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mRNA in the development of autism spectrum disorder

Xema Ariany Anguiano-Hernández, Juan Antonio López-Valdez, Diego Fernando Fernández-Ortiz, Mariana Ceniceros-Medrano, María Fernanda Hernández-Morales, Gloria Daniela Munguia-Reyes * and Brissia Lazalde

Faculty of Medicine and Nutrition, D*epartment of Genetics, Universidad Juárez del Estado de Durango.*

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social interaction, communication, and restricted and repetitive behavior patterns. This disorder can be detected from an early age through warning signs such as lack of response to social stimuli, language difficulties and limited behaviors. In addition, it has a high comorbidity with other disorders, such as sleep problems, gastrointestinal disturbances, and epilepsy, which complicate its diagnosis and treatment [1,2].

Analysing it from a genetic perspective, it has been identified that ASD has an approximate heritability of 80%, involving more than 1000 genes. These include CHD8 and FMR1, which play fundamental roles in neurogenesis, cognitive development, and synaptic plasticity. Mutations in these genes affect the balance between excitatory and inhibitory neurons, resulting in synaptic alterations that contribute to the development of ASD [3-5].

At the epigenetic level, DNA methylation regulates the expression of these genes. This process involves the addition of methyl groups to specific regions of the DNA, affecting its transcriptional activity. Alterations in this mechanism can contribute to deficits in neuronal plasticity, memory and learning processes, all of which are essential for normal brain development [6,7].

MicroRNAs (miRNAs) also play a crucial role in the regulation of post-transcriptional gene expression. These molecules modulate the translation of essential synaptic proteins and are involved in neuronal plasticity. Its dysregulation could amplify the effects of mutations in genes such as CHD8 and FMR1, aggravating the clinical manifestations of ASD [8,9].

Therefore, ASD results from a complex interaction between genetic and epigenetic factors. The CHD8 and FMR1 genes, along with processes such as DNA methylation and microRNA regulation, are key pieces to understanding their etiology. The integration of this knowledge may open up new opportunities to develop targeted therapies that improve patients' prognosis [3,10]

Keywords: Autism Spectrum Disorder; Genetics; Epigenetics; microRNA; DNA methylation; CHD8; FMR1; Neurodevelopment

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that affects multiple aspects of human behavior. Its prevalence has increased in recent decades, and it is currently estimated that 1 in 54 children is diagnosed with ASD [1,2]. This disorder is primarily characterized by persistent impairments in social interaction, difficulties in verbal and nonverbal communication, and restricted and repetitive behavior patterns [1,3].

* Corresponding author: Gloria D Munguia-Reyes

From a clinical point of view, the first signs of ASD usually manifest in childhood, usually before the age of 3. Among these signs are a lack of response to social stimuli such as smiles or sounds, delayed language development, and indifference to the pronunciation of their name. In addition, children with ASD exhibit unusual play patterns and disproportionate attention to specific objects or limited activities [4,5].

ASD is also frequently associated with a variety of comorbidities, including sleep disturbances, eating difficulties such as extreme selectivity, epilepsy, and gastrointestinal dysfunctions, such as chronic constipation [6,7]. Approximately 30% of children with ASD develop epilepsy, with peaks in incidence in childhood and adolescence. These complications reflect the complexity of the medical and behavioral management of the disorder [6,8].

At the genetic level, it has been documented that ASD has a high heritability, close to 80%, and is related to alterations in multiple genes, highlighting CHD8 and FMR1 [9,10]. These genes are involved in essential processes such as neurogenesis, synaptic balance, and neuronal plasticity. Mutations in CHD8, for example, are associated with macrocephaly and alterations in brain architecture, while alterations in FMR1 are linked to fragile X syndrome, a genetic disorder that also exhibits autistic features [11,12].

From the epigenetic approach, DNA methylation and microRNA regulation are key processes that modulate the expression of these genes. Methylation regulates gene transcription and is critical for synaptic plasticity and neuronal development. MicroRNAs, on the other hand, influence the translation of proteins essential for cognitive function, such as those involved in memory and learning [13,14].

Therefore, we can identify that ASD is a multifactorial disorder that results from the interaction between genetic, epigenetic and environmental factors. Understanding these mechanisms not only allows for earlier diagnosis, but also opens the door to more effective therapeutic interventions [13,14]

2. Development

2.1. Epigenetic regulation and the role of DNA methylation

Epigenetic regulation is a central mechanism in neuronal development and in the manifestation of Autism Spectrum Disorder (ASD). One of the most studied epigenetic processes is DNA methylation, which involves the addition of methyl groups to cytosine bases in regions rich in CpG dinucleotides. This process is critical for gene silencing and transcription regulation [1,2].

In the context of ASD, DNA methylation has been observed to play a critical role in the modulation of neurodevelopmental-related genes, such as CHD8 and FMR1. For example, aberrant methylation can alter gene expression in key brain regions, such as the prefrontal cortex and hippocampus, impacting functions such as memory, learning, and neuronal plasticity [3,4].

In addition, methylation is essential during the early stages of embryonic development, where it regulates processes such as neurogenesis and cell differentiation. Alterations in this mechanism can lead to defects in synaptic formation and an imbalance between excitatory and inhibitory neurons, which is characteristic in individuals with ASD [5,6].

The reversibility of methylation by enzymes such as TET1, TET2 and TET3 is also relevant. These enzymes are involved in active demethylation, a process that facilitates synaptic plasticity and neuronal adaptability. Alterations in these enzymes have been linked to susceptibility to ASD and other neurodevelopmental disorders [7,8].

2.2. MicroRNAs: Post-transcriptional regulators

MicroRNAs (miRNAs) are non-coding RNA molecules that regulate gene expression at the post-transcriptional level, primarily by inhibiting the translation or degradation of messenger RNAs (mRNAs). In ASD, miRNAs have emerged as key regulators affecting the expression of genes related to synaptic plasticity and neuronal development [9,10].

For example, miRNAs have been shown to directly regulate the expression of CHD8, a gene essential for cortical development. Alterations in miRNAs that interact with CHD8 may exacerbate synaptic dysfunctions and contribute to phenotypic features of ASD, such as macrocephaly and cognitive deficits [11,12].

Similarly, miRNAs also modulate the translation of FMR1, the gene linked to fragile X syndrome. This syndrome, which shares characteristics with ASD, includes deficits in memory, learning, and social behavior. Studies have shown that

dysfunction of miRNAs that regulate FMR1 directly affects the translation of proteins necessary for neuronal plasticity [13,14].

2.3. Variation in copy number

The main genetic etiology of ASD is changes in gene expression that participate in neuronal development.

These changes can be caused by CNV (Copy Number Variation), which is a phenomenon in which parts of the genome are repeated from individual to individual by deletion, duplication, translocation, and inversion. Below is a Table [7] where some chromosomal loci that are associated with ASD are mentioned.

Table 1 Chromosomal locus associated with ASD and its corresponding affectations [7]

Locus	Function	Genes	Variation
3q21.1-3q21.2	Abnormalities in neuronal maturation and long-term potentiation in the brain, macrocephaly, intellectual disability and facial dysmorphism.	RANDOM	Duplication
5p14.1	Neuronal molecules of cell adhesion.	Cadherin 10 (CDH10), Cadherin 9 (CDH9)	Deletion
6q14.3	Learning disabilities, intellectual disability, behavioral problems.	ZNF292 (zinc finger protein 292)	Deletion
12q24.23	Neuronal cells and poorly regulated neuronal "microexons" in the brain.	nSR100/SRRM4	-
16p11.2	Decreased proliferation of neuronal progenitors, increased cell death during brain development, microcephaly.	KCTD13	Deletion, Duplication
16q24.3	Cognitive impairment, brain abnormality.	ANKRD11, ZNF778	Microsuppression
17q12	Macrocephaly, neurocognitive deterioration.	HNF1B	Deletion
20q13.12	Glutamate releases at the synapse.	RIMS4	-
22q11.2	Physical, behavioral, social communication, cognitive impairments.	-	Deletion
22q13	Cognitive deficits, autistic behavioral symptoms, language and social communication problems.	SHANK3	Deletion
Xq27.3	Synaptic function in the brain.	FMR1	-

2.4. CHD8: A key gene in ASD

The CHD8 gene encodes a protein that regulates chromatin structure, allowing for precise control of gene expression during brain development. Mutations in CHD8 are closely associated with ASD and have been identified as one of the most common genetic causes of the disorder [12,13].

Individuals with CHD8 mutations typically present with macrocephaly, developmental delays, and cognitive deficits. At the molecular level, these mutations affect the regulation of the balance between excitatory and inhibitory neurons, which alters the synaptic circuit in areas of the brain responsible for communication and social behavior [12,14].

Table 2 Chromosomal locus associated with ASD and its corresponding affectations [7]

Description	Detail
Title	Child with genetic alteration in the CHD8 gene
Genetic event	The genetic change occurs in the egg or sperm after fertilization.
Result	A child with a de novo genetic change in a gene associated with autism (CHD8 gene).
Family relationship	- The genetic change is sporadic and not inherited from the parents.

2.5. FMR1: Connection to fragile X syndrome

The FMR1 gene is associated with the production of the FMRP protein, which regulates the local translation of mRNAs into neuronal synapses. Mutations in FMR1, such as CGG triplet expansions, cause fragile X syndrome, which shares clinical features with ASD, including language difficulties, repetitive behaviors, and deficits in social interaction [12,13].

The absence of FMRP alters synaptic function, leading to an imbalance in brain connectivity. This explains why some individuals are able to perform specific cognitive tasks while having significant difficulties in other areas. In addition, recent studies suggest that alterations in FMR1 are also mediated by epigenetic processes such as methylation and miRNA regulation, underscoring the interaction between genetic and epigenetic factors in ASD [11,12].

2.5.1. Relationship between genetics and environment

ASD is a multifactorial disorder that combines genetic and environmental influences. Factors such as prenatal exposure to infections, stress, or toxins can interact with genetic predispositions, amplifying the risk of developing the disorder. For example, exposure to valproic acid during pregnancy has been associated with an increase in the incidence of ASD, likely through epigenetic mechanisms such as altered DNA methylation [13,14].

In addition, environmental factors can also modulate miRNA expression, impacting genes such as CHD8 and FMR1. This suggests that early interventions aimed at mitigating these environmental influences could have a positive impact on patient outcomes [11,12].

3. Conclusion

As we have reviewed up to this point, autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that combines genetic, epigenetic, and environmental factors in its etiology. The characteristic difficulties of ASD, such as problems in social interaction, language, and repetitive behaviors, are profoundly influenced by alterations in molecular processes essential for brain development.

From the genetic approach, the CHD8 and FMR1 genes have been identified as key pieces. CHD8 regulates processes such as neurogenesis and the balance between excitatory and inhibitory neurons, which is critical for the proper development of neural circuits. Mutations in this gene are associated with specific phenotypic features of ASD, such as macrocephaly, gastrointestinal problems, and cognitive deficits. On the other hand, FMR1, related to fragile X syndrome, regulates synaptic plasticity and neuronal function. Mutations in this gene can lead to a synaptic imbalance, resulting in learning and behavioral deficits that are also seen in ASD.

Regarding the role of epigenetic mechanisms, DNA methylation and regulation by microRNAs (miRNAs) have proven to be fundamental. DNA methylation regulates the expression of key genes during neuronal development and can be altered by environmental factors, such as maternal infections or exposure to toxins during pregnancy. This reinforces the idea that environmental factors interact with genetic predispositions, increasing the risk of developing ASD [7,8]. miRNAs, on the other hand, regulate post-transcriptional gene expression and affect the translation of proteins essential for neuronal function. Dysregulation of miRNAs that interact with genes such as CHD8 and FMR1 exacerbates synaptic alterations and contributes to ASD symptoms.

In addition, ASD has a high prevalence of comorbidities, such as epilepsy, sleep disorders and gastrointestinal problems. These conditions, along with the main features of the disorder, complicate clinical management and underscore the importance of adopting comprehensive, multidisciplinary approaches to treatment.

Advances in research have shown that ASD cannot be understood solely from a genetic or environmental perspective, but as a result of the interaction between the two. This has led to the exploration of new therapeutic strategies based on the regulation of gene expression and the correction of epigenetic alterations. For example, approaches aimed at modulating the activity of specific miRNAs or reversing abnormal methylation patterns could open avenues for more personalized and effective interventions.

In conclusion, ASD is a multifaceted disorder whose study requires integrating knowledge of genetics, epigenetics and environmental biology. Delving into these mechanisms not only facilitates early diagnosis, but it also opens the door to different treatments that could significantly improve the quality of life of affected people and their families.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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