., 2003). The findings from these observational studies were further supported by epidemiologic data analyses of alcoholic families and their children. In the studies, 80% of autism in children was linked to the high incidence of alcoholism. Moreover, another study demonstrated the correlation between prenatal alcohol exposure and increased risk of autism (Miles et al., 2003). Furthermore, other studies have linked ASD with other factors such as parental age, environmental agents such as toxins, and certain

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postnatal factors like exposure to certain therapeutic drugs that are linked to increased susceptibility to the development of autism (Lo and Lai, 2020). In the Middle East, a report on the Northern and Eastern regions of Saudi Arabia found that consanguineous marriage, inadequate income, medicine intake during pregnancy, maternal age during pregnancy, and vitamin D deficiency could be risk factors for developing ASD (Oommen et al., 2018).

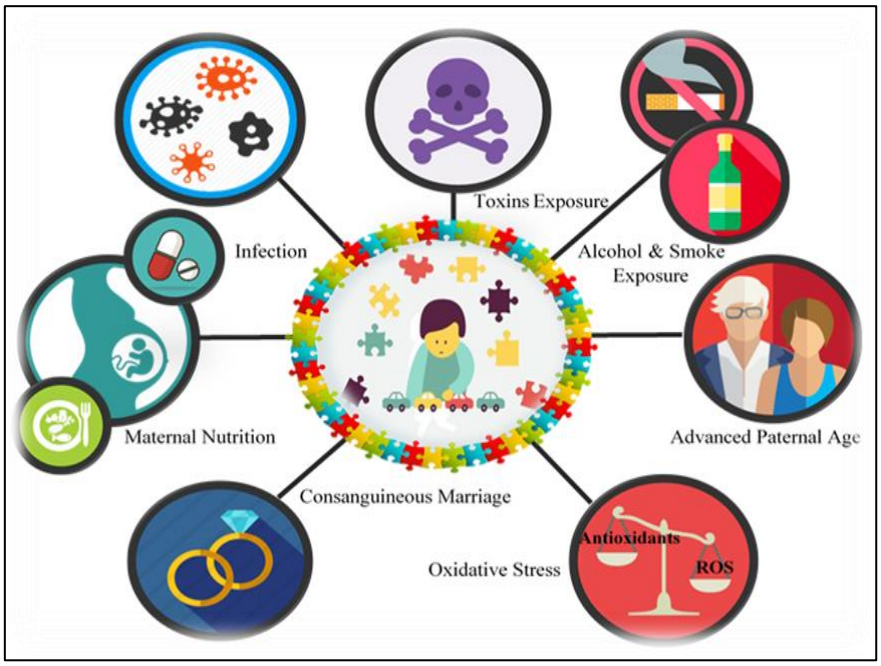

Figure 1. *An overview of environmental factors associated with ASD. Adapted from Grabrucker (2013)*

Genetics of ASD

The prevalence of ASD has gained prominence within the last two decades, yet the molecular basis of ASD is inadequately understood. Consequently, the underlying genetic causes of ASD are a subject of considerable importance to the scientific community. The first indication of a relationship between ASD and genetics was observed in an epidemiological study of autistic twins, during which the rate of ASD prevalence among the monozygotic twin's population was 60% greater than among heterozygous twins (El-Fishawy, 2010). Some studies have also demonstrated that the phenotypic variation of autistic individuals can be related to genetic variation. These genetic variants are recurrent but limited to a small number of patients (Siu and Weksberg, 2017; Tremblay and Jiang, 2019). Recently. chromosomal aberrations were reported as one of the genetic risk factors that result in ASD-related syndrome (Siu and Weksberg, 2017) and many neurological birth syndromes associated with ASD, including Angelman syndrome which is one of the main copy number variants (CNVs) maternal chromosome that has been implicated in ASD (Goldani et al., 2014; Willsey and State, 2015). The most prominent genetic syndrome that has shown relative features of ASD in 30-50% of cases based on the childhood autism rating scale is fragile X syndrome (Demark et al., 2003). More recent studies have confirmed that monogenic diseases such as Rett syndrome, PTEN

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hamartoma tumor, and tubular sclerosis complex which are caused by one gene can be associated with ASD (Chen and Pang, 2021). However, the percentages of potential causes of ASD are represented in *Figure 2* (Tremblay and Jiang, 2019).

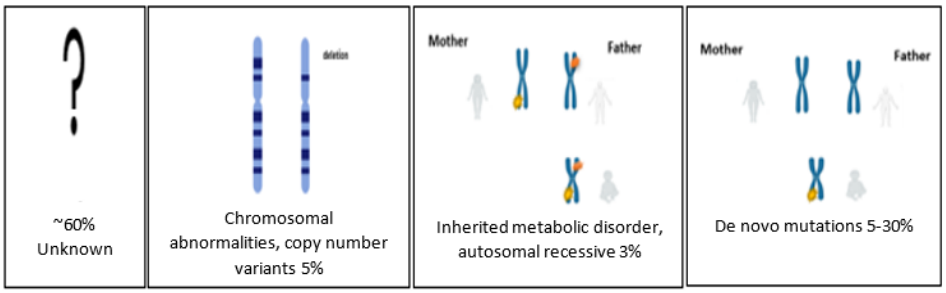

Figure 2. *The percentages of potential causes of ASD. Adapted from Tremblay and Jiang (2019)*

Investigative studies of gene expression in inflammatory, immune, neurodevelopmental, synaptic, and steroid pathways, suggest a direct effect of genetic changes on brain development and increased risk of having ASD (Loke et al., 2015). For instance, studies conducted on inflammatory and immune pathways have shown an association between the human leukocyte antigen (HLA) of autistic children's parents to the development of autism in their children. ASD is associated with other genes involved in the immune system, specifically MET proto-oncogene tyrosine kinase (Gesundheit et al., 2013). In addition, mutation of a single copy of SHANK3 on chromosome 22q1 has been associated with an impairment in language and social communication, which are part of ASD neurobehavioral symptoms (Durand et al., 2007). These findings suggest the involvement of many genes such as *ADNP*, *ANK2*, *ARID1B*, *CHD8*, *POGZ*, and *PTEN* in ASD etiology (Loke et al., 2015). Despite the availability of such genetic data, the contribution of the genetic influence in ASD is considered complicated and still not well understood. However, the genetic heterogenicity of ASD and the epigenetic mechanism may help to further understand the etiology of ASD, and in combination with other genetic tools, may lead the investigators to elucidate the molecular basis of ASD.

The Role of Epigenetics in ASD

The term "epigenetics" was first defined by Conrad Waddington in 1942 as "*the branch of biology that studies the causal interactions between genes and their products which bring the phenotype into being*" (Deans and Maggert, 2015). This term was derived from the Greek word "epigenesis" which means "above the genetics". In general, it was used to characterize all developmental processes that passed through generations from embryogenesis until cell differentiation of a developed organism (Tronick and Hunter, 2016). The epigenetic mechanism works by adding specific molecules onto specific sites in the DNA without changing the DNA sequence, thus allowing molecules to regulate gene expression by turning it on or off (Zhu et al., 2020). Factors found to be influencing epigenetic mechanisms have been explored in several studies (Deans and Maggert, 2015; Homs et al., 2016). As the genetic initiation mechanism depends on the creation of specific proteins, so the genetic bases are important because any genetic variant can influence the gene product that contributes to the regulation of the epigenetic mechanism (Zoghbi and Beaudet, 2016).

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Moreover, few studies have focused particularly on understanding the impact of environment and individual lifestyle on the epigenetic change that influences gene expression (*Figure 3*) (Jirtle and Skinner, 2007). Results from these earlier studies demonstrated a strong and consistent association between ASD and other factors like epigenetic, environmental, and genetic, and correlated with the interaction between the environment and the genes (Loke et al., 2015). Investigators have further attempted to evaluate the impact of epigenetic machinery on major psychosis pathways, normally involved in neuronal functions, and synaptic activities, which are mostly implicated in neurodevelopmental disorders (Bell and Spector, 2011). Additionally, it has been noted that epigenetic factors could play an important role in diabetes, obesity, cancer, heart disease, and the aging process (Mentch and Locasale, 2016). Consequently, in the last decade, there has been a growing recognition of the vital links between the epigenetic mechanism and the neurodevelopmental disorder particularly Huntington's (HD), Parkinson's (PD), and Alzheimer's (AD) diseases (Lardenoije et al., 2015), and the role of epigenetic dysregulation in brain development as an important cause of ASD (Bale, 2015; Forsberg et al., 2018).

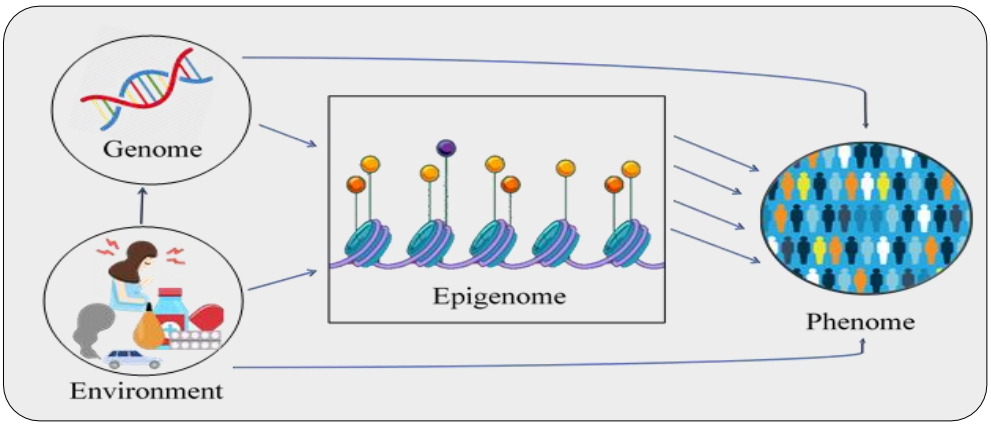

Figure 3. *Epigenomic role in the phenotype traits (phenome) of ASD through environmental factors that altered the gene expression without altering genotype. Adapted from Kanherkar (2014)*

Epigenetic Mechanisms

Epigenetics is identified as a major contributing factor to the hereditary information required for the development of living cells, which plays an important role in controlling DNA replication, transcription and finally gene expression both under normal as well as disease conditions (Schiele and Domschke, 2018). Epigenetic modifications functionally modulate gene expression and chromatin structure without a change in the nucleotide sequences (Schiele and Domschke, 2018). The notable epigenetic mechanism that regulates gene expression at different levels includes DNA methylation, histone modification, chromatin remodeling, and non-coding RNA (Tremblay and Jiang, 2019).

Histone Modification

Recently, Park et al. (2020) stated that histone tails possess post-translational modification processes, which are considered epigenetic regulation processes to control the accessibility of the transcription factors and other regulators to the chromatin to

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repress or activate the transcription process, chromatin compaction, and other processes. Additional investigations in this research area showed that the modification process of histone includes methylation, acetylation, phosphorylation, ribosylation, succinylation, malonylation, and biotinylation; each modification leading to different effects (Gulati et al., 2020). In particular, histone methylation machinery that influences brain function and development has been explored in several studies (Siniscalco et al., 2013). For instance, methylation on lysine of H3 has been associated with the risk of ASD (Siniscalco et al., 2013). Methylation of this histone at position 4 or 9 of this amino acid turns chromatin inactive (*Figure 4*), while demethylation supports activation of chromatin in addition to other modifications in further amino acids, like serine at position 10 and the third lysine at position 14 (Noma et al., 2001) (described in *Figure 5*).

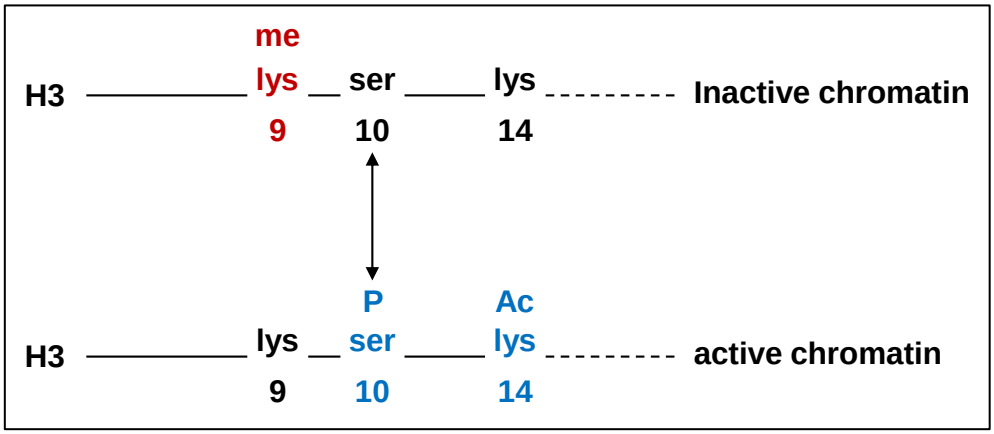

Figure 4. *Chromatin inactivation due to methylation (me) of H3 at position 9 in the amino terminus. Demethylation turns chromatin to be actively accompanied by the occurrence of phosphorylation (P) of serine at position 10 and acetylation (Ac) of another lysine residue at position 14. This figure was created by the author*

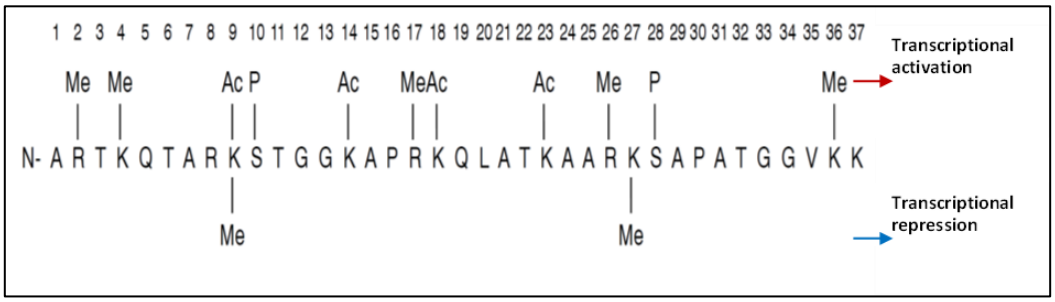

Figure 5. *Structure of 37 amino acids at the N-terminus of H3 referring to active and inactive chromatin due to the type of modification in the histone. Adapted from Noma et al. (2001)*

Also, many supportive studies found that mutation of genes that encode a specific type of histone controls the expression of other genes that play a critical role in cognitive dysfunction and ASD (Siniscalco et al., 2013; Qin et al., 2018). For instance, H1 linker histones are known to have a major role in chromatin structure stability and in controlling gene expression via modifications at the N- and C-terminal tails (Lim et al., 2016). However, a recent study identified a deletion mutation in histone cluster 1 H1 family

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member that is associated with brain dysfunction; the evidence was observed in a patient with ASD and those who are intellectually disabled. This finding supports the role of H1 linker histones in brain development and any deleterious epigenetic modification would adversely result in autism and intellectual disability features (Duffney et al., 2018). Furthermore, a mutation in *SHANK3* gene, which has an impact on synapse function in the brain, was identified as an important epigenetic risk factor for ASD. *SHANK3* gene deficiency is an underlying contributory factor to social performance deficits in autistic patients.

Interestingly, in a follow-up study at the University of Buffalo by Qin et al. (2018), they found that romidepsin, a drug used in cancer treatment, provides a possible cure for autism-like social deficits and reverse the deficiency of *SHANK3* through histone deacetylase 2 (HDAC2) upregulation. HDAC2 is responsible for more than 200 gene represses including *SHANK3* gene. Thus, romidepsin offers a potentially effective therapeutic strategy for activating *SHANK3* gene function and expression, which could ultimately lead to behavioral changes for ASD patients bearing *SHANK3* mutations.

MicroRNA (miRNA)

MicroRNA (miRNA) is a class of RNA, first discovered in nematodes in (1993) (Lee et al., 1993; Hammond, 2015), that is responsible for epigenetic mechanisms. Further studies found that 70% of miRNAs are expressed in the central nervous system (CNS), where it has a major role in CNS development. miRNAs are also involved in other functions of various regions in the brain and have additional roles in neuronal maturation and plasticity (Liu and Xu, 2011; Adlakha and Saini, 2014). It is now well-established that several types of miRNAs play a significant role in dendritic spines because of their abnormal density associated with the development of different neurodevelopmental disorders, including schizophrenia and ASD. This highlights the importance of miRNthe As and the identification of their defect as a leading causative factor of these deleterious disorders (Tonacci et al., 2019). Moreover, studies have revealed the role of miRNAs upregulation in epigenetic modification by targeting the expression of several genes including oxytocin receptor (*OXTR*), which is overexpressed in the brain of autistic patients resulting in a difference in OXTR product levels (Mor et al., 2015). Similarly, Kichukova et al. (2017) found dysregulation of miRNAs in the serum of patients with ASD who are between 3 to 11 years old. These findings revealed the involvement of miRNAs in neurological functions and signaling pathways that are implicated in ASD. However, the precise role of different families of these miRNAs and their role in ASD are not well characterized as they are poorly understood. On the other hand, miRNAs are nowadays become potential biomarkers and are assessed as interesting novel therapeutics and clinical applications for human diseases, thru modulation of the expression of specific miRNAs in vitro as well as in vivo for successful treatment of many diseases in the future. For instance, downregulation of *OXTR* expression is suggested as a possible treatment that may improve social behaviors associated with ASD behaviors phenotypes (Mor et al., 2015). Additionally, data from several studies suggest that the suppression of oncogenic miRNAs, along with stimulation of the expression of tumor inhibitor miRNAs, could offer new therapeutic strategies for reducing carcinoma development (Ray, 2019). Some studies utilized miRNA microarray analysis to profile miRNA expression. And several miRNAs have been suggested as potential biomarkers for ASD children; two up-regulated and sixteen down-regulated miRNAs were among the 18 that significantly changed between the ASD and control groups. ASD was particularly dysregulated in the

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following: miR-6126, miR-3156-5p, miR-1227-5p, miR-6780a-5p, and miR-328-3p. ASD-related genes were also significantly enriched in miR-6126 targets, like *ANK3*, *CACNA2D1*, *NRXN3*, and *PCDH9*. Together, these results shed new light on the possibility of a link between ASD social deficits and miR-6126 (Nakata, 2019).

DNA Methylation

DNA methylation is a frequently reported modification process at the DNA level. It usually occurs on the CpG dinucleotide, which involves binding of the methyl group to a specific site of DNA at carbon 5` of cytosine that results in regulating gene expression (Smith and Meissner, 2013; Kader et al., 2018) (*Figure 6*). This modified nucleotide was shown to participate in the recognition sequence (C↓CGG) of the restriction enzyme HpaII, which loses its ability to cut at this sequence in the presence of methylated C (*Figure 7*).

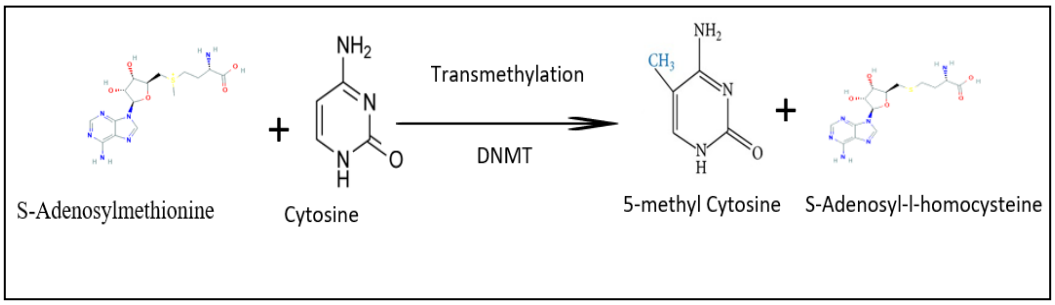

Figure 6. *DNA methylation pathway. Adapted from Li and Zhang (2014)*

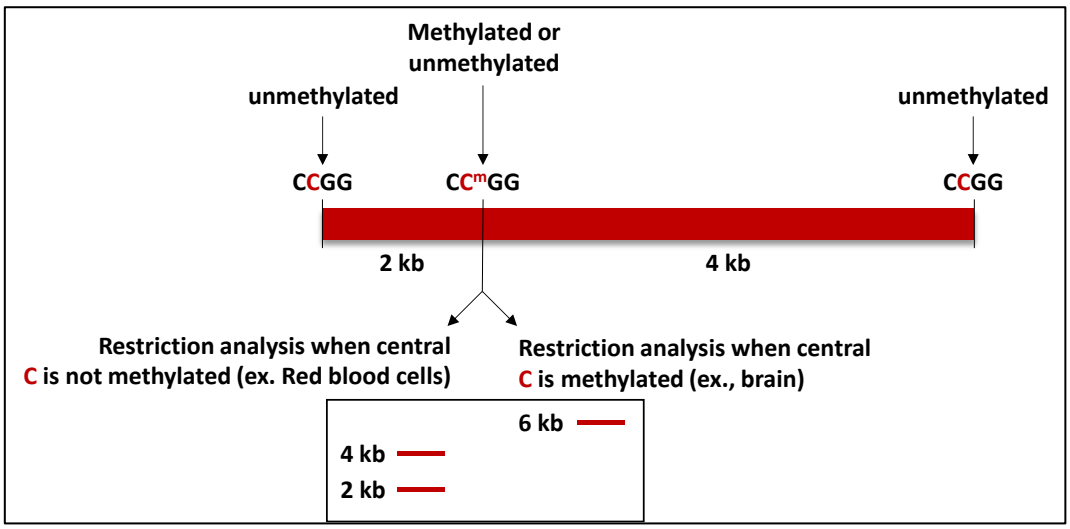

Figure 7. *Restriction pattern when a C nucleotide in a DNA sequence (6 kb) harboring the "CCGG" recognition site for HpaII restriction endonuclease is methylated (CC^{m}GG) in the brain. This figure was created by the author*

It was reported that aberrant DNA methylation can occur in various regions of the brain in the prenatal and early postnatal life of autistic people. Although many experimental studies in this area apply a brain bank that is associated with ASD, however,

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a brain bank is rare and difficult to obtain, especially from live subjects and young children (Loke et al., 2015). Consequently, many investigations suggested the use of peripheral tissues for analyzing DNA methylation and related gene expression in neurodevelopmental disorders, due to the presence of similar levels of methylation of specific genes in both the brain region and the blood in such a neurodevelopmental disorder (Kimura et al., 2019). However, others have suggested the association between DNA methylation and ASD is largely based on genetic mutation in genes that play a known role in DNA methylation, the effect of aberrant DNA methylation on specifically targeted genes, and the genome-wide DNA methylation changes (Tremblay and Jiang, 2019).

Studies by groups of Ellis et al. (2017) and Ladd-Acosta et al. (2014), involving the use of genome-scale screens in cerebral tissue, showed significant differences in DNA methylation at certain CpG sites in ASD. To date, several studies have investigated differential methylation patterns of many candidate genes contributing to ASD. For instance, a study demonstrated that the methylated promoter of *MECP2* is one of the epigenetic regulators that results in a decrease in MECP2 expression (Nagarajan et al., 2008) and is often found in autistic male samples (Mbadiwe and Millis, 2013). Moreover, results from various studies have demonstrated a strong and consistent association between hypomethylation of many other important genes such as *RORA, ERMN, DBT,* and ASD. The results of these studies further showed a difference in the peripheral blood of autistic people (Homs et al., 2016). Additionally, many proteins were identified as potential biomarkers that could be the cause of epigenetic dysregulation. For example, hypomethylated proline-rich transmembrane protein (PRRT1) was detected in the temporal cortex and cerebellum in autistic brains. Also, some studies have revealed a significant aberrant methylation level in zinc finger protein 52 (ZFP52) and Olfactory receptor family 2 subfamily L member 13 (OR2L13) in ASD patients (Forsberg et al., 2018; Andari et al., 2020).

Therefore, understanding DNA methylation and other epigenetic mechanisms in ASD can provide insights into other neuropsychiatric disorders, help elucidate its causal role in these disorders as well as address the need for diagnostic and therapeutic effective interventions.

Conclusion

In summary, ASD prevalence is increasing worldwide, and its incidence is predominantly associated with neurodevelopmental disorders. However, many aspects of autism conditions are relatively either unknown or poorly understood. These lacunae, as well as recent technological advancements in many disciplines, opened many new opportunities - especially on the molecular fronts - to unravel the etiological basis of ASD and to examine the role of genetics and epigenetics in ASD. However, further research studies are required to accurately investigate the impacts of these factors on autistic children. Whilst many recent studies have focused on the role of epigenetic dysregulation in brain development as an important cause of ASD, however, the understanding of the function of many genes encoding the proteins implicated in brain development and ASD was proven to be beneficial in clarifying the etiology of autism. Therefore, further investigations are still required to elucidate the epigenetic effects on the phenotype and alteration in gene expression amongst autistic children, which in turn would improve ASD diagnosis and therapy.

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