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Review article:

Aspects of genetic imprinting: implications, syndromes and therapies

"Genetic Imprinting and Epigenetics: A Comprehensive Overview"

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Abstract

Epigenetic traits, influenced by changes in chromosomes rather than DNA, are crucial for controlling biological processes. Genetic imprinting, a unique aspect of epigenetics, involves intergenerational inheritance and affects gene expression in a parent-of-origin-dependent manner. This abstract explores the concept of genetic imprinting, including its implications in gene regulation and its role in imprinting disorders such as Prader–Willi syndrome and Angelman syndrome. Genomic imprinting theories, such as kinship theory and sexual antagonism theory, shed light on the evolutionary origins and importance of epigenetic information. Gene silence, facilitated by DNA methylation, histone modification, and non-coding RNA, plays a key role in genetic imprinting processes. Clinical trials are underway to better understand and develop treatments for genetically imprinted diseases. Join us as we delve into the complexities of genetic imprinting and its impact on epigenetics.

Keywords: Epigenetics; Genetic imprinting; Mechanisms; Syndromes and clinical trials

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1. Genetic imprinting

Normal development involves the monoallelic and parent-of-origin- dependent expression of a specific subset of genes, which is referred to as genetic imprinting shown in Fig. 1 **(John *et al.*, 2023).** Epigenetic changes, resulting from single or multiple loci modifications influencing the formation, preservation, and deletion of germline epigenetic imprints, are the cause of human diseases **(Monk *et al.*, 2019).** In the 1960s, cytogeneticist Helen Crouse used the word "imprinting" to refer to the degeneration of paternally derived X chromosomes in flies. Pronuclear transfer experiments on freshly fertilized mouse eggs

made it possible to create diploid conceptuses that are androgenetic (having two paternal copies) or gynogenetic (having two maternal copies) as shown in **Fig. 2A.**

The lack of viability of the embryos demonstrated that both a maternal and a paternal set of chromosomes are necessary for early development and that the two parental sets are not functionally equal. Remarkably, these investigations also revealed that whereas androgenetic conceptuses demonstrated underdeveloped embryos, gynogenetic pronuclei- developed conceptuses failed partially, due to damaged extra-embryonic lineages. These results indicated that the maternal and paternal genomes perform complementary roles in maintaining these lineages and contain essential components for both embryonic and extraembryonic development **(Tucci *et al.* 2019).**

The parental genomes were not identical; at the time, it was still unclear if this resulted from a whole-genome effect or from the involvement of certain genes, which generated a lot of discussion. Gene-specific imprinting was fundamentally supported by studies performed by **Cattanach and colleague (1985)**. They utilized Robertsonian and reciprocal translocations to utilize chromosome "non-complementation" analysis, which allowed them to identify areas of the genome where the presence of two maternal or two paternal chromosomal copies caused problems in growth, behavior, and/or viability as depicted in **Fig. 2B (Cattanach and Kirk, 1985; Barlow and Bartolomei, 2014).** Studies reveal that imprinting affects specific genomic regions in humans, affecting gene expression and repression, potentially contributing to syntonic similarities with mouse regions

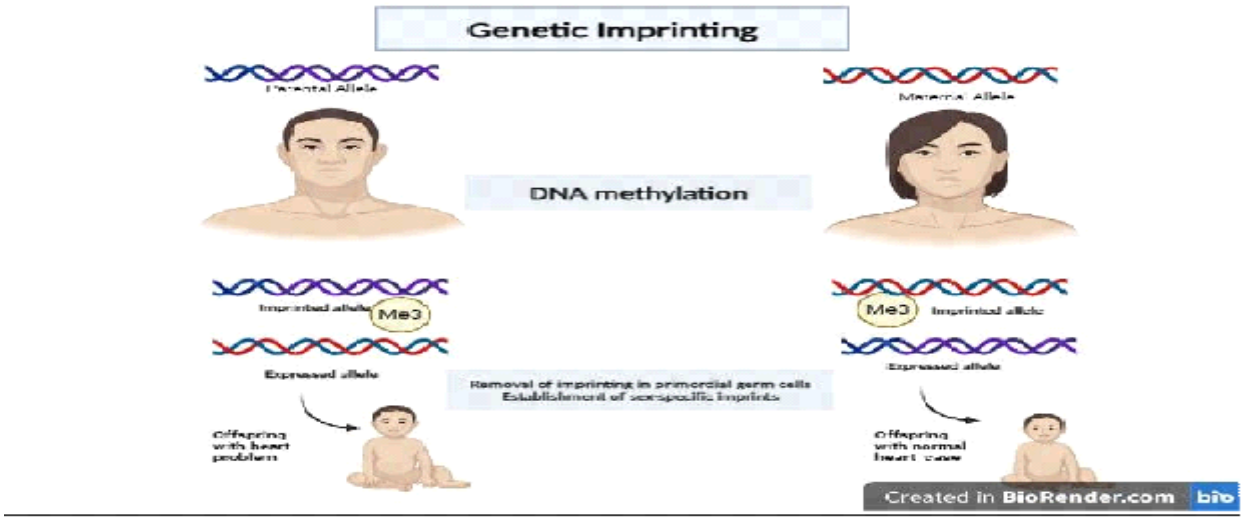

Fig 1: Genetic imprinting process and its impacts on the offsprings

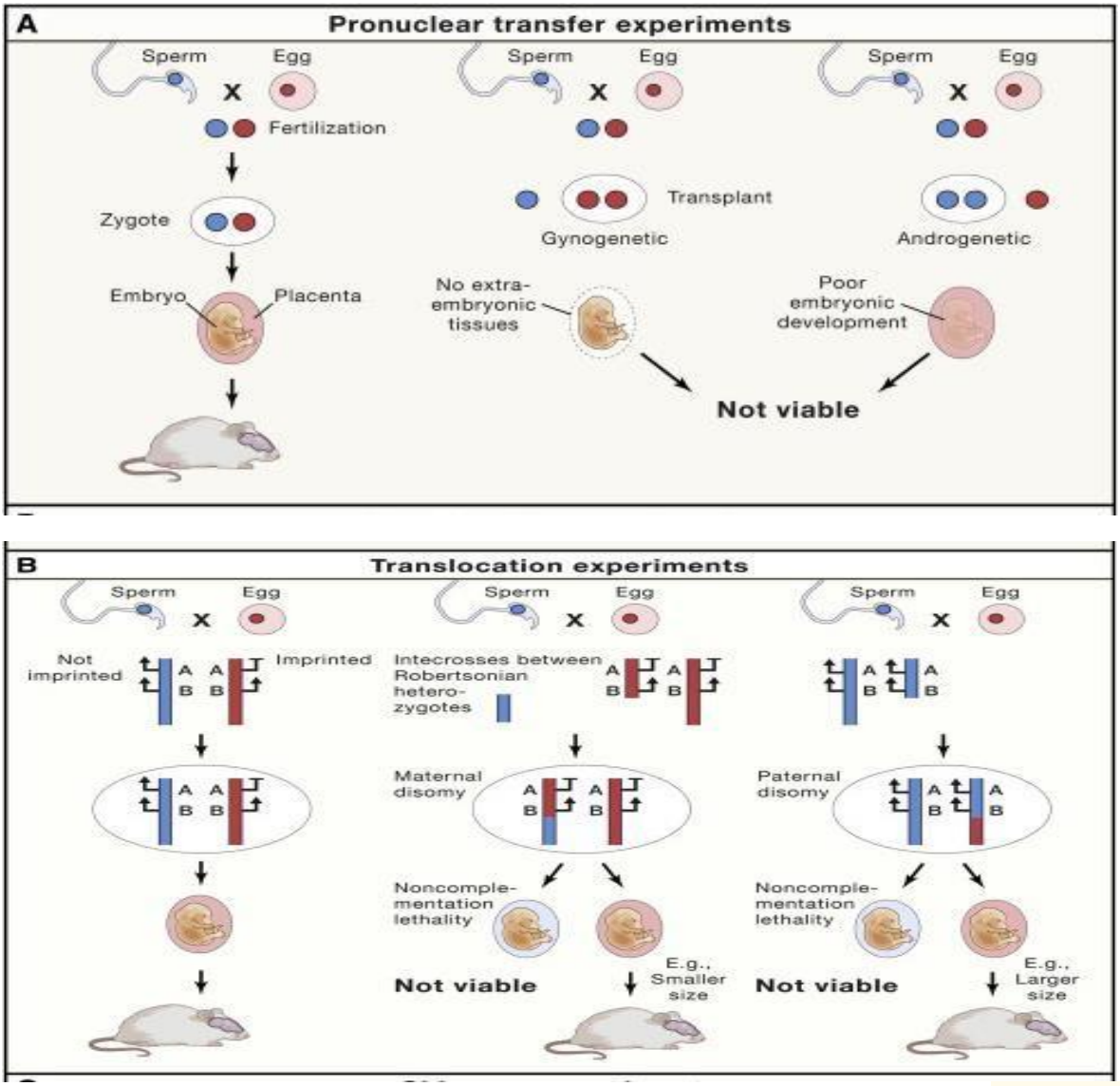

Fig 2: Parental genomic imprinting in the maternal and paternal alleles: A Crucial Element in Embryogenesis with 2 approaches

2. Genetic imprinting theories

The evolution and prevalence of genomic imprinting have been the subject of numerous theories within the scientific community. These theories aim to shed light on the adaptive significance of imprinting, with two prominent viewpoints being Haig and colleagues' kinship theory and Day and Bonduriansky's sexual antagonism theory. In this article, we delve into the contrasting perspectives of these theories and explore their implications for understanding genomic imprinting **(Patten et al. 2014).**

A. The kinship theory

Kinship theory is a kin selection model indicating that matrilineal and patrilineal alleles exhibit distinct patterns of relatedness, influencing their expression and inclusive fitness. Individuals are more likely to have

matrilineal relatives than patrilineal relatives, which can have different effects on their inclusive fitness **(Queller 2019).**

This theory focuses on genes whose expression level determines the extent of a physiological or behavioral interaction between individuals. For instance, the expression of growth factors during prenatal development not only affects the development of the fetus, but also has an indirect impact on the growth and perhaps the fitness of siblings. This is because the growth factors require shared maternal resources as seen in Fig. 3 **(Harris and McDade, 2018).**

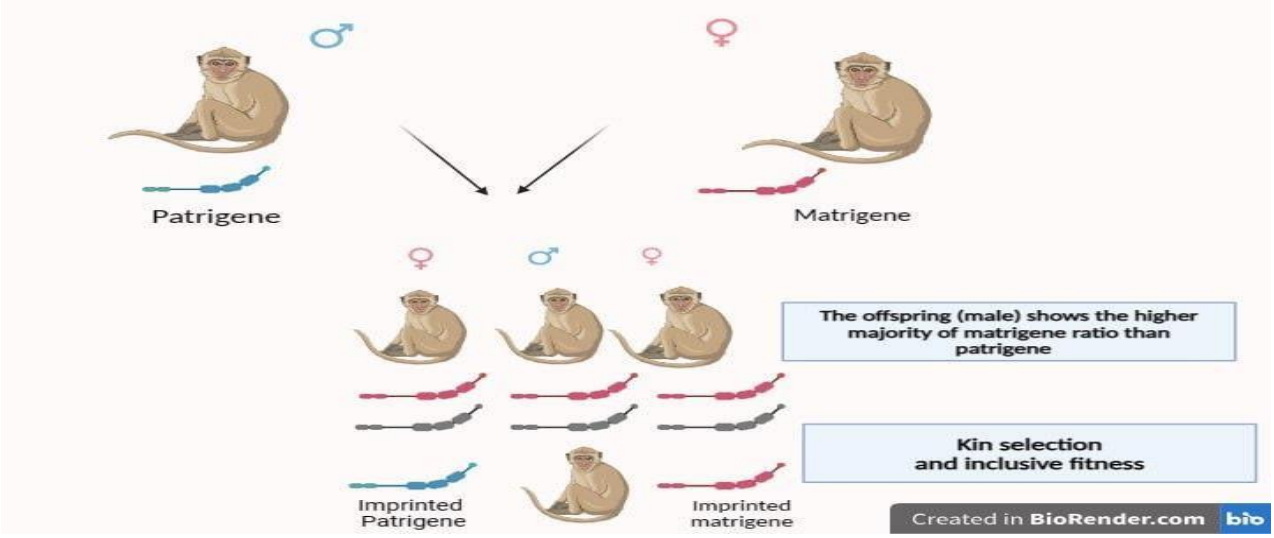

Fig. 3: Kinship theory diagram in a strain of monkey fitting theory approach

B. The sexual antagonism theory

In the evolutionary theory of genomic imprinting, sex-specific selection pressure plays a crucial role in the development of sexual antagonism. This concept revolves around the idea that allele frequencies in eggs and sperm become uneven due to differential selection between males and females. As a result, the maternal and paternal genes of the next generation may be enriched for alleles that confer advantages to either sex **(Muralidhar and Veller, 2018).**

The intricate interplay between genetics and natural selection plays a crucial role in shaping the evolution of imprinting. Two main approaches contribute to the imbalance created in imprinting: the accumulation of alleles that benefit females by the maternal gene, and the gathering of alleles that benefit males by the paternal gene **(Rodrigues and Zilberman, 2015)**. This phenomenon is illustrated in **Fig. 4**, emphasizing the significance of understanding how genetic factors influence imprinting. A novel modulator that can alter gene expression levels in an imprinted and sex-specific manner holds a selective advantage. By expressing the allele originating from the parent with greater selection in the previous generation, there is

a net selective advantage to changing the expression pattern in a conventional imprinting fashion, regardless of the recipient's sex **(Lawson *et al.*, 2013)**. This highlights the complexity and importance of considering both genetic and selective factors in the evolution of imprinting.

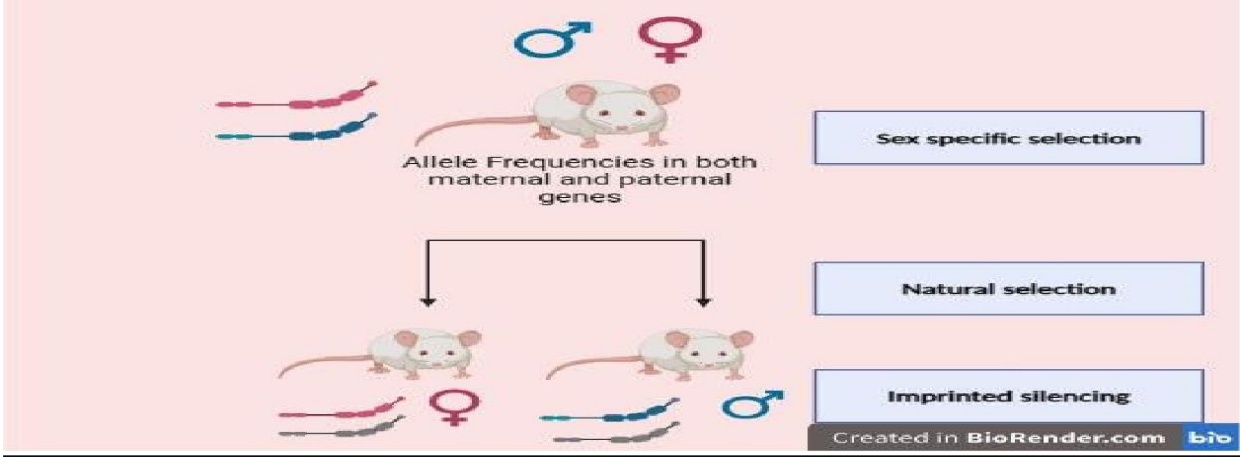

Fig 4: A sexual antagonism theory and the gene- specific selection

3. Genetic imprinting mechanisms

Epigenetic mechanisms play a crucial role in regulating gene expression in animals. Imprinted regions, controlled by DNA sequences, are key players in this regulatory process. Imprinting control regions (ICRs) are specific DNA sequences located near or within imprinted genes, working together to maintain the imprinted pattern of gene expression. These DNA sequences work in harmony to maintain the imprinted pattern of gene expression by initiating the silencing or activation of genes. The coordination of ICRs with enhancers and border elements serves to finely regulate gene expression within specific areas, ultimately shaping the intricate landscape of genetic activity **(Fedoriw et al., 2012)**. In this article, we will delve deeper into the significance of ICRs and their role in maintaining the delicate balance of gene expression.

3.1 DNA Methylation

DNA methylation, a crucial epigenetic modification in the eukaryote genome, involves the attachment of a methyl group to nitrogenous bases. In the eukaryote genome, 98% of cytosines are methylated in CpG dinucleotides, forming CpG islands, which regulate gene expression, genomic imprinting, transposon suppression, and embryonic development **(Jin *et al.*, 2011).** Methylation is reliant on enzyme complexes and is strictly regulated. The methylation process is primarily reliant on the activity of three categories of enzymes: methyltransferases, methyl-binding proteins, and demethylases as shown in

Fig. 5 (Jin *et al.*, 2011; Fedoriw *et al.*, 2012).

Proteins belonging to the DNMT family are considered writers, while proteins possessing the MBD, BTB/POZ, or SET- and RING-associated domains are referred to as readers. On the other hand, proteins of the TET family are classified as erasers **(Sergeeva et al. 2023).** Demethylation can occur through enzymatic complexes or passively within DNA replication. Therefore, the preservation of DNA methylation is crucial. Methylation patterns undergo alterations during embryonic development aging, and the development of cancer. Both aging and cancer exhibit extensive genome- wide hypo-methylation, accompanied by localized hyper-methylation **(Parveen and Dhawan 2021).**

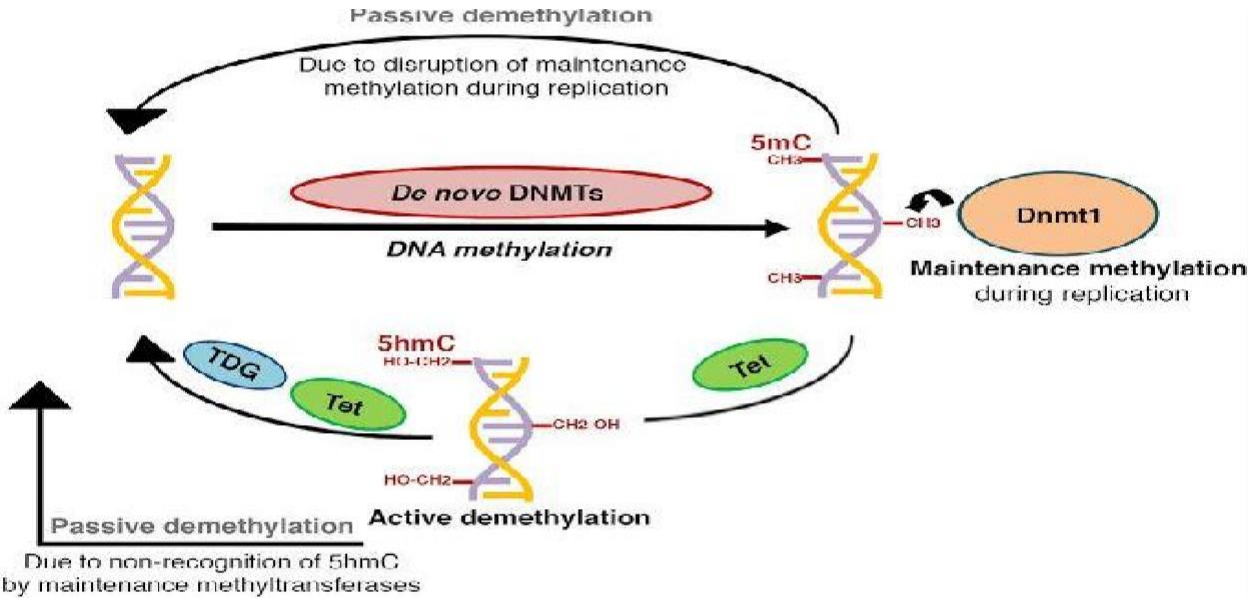

Fig. 5: DNA methylation patterning schematic representation

3.2 Histone modification

Eukaryotic genomic DNA is densely compacted with histones in a hierarchical manner to create intricately ordered chromatin structures. Nucleosomes are the fundamental building blocks of chromatin, consisting of DNA wrapped around histones. A nucleosome is composed of a histone octamer wrapped around a 147-base pair DNA molecule, with two copies each of histones H2A, H2B, H3, and H4 **(Mir *et al.*, 2021).**

Histones undergo a range of posttranslational changes throughout cell growth and development, such as acylation (e.g., acetylation, methylation, phosphorylation and etc…). Histone modifications regulate gene expression by altering chromatin structure and protein-protein interactions, providing or removing binding sites for specific protein complexes, and promoting transcriptional regulator aggregation to maintain gene epigenetic homeostasis.

Histone alterations have a substantial impact on gene expression, particularly on gene transcription and the activation of chromatin **(Mir *et al.*, 2021).** Multiple histone-modifying enzymes have been observed to aid in the addition or removal of specific histone modifications from histone proteins.

A. Histone acetylation:

Acetylation is a reversible biochemical process involving the addition or removal of an acetyl group from histone proteins. This process is facilitated by enzymes called histone acetyltransferases (HAT) and histone deacetylases (HDAC), respectively **(Fig. 6).**

Currently, it is understood that acetylation and deacetylation processes can occur not just in histones but also in other proteins. Studies on the acetylome have revealed numerous non-histone substrates, including AML1, p53, c- MYC, NF-kB, cohesion and tubulin. These substrates have significant involvement in diverse cellular processes **(An *et al.*, 2023).**

Histone acetylation is linked to the activation of transcription, while histone deacetylation hinders gene expression. The primary sites for histone acetylation are H3K4, H3K9, H3K27, H3K56, and H4K16. The addition of an acetyl group to the α-amino group on the lysine residue of a histone is believed to neutralize the positive charge of lysine. Consequently, the connection between DNA and histones is diminished when chromatin de-condenses and transcription is activated. Histone proteins have crucial roles in both the structure and function of various nuclear processes. Abnormalities in these proteins have been linked to disorders such as malignancies, liver damage, viral hepatitis, and Alzheimer's disease **(Zhang and Gao 2022).**

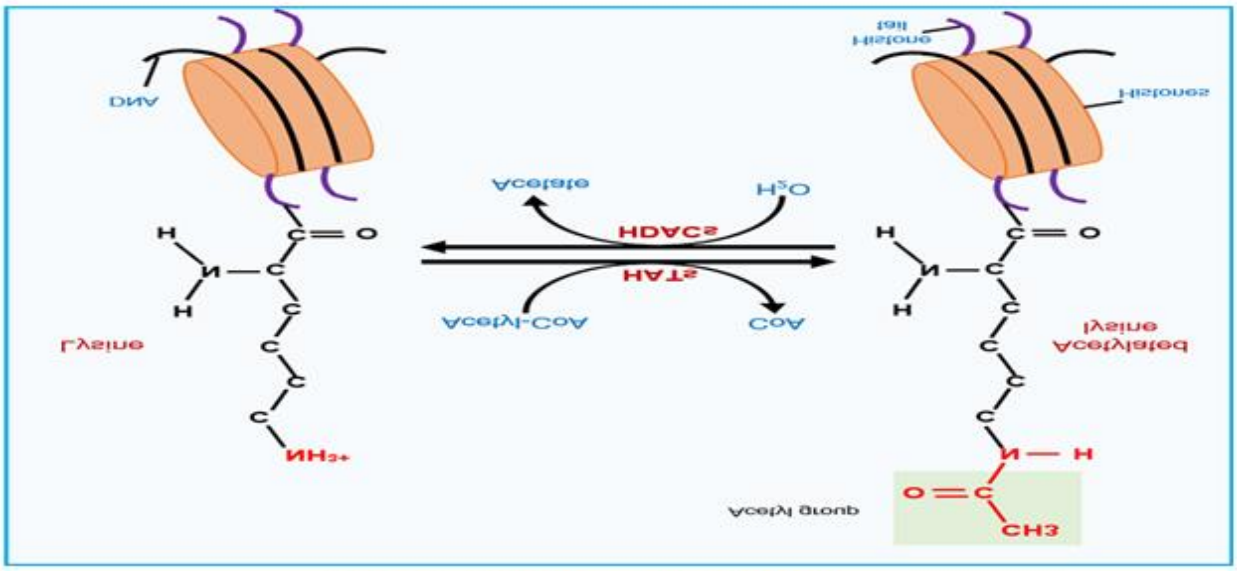

Fig. 6: Histone acetylation

B. Histone Methylation

Unlike DNA methylation, which is linked to the regulation of transcription, histone methylation can have either repressive or activating effects on gene expression **(Fig. 7).** The specific outcome depends on the residue that undergoes methylation, the gene area involved, and the extent of the change. Histone methylation takes place on specific amino acid residues, namely lysine (K) and arginine (R), located on histones H3 and H4. This process involves the addition of one (me1), two (me2), or three (me3) methyl groups. The activation markers include H3K4me1, H3K4me2, H3K36me2, H3K4me3, and H3K36me3, but H3K9me3 and H4K20me3 are not activation markers **(An *et al*,. 2023).**

Histone methyltransferases (HMTs) and histone demethylases (KDMs) cooperate to maintain the equilibrium of histone methylation. Several protein complexes mediate histone methylation and demethylation. The KMT2 family proteins, which include MLL1 (MLL/KMT2A), MLL2 (KMT2B), MLL3 (KMT2C), MLL4 (KMT2D), SETD1A (KMT2F), and SETD1B (KMT2G), are part of the COMPASS complex, which is a group of proteins linked to SET1. They have histone-lysine N-methyltransferase activity **(Mir *et al.*, 2021).**

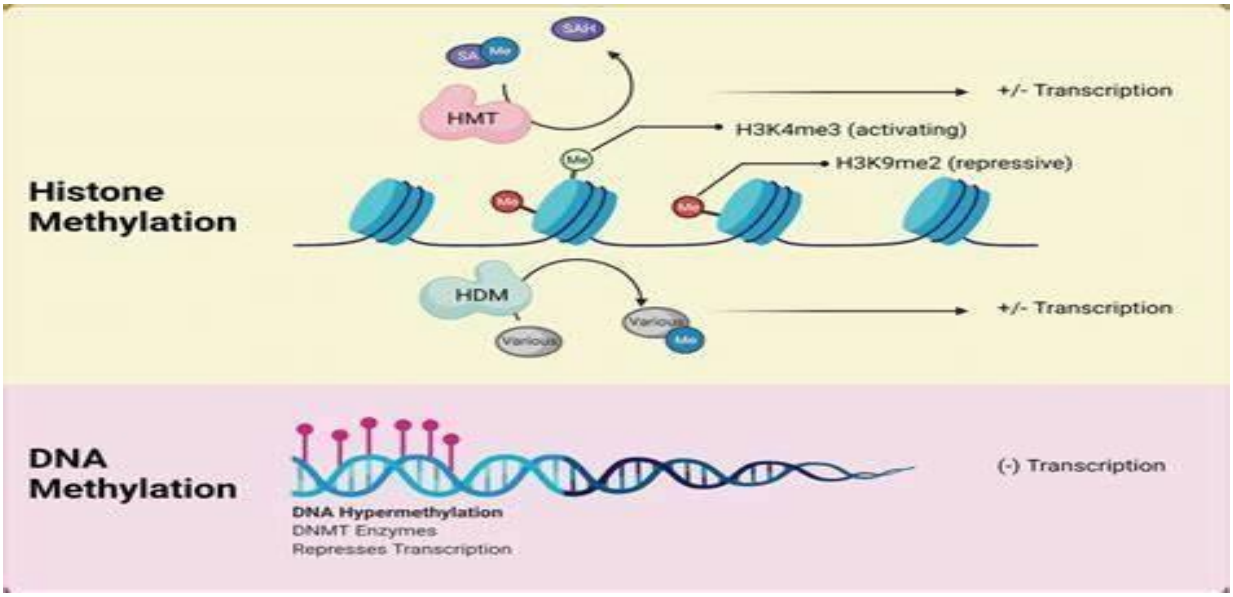

Fig. 7: Histone methylation and DNA methylation

C. Histone phosphorylation

H3 phosphorylation is a downstream event for a number of signal transduction pathways. The kinases RSK2, MSK1/2, PIM1, and IKKα have been demonstrated to directly phosphorylate H3S10. H3 phosphorylation is a crucial component of the transcription

regulation apparatus, as it is targeted by several signaling cascades **(Zhou *et al.*, 2022)**

The histone mark H3S10ph has a role in normal cells by contributing to the construction of protein scaffolds, regulating transcription, preventing the spread of repressive epigenetic information, and inhibiting the establishment of heterochromatin in specific regions. Phosphorylation of histones impacts the compaction and separation of chromosomes **(Fig. 8).** Disruption of the H3S10 phosphorylation deregulates the operation of kinetochores and the separation of chromosomes towards the poles. During cell division, there is an increase in the abundance of H3S10ph, whereas the levels of H3K9me2 methylation and H3K9ac acetylation remain unchanged. The phosphorylation of H3S10 impacts the development of the chromatin structure and arrangement, leading to the displacement of the primary heterochromatin protein HP1 **(Zhou *et al.*, 2022; An *et al*,. 2023)**.

In addition, H3S10ph is involved in the creation of DNA- RNA hybrids known as R- loops, which are produced during the process of transcription **(An *et al.*, 2023).** R-loops make the DNA matrix strand visible, which makes it easier for endonucleases and other enzymes to damage the strand. This damages the chromosome structure and makes the chromosome unstable **(Mir *et al.*, 2021).**

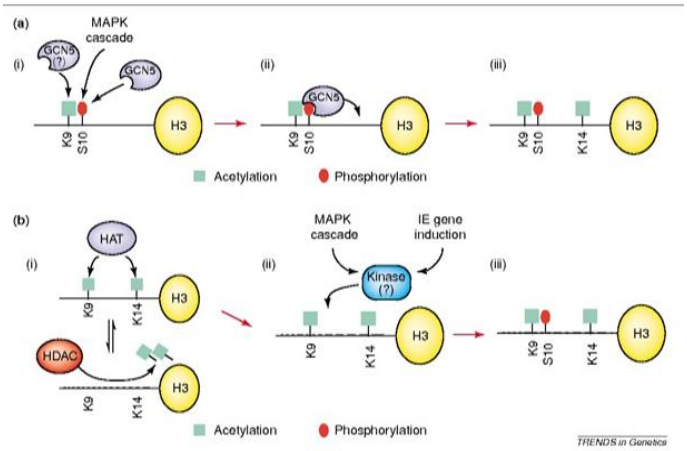

Fig. 8: Histone phosphorylation

3.3 Long Non-coding RNAs

Long Non-coding RNAs (lncRNAs) are a vital component in the intricate orchestration of gene expression, with a particular focus on the regulation of imprinting genes. Specifically, lncRNAs play a crucial role in modulating the timing and spatial distribution of imprinting patterns within extensively studied gene clusters **(Wang *et al.*, 2021).** A significant portion of the genomes of complex organisms is occupied by genes that specify long non-coding RNAs (lncRNAs). The word 'lncRNAs' refers to RNA molecules that are transcribed by RNA polymerase I (Pol I), RNA polymerase II (Pol II), and RNA polymerase III (Pol III), as well as RNA molecules that are derived from processed introns **(Mattick *et al.*, 2023).**

The diverse roles of lncRNAs and their numerous isoforms, as well as their intricate connections with other genes, pose challenges

in the classification and annotation of lncRNAs **(Wu *et al.*, 2020).** lncRNAs have a higher rate of evolution compared to protein-coding sequences. They are specialized for certain cell types and play a crucial role in regulating several aspects of cell differentiation, development, and other physiological processes **(Wang *et al.*, 2021).**

LncRNAs have a close connection with chromatin-modifying complexes. They are transcribed from enhancers and have a role in initiating the formation of nuclear condensates and domains through phase separation. This suggests that there is a strong relationship between the expression of lncRNAs and the spatial regulation of gene expression during development **(Mattick *et al.*, 2023).** lncRNAs also have important roles in the cytoplasm and beyond, including in the regulation of translation, metabolism and signaling. lncRNAs often have a modular structure and are rich in repeats, which are increasingly being shown to be relevant to their function **(Fig. 9).**

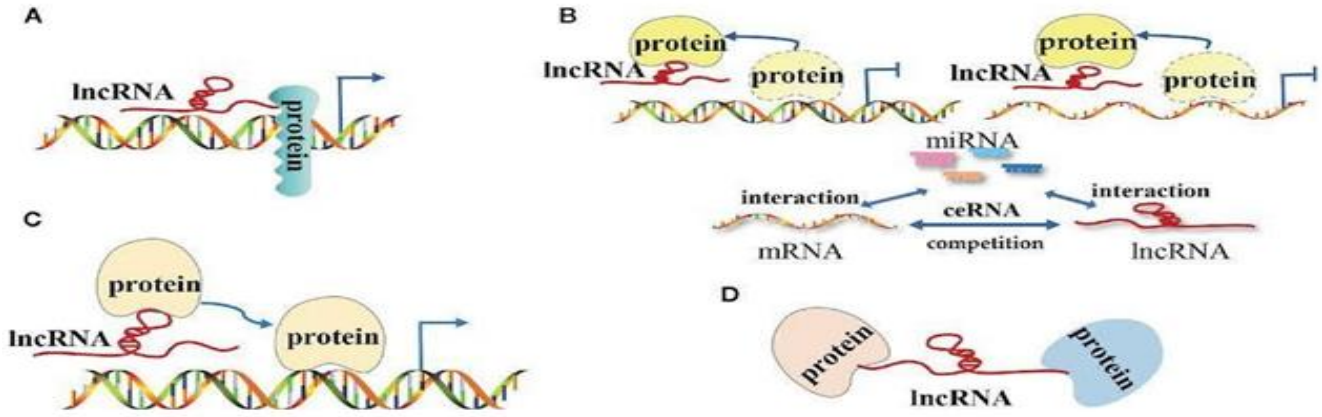

Fig. 9: Long non- coding RNAs (lncRNAs) regulatory mechanism

4. Syndromes Challenges and clinical trials

4.1 Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by defects in the complex genomic mechanism known as genomic imprinting. This mechanism is made up of three molecular genetic classes specific to PWS **(Azor *et al.*, 2019).** Individuals with PWS commonly experience significant hypotonia, difficulties with breastfeeding, and feeding challenges, leading to failure to thrive in infancy. Additionally, PWS is characterized by hypogonadism **(Fig. 10)** in both males and females, motor and cognitive delays, reduced muscle tone, sluggish metabolism, behavioral disturbances, endocrine abnormalities affecting growth, and other hormone deficiencies resulting in dwarfism, infertility, and distinct physical features such as small hands and feet **(Quarello *et al.*, 2023).**

Mild cognitive impairment and behavioral difficulties, including self-injury, anxiety, compulsions, and anger, can accompany childhood. These issues may also manifest as food seeking and hyperphagia, which can progress to severe obesity and a shorter lifespan if left uncontrolled **(Azor *et al.*, 2019).** PWS is widely recognized as the primary cause of severe obesity that poses a risk to life in humans. It affects around 400,000 people worldwide and occurs in approximately one out of every 20,000 births.

Defects in the genomic imprinting of the human chromosome 15q11-q13 region cause this uncommon disorder, though its occurrence is unpredictable. In approximately 60% of cases, a paternal deletion of the 15q11-q13 region causes the predominant abnormality. Next, there is maternal disomy 15, which means both copies of chromosome 15 come from the mother. This is present in around 35% of cases. The remaining individuals either exhibit a malfunction in the imprinting center responsible for regulating the activity of imprinted genes on chromosome 15, or they have chromosome 15 translocations or inversions **(Qiu *et al.*, 2024).**

Individuals belonging to distinct PWS molecular classes exhibit diverse clinical manifestations. If someone has the 15q11-q13 deletion, especially the larger type I deletion, they are more likely to hurt themselves, have compulsions, and have worse mental health than someone with the smaller type II deletion or maternal disomy 15 **(Bellman *et al.*, 2021).** PWS causes severe obesity and increases the risk of developing diabetes, cardiovascular or orthopedic problems, and potentially even death. Respiratory failure is the primary cause of death in individuals with PWS, followed by heart failure, gastrointestinal failure, and infection **(Yamada *et al.*, 2023).**

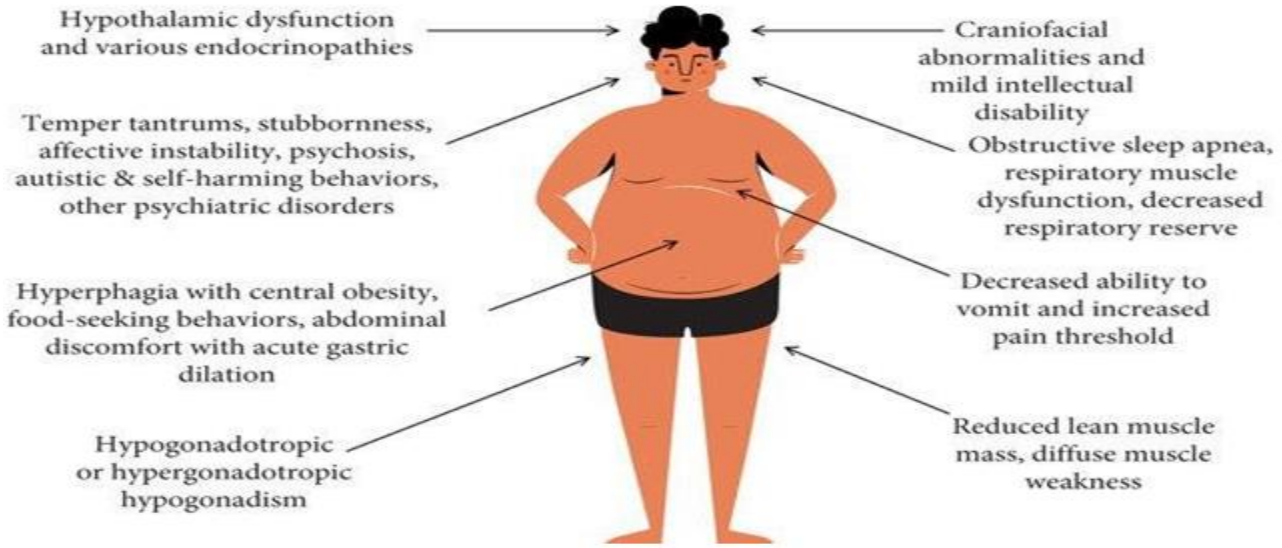

Fig.10: Symptoms of Prader Willi Syndrome

4.2 PWS Clinical trials

Beloranib

Beloranib treatment was undertaken in a large cohort of individuals with genetic confirmation of PWS, aiming to investigate its efficacy and safety over 26 weeks. The treatment inhibits methionine aminopeptidase 2, impacting fat metabolism and reducing food intake, body weight, fat content, and adipocyte size **(Mahmoud *et al.*, 2023).**

Oxytocin

Oxytocin is a neuropeptide hormone that has significant involvement in several aspects of social interactions, social skills, food consumption, anxiety, energy usage, maternal behaviors, and regulation of body weight. Patients with PWS experience significant impairment in all of these metrics. They exhibit a reduced quantity of oxytocin-producing neurons in the hypothalamus periventricular nuclei, along with a limited number of detected periventricular nuclei. The insufficiency of these neurons may be associated with the impaired social discernment and emotional regulation observed in individuals with PWS **(Quarello *et al.*, 2023).**

Setmelanotide:

A study was conducted to investigate the effects of Setmelanotide, a melanocortin (MC)-4 receptor agonist, on hyperphagia and obesity. The drug was administered once a day through subcutaneous injection to individuals with PWS, targeting the satiety and feeding centers to reduce food intake **(Mahmoud *et al.*, 2023).**

Cannabinoid

The cannabinoid-1 receptor (CB1R) controls hunger by being present in both the brain and peripheral tissues. Stimulating CB1R enhances hunger, whilst inhibiting it helps reduce obesity and metabolic issues. Cannabidiol (CBD), a non-psychoactive compound found in Cannabis, exerts an anti-obesity action by acting as an antagonist on CB1 receptors. Nevertheless, the clinical experiment was unsuccessful as a result of unexpected complications **(Mahmoud *et al.*, 2023).**

4.3 Angelman Syndrome:

Angelman syndrome (AS) is an uncommon clinical and neurogenetic disorder that impacts around 1 in every 12,000–20,000 individuals. The symptoms of AS manifest during the first year of life and consist of craniofacial deformities, an unsteady stride, weakness in the limbic system, seizures, profound intellectual incapacity, hyperactivity, and a reported cheerful disposition **(Wolter *et al.*, 2020).** A small proportion of people possess the ability to communicate using word phrases, but the majority of individuals are unable to talk verbally **(Wolter *et al.*, 2020).**

. In contrast to Prader-Wili syndrome, Angelman syndrome (AS) is the result of a malfunction in the chromosome 15 inherited from the mother as well as a combined contribution from

both parents to the 15q11–13 region of the chromosome, which impacts its functioning. Moreover, paternal uniparental disomy, maternally inherited de-novo deletion, or genomic imprinting abnormalities can trigger the syndrome **(Fig. 11).** Approximately 85% to 90% of verified diagnoses with clinical phenotypes include genetic pathways that affect the expression of the UBE3A gene. However, no specific genetic abnormalities link to certain clinical symptoms of AS. Genomic imprinting is responsible for genetic defects on the chromosome 15q11-q13 region **(Wolter *et al.*, 2020; Wolter *et al.*, 2020)**.

The simultaneous occurrence of two or more illnesses in the same person is referred to as comorbidity **(O'Geen *et al.*, 2023).** Comorbid symptoms are common in individuals with autism spectrum disorder (ASD) and are also present in Fragile X, a rare genetic disorder. These symptoms affect a significant percentage, ranging from 78.7% to 95%, of individuals with ASD. ASD is a significant comorbidity since it is present in 42% to 79.9% of patients with AS. There is an overlap in symptomology between ASD and AS **(Trezza *et al.*, 2019).** Hence, it is likely that comorbid conditions, which are frequently observed in individuals with autism spectrum disorder (ASD), may also have an effect on individuals with Asperger's syndrome (AS). Common additional conditions associated with Autism Spectrum Disorder (ASD) include gastrointestinal (GI) issues, epilepsy, and difficulties with nutrition.

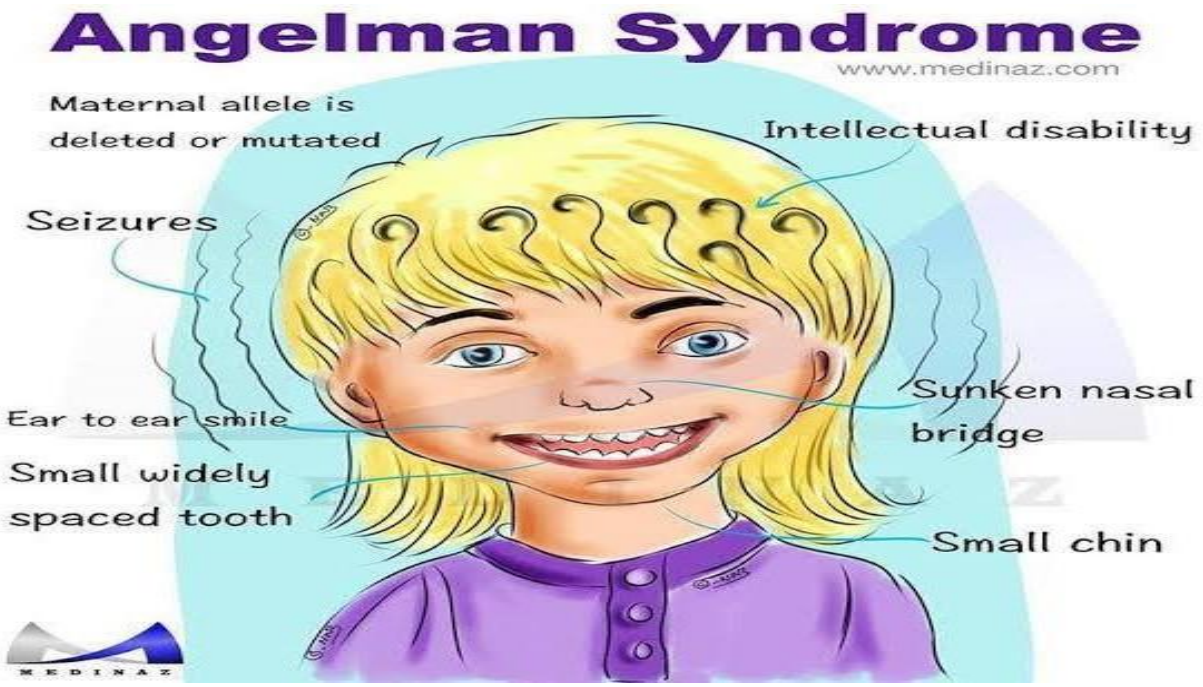

Fig.11: Symptoms of Angelman syndrome

Angelman syndrome Clinical trials

Cas9 gene therapy

A study has shown that Cas9 can activate paternal Ube3a in mouse and human neurons when targeted to Snord115 genes. A short Cas9 variant and guide RNA was administered to a mouse model of Asperger's Syndrome (AS) during embryonic and early postnatal stages, unsilenced paternal Ube3a for 17 months, and rescued anatomical and behavioral phenotypes **(Wolter et al. 2020).**

An artificial transcription factor:

The artificial transcription factor AAV-S1K has the capability to hinder the expression of Ube3a-ATS and reinstate its normal levels in a mouse model of adult Angelman syndrome (AS). After a solitary injection into the tail vein, levels of UBE3A protein are reinstated to 0.25% of their wild-type counterparts. A minimal inflammatory response and behavioral rescue were observed in response to the treatment, which were comparable to the reduced ambulation and velocity observed in patients with AS (**O'Geen et al. 2023)**.

5. Conclusion

In conclusion, genetic imprinting is a complex process that plays a significant role in our genetic makeup and influences our health and development. By understanding the mechanisms behind genetic imprinting, identifying associated syndromes, and exploring potential therapies through clinical trials, we are taking significant strides towards improving the lives of individuals affected by genetic imprinting disorders. As research in this field continues to advance, we can look forward to more promising breakthroughs that could potentially transform the landscape of genetic medicine.

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