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Review Article

The Anomalous DNA Methylation Patterns in Autism Spectrum Disorder (ASD), Prader Willi Syndrome, Fragile X Syndrome, and Angelman's Syndrome

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Received: November 08, 2021; **Published:** December 30, 2021

Abstract

DNA methylation is a usual epigenetic signaling tool used to control gene expression in eukaryotic cells. Cells use this tool to lock genes and disarrange them. DNA methylation has been observed to play an essential role in cell differentiation, the origin, growth and development of an embryo and last but not the least gene expression. Depending on the cell type DNA methylation near the specific promoters differs substantially. In an interestingly coordinated process, proteins that bind to methylated DNA also form complexes with the proteins involved in deacetylation of histones. Therefore, when DNA is methylated, nearby histones are deacetylated, leading to magnified inhibitory effects on transcription. Likewise, demethylated DNA does not attract deacetylating enzymes to the histones, permitting them to stay acetylated and more ambulatory, thus promoting transcription. Errors in this DNA methylation process which plays a critical role in cell differentiation and gene expression can bring about catastrophic outcomes, including various diseases such as autism spectrum disorder (ASD), Fragile X syndrome, Praderwilli syndrome and engelmann's syndrome.

Keywords: *Epigenetic; DNA Methylation; Autism Spectrum Disorder (ASD); Prader Willi Syndrome; DNA Methylated Regions (DMRs); Silver-russell Syndrome (SRS); Fragile X Syndrome; Camurati Engelmann's Syndrome*

Introduction

Cytosine DNA methylation is a heritable epigenetic modification. It involves cellular functions including tissue-specific gene expression, cell differentiation, development, and reprogramming Most DNA methylation studies have been performed on a gene-by-gene basis.

Recent estimates of the prevalence of ASD are one in 59 individuals in the United States.

Fragile X syndrome (FXS; OMIM #300624) is the most common monogenic cause of inherited intellectual disability (ID).

In most FXS patients, the FMR1 gene is epigenetically inactivated which binds mRNAs, mainly in the brain. Altered DNA methylation, play a role in autism in the association of Prader Willi syndrome, an imprinting disorder with autistic features. Autism spectrum disorder (ASD) is a complex neurodevelopment disorder characterized by deficits in communication. The prevalence of ASD among 8-year-old US children to be 1 in 68. Autism spectrum disorder (ASD) is a pervasive neurodevelopment disorder characterized by difficulties in social interaction, language development delays, repeated body movements, and markedly deteriorated activities and interests. Inherited mutations in gene ACTL6B lead to Autism. Most commonly, mutations are caused due to duplications in 15q11-q13 and deletions in 2q37. Autism is highly prevalent in individuals with fragile x syndrome. the FMR1 gene can affect the expression of several genes involved in autism development.

History

Epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence, by which a fertilized zygote developed into a mature, complex organism. DNA is the same in all cells of an organism.

It is a type of post-reproduction adjustment that frequently occurs in cytosines of the CpG dinucleotide arrangement with the help of DNA methyltransferases (DNMTs), which transfer a methyl group from S-adenyl methionine to the fifth carbon of a cytosine residue to form 5-methylcytosine (5 mC). In spite of the efforts to clear up their causes, the hidden molecular mechanisms continue puzzling. It is observed that the pathogenesis changes on chromatin and chromatin-modifying enzymes, can grant to a persistent metabolic phenotype. A group of 12 diseases with clinical characteristics, epigenetic patterns have been shown to affect growth, development, and metabolism

Epigenetic machinery of DNA methylation is neurological dysfunction and, in particular, intellectual disability appears to be a common phenotype in patients. Dynamics and reprogramming of DNA methylation a hot spot for mutation accumulation DNA methylation is dynamic epigenetic modification found in most eukaryotic genomes. Understanding the rate of germ line mutation occurrence and the mechanisms that control it, particularly in humans, is of great importance to finding causes of heritable diseases and evidence for evolution ASD is co morbid with other disorders including epilepsy, Rett syndrome, and Fragile X syndrome. The degree of variation in ASD phenotype caused by genetic variation has been estimated at between 40 and 90%.

How do epimutations contribute to the molecular pathogenesis of autism spectrum disorder? Genetic alterations do not explain the etiology of an elevated number of ASD cases. Recent research is now focusing on the role of environmental/epigenetic factors, which by themselves and/or in combination with classical genetic factors, maybe the root cause of a large number of ASDs. What causes abnormal DNA methylation? DNA methylation dynamics is not known clearly. Enzymatic kinetics and metabolic reactions play a role. DNA methylations, such as chromatin modifiers, are known to modulate DNA methylation. The amazing effects of these dynamics are yet to be determined. Several environmental influence DNA methylation in mammals. In mice, supplementation of maternal diet with methyl-donor precursors is capable of increasing the methylation in the agouti locus and altering the coat color in offspring, which provides direct experimental evidence that environmental factors can have lasting effects on DNA methylation of offspring. In humans, in utero exposure to environmental burdens including organic pollutants, tobacco, alcohol, obesity, asthma, and maternal stress and care have been shown to impact DNA methylation of offspring.

Fragile x syndrome

Fragile X syndrome (FXS) is the most common known cause of inherited intellectual disability It is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment.

Incidence:

1 in 3600 to 4000 males 1 in 4000 to 6000 females.

Inheritance

It is an x-linked dominant disorder. Usually, males are more severely affected by this disorder than females. When the mother is a carrier of fragile x chromosome each child has 50% chance of inheritance. Since females have two x chromosomes they are less severely affected.

It is a genetic disorder in which the development of individuals is affected mainly behavior and learning abilities. It can also affect an individual's communication skills, physical appearance, sensitivity to light, noise and other sensory information too. It is the most common cause of inherited intellectual and developmental disability People with fragile x syndrome do not have much noticeable symptoms sometimes, and sometimes can have serious symptoms which might range from simple learning difficulties to cognitive and behavioral problems also. Fragile X syndrome can be caused by mutation in the gene FMR1 which is found on X chromosome. This mutation affects the individual's body on how it makes Fragile X Mental retardation protein (FMRP). Individuals with Fragile X can have intellectual problems and functioning that might affect individual's ability to think reason and learn. Physical signs such as narrow face, large ears and head, joint flexibility, flat feet and forehead prominence. Behavioral, social and also emotional problems can be present along with speech and language impairment.

Autistic spectrum disorder (ASD)

Autism is a complex developmental disability that includes problems with communication and behavior appearing during childhood. It is a multifactorial disorder Caused due to interaction of genetic and environmental factors. Mutations implicated in Autism are spontaneous or de novo mutations which are not inherited.

The onset of autism is usually before age 3 years; in most cases, in the first years of life where developmental problems are evident. The social problems of autism children are severe and present persistently. Some children with autism may have speech which is remarkable for echoed language (echolalia), problems with usage of pronouns, idiosyncratic use of words and sentences, and problems with prosody of speech and maintaining the speech rhythm. Stereotyped behaviors and sometimes movements, unusual responses to the environment are present frequently.

Research studies have revealed specific genetic causes for cases as well as a some candidate genes and chromosomal regions indicated across multiple autism studies, which include chromosomes 2q, 7q, 15q, 17q, 11.ASDs is recognized to be neurodevelopmental disorders, with differences beginning early in childhood. Decreased numbers of Purkinje cells and granule cells in the cerebellum have been described. Children with Asperger's disorder do not come to attention until they join preschool due to preserved language relative to adults. Children with autism and associated conditions often make major developmental gains and improvements in the elementary school years particularly if they receive early interventions. Early identification and intensive treatment can help the child attain good improvement.

Prader-willi syndrome (PWS)

- Prader-Willi Syndrome is a non- inherited genetic disorder that causes obesity and intellectual disability.
- It occurs as the result of absence of expression of paternal genes from chromosome 15q11.2-q13.
- Normally, individuals inherit one copy of chromosome 15 from each parent.
- Some genes are active only on the paternally inherited copy.This parent specific gene activation is caused by genome imprinting.
- Most cases of Prader Willi syndrome are and due to random events during the formation of egg or sperm cells or in early fetal development.
- This is usually the case when PWS is caused by a deletion in the paternal chromosome 15, or by maternal Uniparental disomy.
- Loss of particular group of sno RNA genes (SNORD116 cluster) play an important role in causing the signs and symptoms of Prader-Willi syndrome.
- In some cases, loss of gene OCA2 is associated with unusual fair skin and light coloured hair.

Incidence

- 1 in 20,000 live births.

Clinical features

- Mental retardation
- Hypotonia
- Profound Hypophagia
- Small hands and feet
- Hypogonadism
- Chronic feeling of hunger.

Complications in PWS if present may adversely affect morbidity and mortality, such as obesity, heart failure and diabetes. If left untreated or unresolved, it can shorten the life expectancy of the individual. Death typically occurs in the fourth decade of life with a mean age of females being 31 years and 29 years in males; but if weight is controlled, then PWS adults may have an extended life up to seventh decade or beyond.

Camurati engelmann's syndrome (CES)

It is a skeletal condition that is characterized by abnormally thick bones (hyperostosis) in skull, arms and legs. The limb bones may lead to pain due to thickness and muscle weakness in the upper limbs and lower limbs because of which these individuals get tired quickly. Bone pain may be mild to severe and can increase with excessive stress, activities, or even cold temperatures. Lower limb weakness can cause difficulties in standing up from a sitting position and some individuals may develop unsteady gait. Additional limb abnormalities may be joint abnormalities, knock knees, and flat feet (pesplanus). Swelling and redness of the limbs and abnormal curvatures of the

spine can also be present. Individuals with this disease have a thick skull, which can lead to macrocephaly and bigger size of mandible, frontal bossing, and ocular proptosis. These changes to the head and face become more prominent as age progresses and are noticed more in affected adults. Mutations in the TGFB1 gene cause Camurati-Engelmann disease. The TGFB1 gene provides instructions for production of the factor transforming growth factor beta-1 (TGFß-1). The TGFß-1 protein assists in triggering chemical signals which regulate various cellular activities like proliferation of cells, maturation of cells to carry out specific functions like differentiation, cell motility, and controlled cell death (i.e., apoptosis). This abnormal activity of TGFß-1 protein causes increase in signaling, which leads to more bone formation because of which the bones in the arms, legs, and skull are thicker than usual, which contributes to the movement disorders and neurological problems in individuals with Camurati-Engelmann disease.

Angelman syndrome

Angelman syndrome (AS) affects approximately around 1 in 15,000 individuals and characterized by dysfunction in motor abilities, intellectual disability, seizures, hyperactivity, speech impairment.

Developmental delay in individuals with this syndrome is usually seen in the first year of life. Less impairment in Receptive language is observed. Seizures may occur in more than 80% of patients and onset may be usually before 3 years of age. Movement disorders include ataxia, tremors and jerkiness. The characteristic features of AS include mouthing of objects, happy demeanor with easily provoked laughing spells, attraction towards water, hyperactive behavior and altered sleep pattern with disturbed sleep.

Severe Language impairment is observed. In many cases, appropriate use of one or two words in a consistent manner is rare. It is observed that receptive language skills are always more advanced than expressive language skills.

Recent advances in diagnostic technology and breakthrough treatments

Fragile X syndrome

Laboratory Tests: DNA studies are used to test Fragile X Syndrome. Examination of the size of the trinucleotides repeat segment and the methylation status of the FMR1 gene can determine if an individual is at risk or a carrier of this mutation. The Fragile X Mental Retardation - 1 gene test was introduced in 1991 and is still the most accurate test for detecting Fragile X Syndrome. Other available test includes chromosome test used in most labs for a variety of diagnostic purposes. Current Treatment: there is currently still no cure Fragile X syndrome though FRAXA Research Foundation is working to find specific treatments and ultimately a cure for Fragile X.

Autism spectrum disorder

Laboratory tests

There is no specific medical test, like blood test, to diagnose ASD making it difficult to detect at an early age. Doctors have to search through the child's developmental history and behavior to make the diagnosis. As published by the Australian Journal for Pharmacy on March 17, 2017 stated that "A new blood test can determine if a child is on the autism spectrum with 96% accuracy and might allow for diagnosis under the age of two." In a new study conducted by Juergen Hahn and Daniel Howsmon of Rensselaer Polytechnic Institute, New York, and colleagues presented a method to identify a child as being on the autism spectrum disorder based on blood samples with concentrations of specific substances. These substances known as the Folate-dependent one-carbon (FOCM) metabolism and transulfuration (TS)are produced by metabolic processes, both of which are either increased or decreased in children with autism. The scientist collected blood sample data at the Arkansas Children's Hospital, from 83 children with Autism and 76 neurotypical children, all between 3 and 10 years old. Current Treatment: it would benefit people with ASD to receive treatment, regardless of age or when they are diagnosed. People who get proper treatment like therapies and interventions often shows a lot of improvements despite of their age or level of abil-

ity. Currently, there is no one standard treatment for autism spectrum disorder (ASD). Behavioral management therapy Cognitive behavior therapy Early intervention Educational and school-based therapies Joint attention therapy Medication treatment Nutritional therapy Occupational therapy Parent-mediated therapy Physical therapy Social skills training Speech-language therapy.

Prader willi syndrome

Laboratory tests: The diagnosis is confirmed by a blood test called "methylation analysis," and is the preferred method of testing which detects >99% of cases, including all of the major genetic subtypes of PWS (deletion, uniparental disomy, or imprinting mutation). Treatment: there is currently no cure for PWS. The lives of people with PWS can be improved with an early diagnosis and careful management of symptoms together with more effective therapies. The treatment of PWS is currently based on treating the symptoms of the disorder as they arise.

Camurati-engelmann syndrome

Laboratory tests: Diagnosis of Camurati-Engelmann disease is through physical examination and radiographic findings and can be confirmed by molecular genetic testing. Known to be associated with Camurati-Engelmann disease is the geneTGFB1. Treatment: To manage the pain caused by the thickening of the bones, individuals may be treated with corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs).

Corticosteroids have shown to be beneficial for the affected individuals. Although corticosteroids help to improve walking, it does has side long term side effects including high blood sugar, increased risk of infections, and suppressed adrenal hormone production. Losartan has been the medication of choice to help reduce limb pain and increase muscle strength in some cases. Some individuals have complained of hearing problems caused by the thickening of the bones of the base of the skull, this is treated by decompression surgery in which a small piece of the base of the skull is removed. This procedure however can result in an increased risk of complications as well as the possibility for bone to re-grow after the surgery.

Angel man syndrome

Syndrome is genetic condition caused by problems of a gene called UBE3A on chromosome. Normally, people inherit one copy of the UBE3A gene from each parent but only one copy will be active and that is usually the maternal copy. This specific gene activation from a specific parent is called Genomic imprinting. In most cases, the child's maternal copy of the UBE3A gene is lost or damaged because of a chromosomal change or a gene mutation. This means the child will have no active copies of the gene in any part of the brain.

Angel man syndrome laboratory tests

Blood test is performed to come to a definitive diagnosis. The genetic test performed can help identify any abnormalities in you're the child's chromosomes that can indicate Angelman syndrome. A Parental DNA pattern testing, known as a DNA methylation test, can also be performed to screens for three of the four known genetic abnormalities that cause Angelman syndrome. Treatment: There is no specific therapy for Angelman syndrome at this time. The best treatment is based on the symptoms like giving medications to minimize seizures, anxiety, and gastrointestinal issues and maximize sleep through therapy.

Future directions and challenges

The key novel findings were that analysis in infants was predictive of intellectual functioning and autism features when they become children affected with FXS. This has the potential to open new avenues for detection of FXS FM alleles in newborn blood spots in both

sexes and for prognostic testing in newborns and children as they develop sequencing and detection of DNA modifications have made methylation-dependent regulation of transcription an attractive hypothesis for being a causative factor in autism spectrum disorder (ASD), Prader Willi syndrome, Fragile X syndrome, Camurati Engelmann's Syndrome and Angelman Syndrome etiology in newborns and children as they develop.

Conclusion

An opinion arrived at through a process of reasoning

Stable and plastic epigenetic regulation might help researchers to understand the molecular basis of heritable and non-heritable factors, but we still need a considerable effort to get as much evidence as possible on the evolutionary bases of the epigenetic phenomenon. DNA methylation is an essential epigenetic modification for mammalian embryonic development. The DNA methylation pattern across the genome, together with other epigenetic signals, is responsible for the transcriptional process of a cell and helps in preservation of the cell's identity. Environmental factors can influence DNA methylation in mammals. Organic pollutants, tobacco, alcohol, obesity, asthma, and maternal stress and care have an impact on DNA methylation. Fragile X syndrome, Autistic spectrum disorders, Prader Willi syndrome and Engelmann syndrome are some of the genetic diseases in which DNA methylation is affected. Specific treatments and cure is not available for these genetic diseases but interventions to improve lifestyle and behavioral modifications are available to improve the quality of life. Interventions for behavioral modification include Cognitive behavioral therapy; Parent mediated therapy, Social skills training, and Speech and language therapy [1-48].

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Volume 14 Issue 1 January 2022