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Chromatinopathies: a group of rare chromatin dysregulation human disorders: An update

Kiran Kumar H. B.[1], Poornima R.[2]
[1]Government Science College, Nrupathunga University, Nrupathunga Road, Bangalore-560001, India.
[2]Department of Biotechnology, Government Science College, Nrupathunga University, Nrupathunga Road, Bangalore-560001, India.

ABSTRACT

Chromatinopathies are a group of rare monogenic neurodevelopmental disorders caused by chromatin dysregulation characterized by highly overlapping clinical traits. Under healthy conditions epigenetic marks including DNA methylation, histone post-translational modifications and ATP-dependent remodeling complexes act as molecular switches that modulate the chromatin structure during cellular differentiation and gene expression. Conversely, chromatin dysregulation leads to diverse pathological states such as cancer, neurological disorder, cardiovascular diseases, metabolic and inflammatory disease thus highlighting the importance of chromatin. Regardless of their distinct genetic cause, chromatinopathies pose significant challenges for clinicians due to their several clinical overlaps. The present review provides background literature on rare disorders, chromatin and epigenetics in normal and disease states. The next sections focuses on clinical overlaps, episignatures and chromatinoapthies. The current and therapeutic methods and future scope towards diagnostic biomarkers is described. Methods to uncover overlapping phenotypes, reclassification variants of uncertain significance and to gain insight into disease mechanism are discussed. Ultimately, integration of genome-wide DNA episignatures with machine learning algorithm to analyze the functional readout of sequence variants will lead to precision medicine a need for these disorders.

KEYWORDS: chromatin modifiers; imprinting; Wiedemann-Steiner syndrome; Kleefstra syndrome; Selective IgA deficiency.

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Corresponding Author:
Poornima R.

1. RARE HUMAN DISORDERS

Rare human genetic illnesses are conditions produced by anomalies or mutations in an individual's DNA that typically affect one in every 2,000 people in the European Union and fewer than 200,000 people in the United States (Lee et al., 2020). The majority of these diseases have a genetic etiology with 39% being caused directly by specific genetic variations (Ferreira, 2019). The remaining 60% of rare disease genetic insights are often unavailable, as small patient groups make population genetic research impossible (Ferreira, 2019). As a result, 88% of uncommon disorders have fewer than ten gene connections (Ferreira, 2019). They are considered an unviable market for therapeutics in the absence of appropriate incentives and support, and too rare to be fully investigated and appropriately managed by professionals (Orphanet, 2020).

Approximately 83% of uncommon genetic illnesses first appear in children (Xie et al., 2026). The neurological system is impacted by over 70% of uncommon genetic disorders; in pediatric conditions, this number rises to nearly 90% (Xie et al., 2026). Local frequencies of particular founder mutations are frequently greater among populations with high rates of consanguineous marriage or rigorous community-based inbreeding, such as isolated religious communities or some groups in countries like India aiding the occurrence of rare diseases (AlZahrani et al., 2024). Approximately 4,000 genes have been found to have mutations resulting in approximately 6,500 diseases (Nguengang Wakap et al., 2020). Children are disproportionately affected by rare illnesses, yet

ironically, most of the genes that cause these conditions are widely expressed in human tissues and have a long evolutionary history (Toncheva et al., 2022). Due to overlapping symptoms and clinical rarity, patients frequently have to wait more than four years on average to acquire an appropriate diagnosis (Fitzsimmons et al., 2024).

Hutchinson-Gilford Progeria Syndrome (HGPS), an autosomal dominant mutation in the *LMNA* gene that affects roughly 1 in 4 million to 20 million infants, is one example of a rare condition (Lamis et al., 2022). With an average life expectancy of about 13 years, symptoms include rapid premature ageing, hair loss, stiff joints, and cardiovascular degeneration (Lamis et al., 2022). Fibrodysplasia Ossificans Progressiva (FOP), which is caused by mutations in the *ACVR1* gene, is another example (Qi et al., 2017). Ossification is the gradual replacement of muscle and connective tissue (such as tendons and ligaments) by bone, creating a "second skeleton" that limits movement (Qi et al., 2017). Unusual diseases also include illnesses brought on by infectious or poisonous substances, as well as non-genetic unusual diseases including autoimmune disorders and uncommon malignancies (Orphanet, 2020). An extensive panorama for identifying basic mechanisms implicated in common diseases and necessary for human development is provided by the annotated phenotypes of unusual disorders (Ravandi et al., 2024). Rare diseases are excellent study subjects for identifying evolutionarily conserved biological mechanisms that malfunction in common human diseases due to the genetic tractability of monogenic defects, their penetrance in early life, and the growing collection of human mutations and curated phenotypes (Ravandi et al., 2024). A few examples include common illnesses like Parkinson's disease, the uncommon monogenic disorder of copper metabolism, and Menkes disease, which provided insight into basic biology (Zlatic et al., 2015). Additionally, a small number of monogenic abnormalities have affected our comprehension of significant biological issues like ossification (Trajanoska & Rivadeneira, 2020). Literature search was carried out from PubMed, ResearchGate, Google Scholar. The literature was scanned for relevance and correctness to the topic. Included few reviewers to collate literature. The most updated reviews and literature was included with few exceptions. No inclusion exclusion criteria were set.

2. CHROMATIN BIOLOGY AND ITS ROLE IN HUMAN DISEASE

The main purposes of the heritable genetic material, aside from gene expression, are replication, faithful inheritance of the genome to descendant somatic cells, and evolutionary alterations of the genome (Haider et al., 2025). Complex gene regulatory circuits are created through feedback by transcription factors that are encoded in the genome and usually bind to particular DNA regions (Zhu & Li, 2015). Furthermore, information can be imposed along the DNA sequence since the DNA itself is arranged in a chromatin fibre (Li & Zhu, 2015). Additionally, chromatin facilitates the conversion of this epigenetic information into regulatory processes that impact transcription, replication, repair, and, in certain specific situations, even alter the DNA sequence (Alberts et al., 2022). The bulk of a cell's DNA is arranged using a single repeat unit called a nucleosome (Robert et al., 2020). Eight histone proteins and 146 base pairs (bp) of DNA encircling them in two left-handed turns make up a nucleosome (Robert et al., 2020). The negatively charged phosphate groups of the DNA backbone interact with the positively charged surfaces of basic amino acid side chains that make up the octamer complex that histone proteins create (Castillo et al., 2017). Two of each of the histone H3/H4 and H2A/H2B dimers is used to build the octamer (Nozawa et al., 2022; Hirano et al., 2021). The nucleosome's core is occupied by the histone H3/H4 dimers (Nozawa et al., 2022), whereas the H2A/H2B dimers are more loosely connected (Hirano et al., 2021). Histones H2B and H4 seem to be primarily canonical, but variations of histones H3 and H2A are widespread (Borg et al., 2021; Lai et al., 2024). While histone H3.3 is implicated in histone exchange at active transcription units and at pericentric and telomeric heterochromatin (Bano et al., 2017), histones H3.1 and H3.2 are deposited during DNA replication in S-phase in mammals (Thiriet, 2022). Histones H3.1 and H3.2 are incorporated into DNA during S-phase by chromatin assembly factor 1 (CAF-1) (Cheng et al., 2019), while H3.3 is incorporated into transcribed genes by histone cell cycle regulator (*HIRA*) (Morozov et al., 2023). *ATRX/DAXX* is necessary for the inclusion of histone H3.3 at the pericentric and telomeric heterochromatin (Voon & Wong, 2016). *CENP-A*, which has a more compact structure and a variety of amino acid variations, replaces canonical histone H3 in the centromere of human cells (Ohta et al., 2022). Post-translational changes can occur in histone proteins (Alberts et al., 2022). Specifically, the N-termini of histones can be altered in a number of ways, including methylation of arginine (Clarke, 2013), acetylation and methylation of lysine (Wang & Lin, 2021), and phosphorylation of serine (Liu et al., 2023). Notably, lysine and arginine can have more than one methyl group added to them, making them more complicated (Clarke, 2013; Wang & Lin, 2021). Co-factors from metabolic pathways are used in chemical processes that result in post-translational changes of proteins (Zhong et al., 2023). Histones are acetylated, methylated, and phosphorylated by acetyl-Co-enzyme A, S-adenosyl-methionine, and ATP, respectively (Zhong et al., 2023). Histone acetyltransferases (HATs), histone methylases (HMTs), and histone kinases (HKs) are the names given to the corresponding enzymatic activity (Berry & Lu, 2020; Li et al., 2024). Similarly, mono-ubiquitinylation is catalysed by histone ubiquitin-transferases (Oss-Ronen et al., 2022). Histone alterations have been linked to both the creation of a heritable signal for repression (Larkin et al., 2022), and the transcription of genes (Kolady & Wang, 2026). Histone alterations have varying durations based on their chemical makeup (Molina-Serrano et al., 2019). Phosphatases can easily reverse phosphorylation, however tri-methylated lysine alterations might last for a long time (Molina-Serrano et al., 2019). Histone demethylases (HDMs), or lysine demethylases (KDMs) and histone deacetylases (HDACs) remove acetyl and methyl groups from lysine, respectively (Sterling et al., 2021).

A few unique characteristics have been inferred from correlations between gene activity and histone modifications along transcription units based on research in various cell types. Histones H4 and H3 have acetylated lysine, and gene promoters are often identified by H3K4me3 (Koestler et al., 2024). H3K36me3 frequently marks the gene body of activated genes (Koestler et al., 2024). A sign of transcription is the presence of H3K4me3 at the promoter and H3K36me3 over the gene body which has been utilised to find novel genes (Paro et al., 2021). On the other hand, genes with H3K9me2 or H3K9me3 are typically transcriptionally inactive (Padeken et al., 2022). The activity of PcG polycomb complexes, which are well-known repressors of developmentally regulated genes, is also linked to H3K27me3 and H2AK119ub (Chen et al., 2021). These marks may also co-occur with the active mark H3K4me3 in progenitor cells and embryonic stem cells (Seneviratne et al., 2026). Bivalent chromatin at promoters with seemingly active H3K4me3 and repressive H3K27me3 alterations have been found as a result of this study (Seneviratne et al., 2026). During development, distinct gene expression patterns are produced by dynamic changes in chromatin state (Kazakevych et al., 2017). Transcription factors, enhancers, and promoters establish transcriptional regulatory circuits with the help of chromatin modifiers in open chromatin areas (Mazina & Vorobyeva, 2021).

Furthermore, it has been demonstrated through research that they are essential components of trans-regulatory elements, or transcriptional regulatory circuits (Shibata et al., 2015). DNA methyltransferases (DNMTs), histone modifiers including histone methyltransferases (HMTs) and HDACs and chromatin-remodeling complexes are classified as chromatin moderators (Carlberg & Molnár, 2016). Human health and disease may be impacted by this regulation's substantial effects on chromatin accessibility and transcription factors capacity on the DNA (Mansisidor & Risca, 2022). A class of enzymes known as chromatin modifiers is important for DNA and histones modification (Nieborak & Schneider, 2018). They aid in the chemical transformation of pyrimidine and amino acid residues, including tyrosine, lysine, serine, and arginine in histones and cytosine in DNA (Nieborak & Schneider, 2018). The modifiers control crucial gene expression during each development cycle and differentiation by interacting with transcription factors, cofactors, *CTCF*, and DNA-related regulatory elements (Arcipowski et al., 2016; Dehingia et al., 2022). Chromatin modifiers alter the size of the chromatin open region by controlling the amount of physical interaction between chromatin DNA and cis-regulatory factor-transcription factor (Vachon et al., 2018). Consequently, transcription factor binding to gene enhancers and promoters is either encouraged or inhibited (Vachon et al., 2018). Cell type dynamic and particular gene expression properties are conferred by this regulation (Klein & Hainer, 2020). The necessity for additional research into the processes mediated by modifiers is highlighted by the growing evidence that aberrant alterations are closely associated with disease (Rezazadeh et al., 2025). Modifications associated with histones are primarily categorized as "writers, erasers, readers" (Kim et al., 2023). HATs, HDACs, HMTs, histone demethylases (HDMs), histone phosphorylases, and others are examples of histone-modifying enzymes (Kim et al., 2023). In order to relax or tighten the chromatin in response to external stimuli, writers resort to enzymes that control histone modification (Marmorstein & Zhou, 2014). By relaxing DNA's binding to the nucleosome and increasing the open region of chromatin, the modifiers control gene expression (Zhang et al., 2023). However, they may cause chromatin condensation, with a consequent reduction of the open region, thus hindering access to the promoter, and impairing transcriptional regulation (Teijido, 2019).

Histone phosphorylases modify the delicate structure of chromatin, which affects transcriptional control, and provide histones a negative charge, which facilitates the interaction of chromatin regulatory mechanisms with transcription factors (Cao & Dang, 2018). DNA repair, mitosis, and cell-cycle regulation are linked to HMTs, which aid in histone methylation and alter histone arginine or lysine residues (Des Jarlais & Tummino, 2016). They also contribute to chromatin status maintenance (Des Jarlais & Tummino, 2016). In normal cells, precise transcriptional regulation is made possible by the balance of HMT and HDM activity (Tweedie-Cullen et al., 2012). However, transcriptional regulation is impeded when this equilibrium is upset (Tweedie-Cullen et al., 2012). DNMTs are involved in transcriptional control, gene expression, and DNA methylation regulation (Tajima et al., 2022). By covalently attaching the methyl group of S-adenosylmethionine to the cytosine base, DNMTs aid in DNA methylation (Tajima et al., 2022). This regulatory activity, which suppresses chromatin and gene expression, is primarily found in the promoters of genomes rich in CpG islands (Tajima et al., 2022). Through methylation, several protein families have distinct transcriptional regulatory functions. ATPases are used by ATPase-dependent chromatin-remodeling complexes to hydrolyse ATP. Histone–DNA connections are disrupted by the energy generated by ATP. The dynamic sliding or repositioning of nucleosomes to attract transcriptional coactivators and corepressors to DNA promoters for epigenetic regulation is made possible by the non-covalent regulation of local or global chromatin architecture. The changed transcriptional regulatory circuit, post-transcriptional regulation, and protein translation process are all impacted by chromatin modifiers, which are also a component of the epigenetic regulators linked to chromatin accessibility.

When subjected to external stimuli, chromatin modifiers display distinctive modifications (Pecinka & Mittelsten Scheid, 2012). They alter chromatin accessibility to either enhance or reduce the amount of physical contact between chromatin DNA and transcriptional regulatory circuits (Pecinka & Mittelsten Scheid, 2012). These changes may lead to organ dysfunction, impact the prognosis of disorders, and raise the risk of linked illnesses (Costello & Schones, 2018). Mutations in gene loci are brought on by changes in the internal or external environment, and they can even trigger a variety of diseases. A few instances are the formation of aberrant DNA hybrids, transcription-replication conflict in oncogenes, and the promotion of DNA transcription in the S phase

when *KMT5B* (HMT) is deleted in muscle stem cells (Liu et al., 2026). Rhabdomyosarcoma develops as a result of the ongoing stimulation and proliferation of dormant muscle satellite cells (Liu et al., 2026). According to research, chromatin modifiers may influence pathophysiological processes like glycolipid metabolism, oxidative stress, inflammatory response, and programmed cell death, which could lead to the development and progression of cardiovascular illnesses (Bauer & Martin, 2017). Neurodevelopmental diseases are tightly associated with chromatin modifiers. Research has verified that individuals with mutations in the HMT *SETD2* gene exhibit skeletal system abnormalities, intellectual incapacity, and developmental delay (Wu et al., 2023). Similarly, microcephaly is linked to mutations in the area between HMT *NSD1* exons 10 and 22, indicating a close relationship between histone methyltransferases and neurodevelopmental diseases (Romero et al., 2022). Chromatin modifiers may serve as biomarkers and diagnostic targets in clinical medicine (Hlady & Robertson, 2016). They have the potential to be predictors of both disease prognosis and therapeutic development (Liu et al., 2023; Paul et al., 2021). Chromatin's reversible properties allow for the development of therapeutic approaches which render the altered gene expression and chromatin structure back to normal (Upadhyaya, 2026). Table 1 outlines human epigenetic genes by their biochemical roles.

3. ROLE OF EPIGENETICS IN GENOME MAINTENANCE AND DISEASE

The heritable, regulatory components of a genome that are distinct from its fundamental DNA sequence are referred to as epigenetics (Saini et al., 2023). The most well-known epigenetic markers are DNA methylation and post-translational changes of key histone proteins (Zhang et al., 2023). Epigenetic marks are widely acknowledged as heritable chemical alterations of DNA and chromatin that cause chromatin structural changes that impact gene activity and have widespread impacts on genomic integrity (Kumar et al., 2018). Enzymes and epigenetic markers play a variety of roles in retaining genetic material, including nucleotide sequences like repeating motifs (Fitz-James & Cavalli, 2022), preventing DNA damage (Karakaidos et al., 2020), playing a role in chromatin restoration (Rudenko & Tsai, 2014) and DNA repair processes (Fernandez et al., 2021), and determining chromosomal architecture through centromere effects (Wong et al., 2020). Chromatin structure provides the systematic packing and organization of a cell's enormous amount of DNA, which is necessary to control genetic information. DNA methylation is a covalent alteration of DNA that mostly takes place in vertebrates at the carbon-5 position of cytosine nucleotides followed by a guanine (CpG) (Wu & Lu, 2019). DNA methylation patterns are localized and tightly linked to transcriptional regulation (Rimoldi et al., 2024) and are localized to domains of heterochromatin (Grewal, 2023). Cellular function depends on the establishment of appropriate DNA methylation patterns and their maintenance during mitotic division (Ming et al., 2021). By using diverse methods, the DNA methyltransferases (DNMT) *DNMT1*, *DNMT3A*, *DNMT3B*, and *DNMT3L* actively contribute to and determine the DNA methylation patterns in human cells (Tajima et al., 2022). Methyl-CpG-binding proteins, such as *MBD1*, *MBD2*, *MBD3*, and *MeCP2*, interpret DNA methylation marks. These proteins typically suppress gene expression and attract histone deacetylases (HDACs), which are necessary for chromatin condensation (Musselman et al., 2019; Leighton, 2020). DNA methylation is determined by factors and stimuli which determine how methylation patterns are established spatio-temporally. Research conducted on Arabidopsis demonstrates a direct correlation between the patterning of DNA methylation and nucleosome placement along DNA (Rothi et al., 2020). Similarly, post-translational changes that control DNA methylation patterns, chromatin rearrangement, and transcriptional effects are present in the histones that make up the nucleosome core (Jiang et al., 2026). The stability of microsatellites within the genome has been linked to DNA methylation and DNA methyltransferases, allowing for genome integrity (Sriraman et al., 2020).

Repetitive regions of DNA can expand or shrink when single-stranded DNA is exposed, leading to the formation of secondary structures, such as DNA hairpins (Li et al., 2025). This often occurs during processes like replication, transcription, and DNA repair (Li et al., 2025). These structures may be incorrectly resolved by the mismatch repair system or can cause DNA polymerases to slip during replication, leading to errors (Chakraborty & Alani, 2016). Epigenetic mechanisms help prevent microsatellite instability in two ways: directly and indirectly. For example, disrupting DNA methylation or the DNA methyltransferases (DNMTs) can destabilize repetitive sequences through changes in chromatin structure, such as increased transcription, or through other unknown mechanisms (Sepehri et al., 2019; Pappalardo & Barra, 2021). DNA methylation can also impact the stability of repeats indirectly by causing widespread changes in gene expression, which in turn affects the activity of proteins involved in maintaining repeat stability, such as those in the mismatch repair (MMR) system (Dhar et al., 2021). When genes near or within microsatellites are transcribed, it can lead to the formation of single-stranded DNA structures that might be incorrectly repaired by the MMR process. DNA methylation might help stabilize these regions by reducing the likelihood of their transcription (Pandiloski et al., 2024). Additionally, *DNMT1* influences the suppression of gene expression and microsatellite instability (MSI) by altering the structure of chromatin (Kim, 2025). After DNA replication, *DNMT1* contributes to the suppression of gene activity and the tightening of chromatin structure by working with histone deacetylases *HDAC1* and *HDAC2* (Holloway & Kingsley, 2024). DNA methylation and the organization of chromatin have a strong impact on other types of genomic instability, such as mutations and rearrangements of chromosomes (Kovalchuk, 2021). Knockout studies showed that when Dnmt1 was ablated in mouse embryonic stem cells, there was a significant increase in gene mutations, deletions, and missing chromosome parts (Liao et al., 2015). Similarly, when both *DNMT1* and *DNMT3B* were knocked out in cancer cell lines, there were large, random changes in chromosomes, including translocations and an abnormal number of chromosomes (Scelfo et al., 2024). DNA methylation is known to help prevent a type of

repair process called non-canonical homologous recombination (HR), which is involved in many mutation events (Zhao et al., 2025). This is because transcription increases the frequency of HR by making single-stranded DNA available for it to pair with a matching sequence. On the other hand, DNA methylation leads to reduced transcription, which in turn lowers the probability of HR taking place. After a DNA double-strand break (DSB) occurs, homologous recombination (HR) is used to create a connection between similar chromosomes. This process can lead to changes such as gene conversion, insertion of new DNA, deletion of existing DNA, or larger loss of chromosomal material (Northall et al., 2016). *DNMT1* plays a role in repairing DSBs, which is separate from its usual function of maintaining DNA methylation (Wu et al., 2025). Proliferating cell nuclear antigen (*PCNA*) is involved in several DNA repair mechanisms, including mismatch repair and nucleotide excision repair (Hosalkar et al., 2018). *DNMT1* is also found to support this repair function (Ding et al., 2016). The repair of DSBs happens within the complex structure of chromatin, and it helps restore both the structure and the epigenetic features at the damaged DNA site (Chiaramida et al., 2026). Chromatin remodeling, similar to the repair of DNA, plays a key role in maintaining the stability of the genome (Luo et al., 2026). When DNA is damaged, the chromatin structure becomes less condensed, which opens it up and allows repair mechanisms to access the damaged DNA (Stadler et al., 2017). This process of chromatin remodeling after DNA damage is also controlled by the DNA damage checkpoint kinase *CHK1*. In healthy, undamaged cells, *CHK1* is attached to the chromatin and specifically adds a phosphate group to histone H3 at threonine 11 (H3T11), which helps increase the acetylation of histone H3 at lysine 9 (H3K9) (Smits & Gillespie, 2015). This helps ensure that genes involved in controlling the cell cycle remain active and functional. A properly functioning centromere is essential for preventing chromosomal instability during cell division (Nassar et al., 2023). It ensures accurate segregation of DNA, stops chromosomal rearrangements, and avoids changes in the number of chromosomes (Nassar et al., 2023). Cytologically, the centromere is seen as a narrow region of the chromosome, but it actually has a distinct and complex arrangement of chromatin at the molecular level (Fukagawa, 2012). The chromatin in the centromere forms a tightly packed structure that serves as a site for attaching kinetochore proteins and spindle microtubules (Chu et al., 2014). The chromatin surrounding the centromere, known as pericentromeric chromatin, has a high concentration of cohesin molecules, which helps in connecting sister chromatids (Natsume et al., 2013). Epigenetic factors that determine the centromere are beneficial because they offer a dependable way to pass on genetic material even if there is some mutation, unlike specific DNA sequence-based determinants. Both centromeric and pericentromeric chromatin have unique and largely different patterns of histone modifications that are essential for the proper functioning of the centromere (Biggs et al., 2025). Centromeric heterochromatin contains a characteristic combination of both euchromatic and heterochromatic marks (Morrison & Thakur, 2021). For example, condensed transcriptionally inert heterochromatin is defined by H3K9 di- and tri-methylation, but immunofluorescence studies showed that centromeric chromatin, despite being highly condensed, does not contain these marks (Sullivan & Karpen, 2004). The equilibrium between open and condensed structural baselines is underlying principle of how local chromatin configurations define the elementary functions of the genome. Figure 1 illustrates chromosomal organization, the trans-actions of chromatin regulators (left) are translated into, histone marks and structural variants (right) define the epigenetic foundation required for structure and mitotic segregation. When these highly coordinated homeostatic baselines are lost, the structural instability they foster poses a direct threat to the overall maintenance of the genome and leads to the development of complex clinical phenotypes (Zoghbi & Beaudet, 2016).

Definitive proof that epigenetics plays a role in human diseases has emerged once the concept of genomic imprinting was understood and it was found that several genes are controlled by this process (Chakrabarti & Chattopadhyay, 2024). Conditions such as Beckwith–Wiedemann syndrome (BWS), pseudohypoparathyroidism (PHP), and Silver–Russell syndrome (SRS) added more examples and raised many interesting questions about how epigenetic issues can lead to specific disease characteristics. Similar to genetic mutations, epigenetic changes, or epimutations, can either have no effect or cause disease, and they can occur frequently or rarely (Farsetti et al., 2023). Epigenetic changes involve changes in DNA methylation and/or differences in how histones are modified. Areas of the genome that are imprinted are especially prone to diseases mainly because the genes in these regions express from only one copy, rendering the single active allele crucial. An example is Prader-Willi syndrome (PWS; OMIM 176270) and Angelman syndrome (AS; OMIM 105830), which are mostly caused by the same 5- to 6-Mb deletion in the 15q11-q13 region (Szabadi et al., 2022; Ouskri et al., 2026).

However, the symptoms of these two conditions are very different due to genomic imprinting. In PWS, the deletion is inherited paternally, while in AS, the deletion is maternal. The lack of pigmentation, or hypopigmentation, is due to a deficiency in a gene (*OCA2*) that is not subject to imprinting (Neissi et al., 2025). This deficiency appears in individuals who have the deletion. About 70% of PWS cases are caused by paternal deletions in 15q11-q13, while 70% of AS cases result from maternal deletions in the same region. About 25% of PWS cases result from maternal uniparental disomy (UPD) of the 15q11-q13 region (Kim et al., 2025), while paternal UPD of the same area is responsible for 2% to 5% of AS cases (Mathews et al., 2020). Imprinting defects are another type of mutation that can lead to PWS or AS symptoms (Ma et al., 2023). These defects occur when a chromosome from one parent has an altered epigenetic profile, usually resembling the chromosome from the other parent. Imprinting defects often involve the deletion of the imprinting center (IC), but there are cases where the cause is an epigenetic change that does not affect the DNA sequence itself (Butler & Duis, 2020). The effects of these imprinting defects-whether due to imprinting center deletion or changes in the epigenetic makeup of the region-are similar to those seen in larger deletions in the imprinted area or in uniparental disomy. At the

chromatin level, these defects lead to changes in DNA methylation, histone post-translational modifications, chromatin structure, and ultimately, gene expression patterns (Weaver & Bartolomei, 2014). These pathogenic variations are consistent with the broader molecular themes of locus-specific changes in chromatin structure as illustrated in Figure 2. (A). The switches occur via two contrasting mechanisms: either through repeat expansion and subsequent dense CpG hypermethylation of (usually) heterochromatic transition, as exemplified at the *FMR1* gene. (B). The repeat contraction and subsequent collapse of regional Polycomb-mediated repression, resulting in an unlocked euchromatic conformation with hyperactivation of transcription factors, as exemplified at the 4q35 array.

Unlike these otherwise generic repeat-dependent switches, parent of origin imprinting conforms to specific regional epigenetic constraints. Extensive locus mapping within these unique domains has been crucial for isolating single-gene causes in complex neurodevelopmental disorders. These specific locus-mapping results, along with human data, identify the *UBE3A* gene as the cause of AS. Both paternal uniparental disomy and maternal deletions in the 15q11-q13 region result in the loss of *UBE3A* expression in Purkinje cells (Frohlich et al., 2019).

It seems that an antisense transcript, which is normally expressed from the paternal chromosome in the imprinting center region, is instead expressed from the maternal chromosome due to an imprinting defect, leading to reduced expression of *UBE3A* (Lopez et al., 2019).

The increasing number of human diseases linked to mutations in genes that encode proteins involved in chromatin structure and remodeling emphasizes the significance of properly regulated chromatin structure for human health (Liang & Wan, 2026). These conditions are not caused by direct epigenetic sequence mutations, but rather by genetic mutations in genes that later affect global chromatin states which are essential parts of the epigenotype. Rubinstein–Taybi syndrome (RSTS; OMIM 180849) is characterized by intellectual disability, broad thumbs and toes, facial abnormalities, congenital heart defects, and increased risk of tumor formation (Milani et al., 2015). Cytogenetic abnormalities involving 16p13.3 were identified in several RSTS patients and found to map to the region that contains the CBP (or *CREBBP*) gene (Lai et al., 2012). Heterozygous mutations in *CREBBP* showed that haploinsufficiency of CBP causes RSTS (Korzus, 2017). CBP is a coactivator of the cAMP-responsive binding protein, CREB. Once bound, CBP, in turn, activates transcription from a cAMP response element–containing promoter through the acetylation of all four core histones in the adjacent nucleosomes (He et al., 2021). CBP also interacts through a region in its carboxyl terminus directly with the basal transcription factor *TFIIIB* (Garg et al., 2019). In vitro functional analysis of one of the CBP missense mutations (Arg-1378 to proline) that cause RSTS revealed that this mutation abolishes the histone acetyltransferase (HAT) activity of CBP (Cross et al., 2020). Consistent with the role of decreased HAT activity in disease is the discovery that mutations in a second gene, *p300*, encoding another potent HAT and transcriptional coactivator, cause some cases of RSTS (Cacabelos, 2019). The aberrant pregnancy known as complete hydatidiform mole (CHM) or recurring hydatidiform mole 1 (OMIM 231090) is characterized by hyperproliferative vesicular-appearing trophoblasts, or extraembryonic tissue, but no embryonic development (Carey et al., 2015). Due to the high levels of human chorionic gonadotropin secreted by the molar tissues, individuals may experience additional symptoms, such as early-onset preeclampsia, and CHM may develop into an invasive and malignant condition (Otto et al., 2026). The fertilization of an egg without a functioning nucleus is proposed to be the source of most CHMs, which are androgenetic (made exclusively of DNA of paternal origin) (Fisher & Sebire, 2017). This was demonstrated by multiple studies that revealed loss of methylation at the differentially methylated regions of the majority of paternally expressed, maternally imprinted genes, similar to what is observed in andro-genetically inherited moles (Demond et al., 2019). The *NLRP7* gene is homozygously mutated in women with recurrent biparental CHM (BiHM) (Fallahi et al., 2019). *NLRP7* is a cytoplasmic protein that belongs to the nucleotide oligomerization domain-like family (Carriere et al., 2021). It has a carboxy-terminal leucine-rich repeat region, an amino-terminal pyrin domain, and a NACHT domain that is present in proteins involved in apoptosis (Carriere et al., 2021). Biallelic mutations in *C6orf221* (also known as KHDC3L) are now classified as HYDM2 (OMIM 614293), suggesting that the gene regulates oocyte genomic imprinting (Sanchez-Delgado et al., 2015). A rare autosomal recessive chromosomal breakage disorder is known as ICF syndrome (OMIM 242860) (Martins-Ferreira & Ballestar, 2025). Immunodeficiency and cytogenetic abnormalities are the two invariant characteristics that ICF patients exhibit (Ehrlich et al., 2008). Craniofacial abnormalities, such as a broad and flat nasal bridge, epicanthal folds, high forehead and low-set ears, psychomotor delay, and intestinal dysfunction, are very varied and less penetrating phenotypes. The most prevalent immunological abnormality is a drop in serum IgG levels, although B or T cell counts can also be reduced (Weemaes et al., 2013). Routine karyotype examination of ICF patients' blood and cultured cells reveals abnormalities in chromosomes 1 and 16, and to a lesser extent in chromosome 9 (Arunachalam et al., 2023). Long before the gene responsible for ICF was discovered, hypomethylation of juxta-centromeric repeat regions on chromosomes 1, 9, and 16 was noted (Velasco et al., 2014). Near their centromeres, these chromosomes have the biggest blocks of satellite tandem repeats. A decrease in methylation at centromeric satellites 2 and 3 was explained by the discovery that loss-of-function mutations in the de novo DNA methyltransferase gene (*DNMT3B*) cause ICF (Cho et al., 2024). Studies show that cells from ICF patients have reduced methylation patterns at the promoters of several genes (Velasco et al., 2018). A decrease in restrictive H3K27 tissue dynamics and an increase in activating H4K9 acetylation and H3K4 trimethylation markers accompanied these methylation alterations, which leads to an increase in gene expression (Unoki, 2024). DNMT3B gene deletion increases the quantity of proto cadherins (PCDH) expressed in

single Purkinje cells (Toyoda et al., 2014). Similar to neuronal "short-circuiting," the PCDH decrease leads to aberrant dendritic arborization which is harmful to the development of completely functional neural circuitry (Garrett et al., 2012).

It is becoming more evident that, in cases without exonic mutations, epigenetic alterations can also impact gene expression in cis and cause various Mendelian illnesses (Fahrner & Bjornsson, 2014). The most prevalent single-gene illnesses worldwide are thalassemias (Sadiq et al., 2024). Reduced amounts of one or more hemoglobin globin chains are the cause of this diverse set of hemoglobin production diseases (Sadiq et al., 2024). Abnormal erythropoiesis and severe anemia are caused by an imbalance in the synthesis of different globin chains (Kaur et al., 2024). Although hundreds of coding and splicing mutations have been found, it was the deletions of regulatory regions that demonstrated how chromatin structure alterations can account for certain thalassemia subtypes (Ferrer-Benito et al., 2025). In particular, the deletion of 100 kb upstream of the α-globin gene (while leaving the gene intact) caused γδβ-thalassemia and helped identify the locus control region (LCR) that regulates β-globin expression (Lee et al., 2021). Deletions resulted in an altered chromatin state at the β-globin locus despite being tens of kilobases upstream of the coding region. Continued research has, particularly, brought an understanding of epigenetic gene control from a chromatin topological and nuclear organizational point of view, showing how chromatin looping can bring distal regions together to ensure correct gene regulation (Corso-Díaz et al., 2018).

The impact of these epigenetic anomalies can manifest locally on a specific gene locus or globally across the host genome. Table 2 compares genetic disorders that affect chromatin structure via cis or trans mechanisms.

4. CLINICAL MANIFESTATIONS AND PHENOTYPES IN CHROMATINOPATHIES

Chromatinopathies, also termed Mendelian disorders of the epigenetic machinery (MDEMs), encompass a class of over 100 rare neurodevelopmental disorders caused by germline mutations in dosage-sensitive genes encoding epigenetic writers, erasers, readers, and chromatin remodelers (Fahrner & Bjornsson, 2019; Vos et al., 2024). These regulatory complexes function in trans in a way to orchestrate gene expression globally and impairments lead to diverse broad-spectrum, pleiotropic multisystemic phenotypes. Despite unique molecular causes, patients display clinical intersection with a typical constellation of features with the majority of individuals affected by central nervous system, craniofacial, growth, and general systemic abnormalities (Bukowska-Olech et al., 2024; Kerkhof, Squeo, et al., 2021; Koparir et al., 2026; Marchetti et al., 2026).

A. Neurodevelopmental and Cognitive Profile

Global developmental delay and variable intellectual disability (mild to severe) is the phenotypic hallmark of MDEMs, with abnormal synaptic plasticity and disruption of the excitation-inhibition balance (Vos et al. 2024).

Behavioral disturbances affect roughly two-thirds (~68%) of individuals across cohorts, the majority of which are characterized by autism spectrum traits, hyperactivity, anxiety, and sleep disturbances (Marchetti et al., 2026). Behavioral signatures sub-phenotypes associate with specific syndromes: elevated clinical thresholds for anxiety are observed in the *KMT2D* or *KDM6A*-variant form of Kabuki syndrome, whereas hyperactivity and emotionality and impairments in sleep circadian regulation define Wiedemann-Steiner syndrome (*KMT2A*) (Marchetti et al., 2026; Vos et al., 2024). Neurologic impairments are most common: from 73% up to 93% of all the aforementioned chromatinopathies manifest neurologic dysfunction.

Neuroimaging frequently highlights CNS anomalies, with recent large-cohort data demonstrating brain Magnetic Resonance Imaging abnormalities in up to 82.7% of patients (Marchetti et al., 2026). Frequent anomalies include corpus callosum thinning, ventriculomegaly, or delayed myelination (Goel, 2026; Marchetti et al., 2026).

B. Craniofacial and Morphological Dysmorphism

Unique dysmorphic signs can be used for clinical diagnosis, serving as teratological macroscopic signs of a structural gene dysregulation during very first phases of embryogenesis (Kerkhof, Squeo, et al., 2021, Parenti & Kaiser, 2021). The forewarned signs are the recognisable facial allants, micro and macrocephaly along with isolated skeletal, hand and foot malformations (Avagliano et al., 2020, Bukowska-Olech et al., 2024).

Common features include low-set ears, slanted palpebral fissures, broad or depressed nasal bridges, and specific mouth or lip shapes. In the classic paradigm of Cornelia de Lange syndrome (CdLS), cardinal features include synophrys, thick eyebrows, a short nose with an upturned nasal tip, a long or smooth philtrum, and a thin upper lip vermilion (Parenti & Kaiser, 2021). Dental anomalies commonly manifest as macrodontia and widely spaced teeth (Bukowska-Olech et al., 2024; Melo et al., 2022). Skeletal anomalies include hand or foot oligodactyly or adactyly, prominent clinodactyly of the fifth finger, persistent foetal finger pads, and delayed bone age (Marchetti et al., 2026; Parenti & Kaiser, 2021).

C. Growth Deviations: Growth Restriction versus Somatic Overgrowth

An example of the classical paradigm of chromatinopathies includes aberrant bidirectional regulation of physical growth, also demonstrating the highly dosage-sensitive nature of growth-related tissues to specific epigenetic changes (Fahrner & Bjornsson, 2019).

Long-term phenotype tracking show aberrant growth curves that can feature absent or attenuated pubertal height spurt usually in combination with advanced or delayed skeletal maturation (Goel, 2026; Marchetti et al., 2026; Parenti & Kaiser, 2021).

Prenatal and postnatal growth deficiency paired with microcephaly are common to conditions like CdLS and Kleefstra syndrome (Marchetti et al., 2026; Parenti & Kaiser, 2021). As many as 72% of the patients investigated for immunological abnormalities present with deep hypogammaglobulinemia (Schoch et al., 2026). Selective IgA deficiency (78.5%) and a certain loss of memory B cells (CD19CD27, 86%) are the most frequent abnormalities, recorded among some writers such as KMTs and KATs (Marchetti et al., 2026; Schoch et al., 2026).

Conversely, loss-of-function variants in repressive epigenetic machinery-such as the polycomb repressive complex 2 (PRC2) component *EZH2* in Sotos syndrome-cause accelerated skeletal maturation and paradoxical somatic overgrowth (Fahrner & Bjornsson, 2019; Marchetti et al., 2026). Interestingly, patients with overgrowth phenotypes like Sotos syndrome often retain significantly higher median IQs compared to those with severe growth restriction (Marchetti et al., 2026).

D. Immunological and Infectious Phenotypes

Recently, systemic surveillance has revealed a systemic immune dysregulation that had not been previously appreciated in different cohorts (Schoch et al., 2026). Recurrent, infections are reported in 35%–37% of individuals, predominantly presenting as respiratory infections like otitis media and pneumonia (Schoch et al., 2026). Up to 72% of the patients investigated for immunological abnormalities present with deep hypogammaglobulinemia (Schoch et al., 2026). Selective IgA deficiency (78.5%) and a certain loss of memory B cells (CD19CD27, 86%) are the most frequent abnormalities, recorded among some writers such as KMTs and KATs (Marchetti et al., 2026; Schoch et al., 2026).

This clinical immunodeficiency state frequently mimics Common Variable Immunodeficiency (CVID) and is most pronounced in ICF syndrome type 1 and Kabuki syndrome type 1 (Schoch et al., 2026).

E. Systemic and Multi-Organ Involvement

Over half of the cohorts profiled (Marchetti et al., 2026) are impacted by congenital abnormalities affecting heart structure - for instance the ventricular and atrial septal defects.

These commonly include cryptorchidism, renal anomalies, severe gastroesophageal reflux, and diaphragmatic hernias (Bukowska-Olech et al., 2024; Marchetti et al., 2026). Caused by variants in cohesin-related genes (*NIPBL, SMC1A, SMC3, HDAC8, RAD21*), conditions like CdLS are characterized by synophrys, a long or smooth philtrum, severe growth restriction, and limb reduction defects (Bukowska-Olech et al., 2024; Minale et al., 2026).

Rubinstein-Taybi Syndrome (RSTS): Caused by mutations in *CREBBP* or *EP300*; marked by broad thumbs and toes, distinctive facial features, and intellectual disability (Di Fede et al., 2021).

Kabuki Syndrome: Caused by variants in *KMT2D* (Type 1) or *KDM6A* (Type 2); features long palpebral fissures with eversion of the lower lateral eyelid, skeletal anomalies, and persistence of fetal finger pads (Carosso et al., 2019; Goel, 2026; Jans et al., 2026).

Wiedemann-Steiner Syndrome (WDSTS): Caused by *KMT2A* variants; recognized by hairy elbows (hirsutism cubiti), short stature, and distinctive facial dysmorphism (Di Fede et al., 2021).

KBG Syndrome: Caused by *ANKRD11* mutations; characterized by macrodontia of the central upper incisors, short stature, and developmental delay (Melo et al., 2022).

Chromatinopathy syndromes are organized by assigned epigene, OMIM number, and mode of inheritance are represented in Table 3.

5. EPISIGNATURES IN CHROMATINOPATHIES

Genetic perturbations in non-DNA chromatin-regulatory complexes generate a specific molecular signature on the host genome, even in the absence of mutations in the core machinery of the DNA methyltransferases themselves (Fahrner & Bjornsson, 2019; Wojcik & Fahrner, 2024). The crosstalk between all components of the epigenetic environment is responsible for the different DNA methylome signatures driven by mutant histone modifiers or ATP-dependent chromatin-remodeling complexes.

For example, methyl-CpG-binding domain (MBD) proteins act as a bridge by recognizing methylated cytosines and subsequently recruiting multi-protein co-repressor complexes, such as histone deacetylases (HDACs) and histone methyltransferases.

When subunits of these interconnected chromatin complexes-such as the SWI/SNF (BAF) chromatin remodeling complex-are structurally altered, the equilibrium between open euchromatin and condensed heterochromatin is disrupted. This structural disequilibrium alters the physical accessibility of the DNA strand to native DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) dioxygenases. This secondary epigenetic perturbation presents as a unique, highly reproducible, and syndrome specific, constellation of aberrant methylation signatures throughout the genome at particular cytosine-phosphate-guanine (CpG) locations called an episignature (Sadikovic et al., 2020). Based on genome-wide methylation profile (DNAm), these signatures or "footprints" originate from pathogenic variations associated with known syndromic conditions in approximately 154 different epigenes (Levy et al., 2022). They are typically delineated in genomic DNA isolated from PBMCs by using high-density microarrays such as the Infinium Methylation EPIC microarrays of the Illumina platform, offering a functional downstream molecular biofluid signature of cellular chromatin disbalance (Aref-Eshghi et al., 2020; Sadikovic et al., 2020).

Hierarchical Stratification of Episignatures

Episignatures exhibit an ultra-high resolution throughout the hierarchy of protein complexes to single genes and up to sub-gene domains (Levy et al., 2022). Unsupervised and supervised clustering models demonstrate that individual chromatinopathies can be clearly separated into tight, non-overlapping epigenetic clusters that reflect the specific tier of the epigenetic machinery that is impacted. (Aref-Eshghi et al., 2020).

Chromatin Remodeling Complexes (The BAFopathies): Unique signatures for SWI/SNF complex defects such as those manifesting in Coffin-Siris and Nicolaides-Baraitser syndromes (Aref-Eshghi et al., 2020). Shared indistinguishable episignatures are observed in phenotypically related conditions such as Coffin-Siris syndrome and Nicolaides-Baraitser syndrome that arise from mutations in different genes in the complex, including *ARID1B, SMARCB1, SMARCA4* and *SMARCA2* (Aref-Eshghi et al., 2020; Levy et al., 2022). Mutations in *SRCAP* are associated with Floating-Harbor syndrome and *ATRX* abnormalities with profiles in alpha-thalassemia X-linked intellectual disability.

Histone Methylation Machinery: Machine-learning classifiers identify precise profiles for Kabuki syndrome type 1 (*KMT2D*) and type 2 (*KDM6A*), while *KMT2C* loss shows a profile distinct from Kleefstra syndrome (Aref-Eshghi et al., 2020; Levy et al., 2022).

Direct DNA Modifiers: Variations in maintenance or removal enzymes lead to recognizable patterns like *TET3* deficiency in Beck-Fahrner syndrome (Levy et al., 2021) and *DNMT3A* hypomethylation in Tatton-Brown-Rahman syndrome.

6. CURRENT TREATMENT OPTIONS

At present, no curative therapies have been approved for the treatment of chromatinopathies, therefore the standard of care currently involves personalized, symptom-specific treatment that is dictated by a team of specialists (Fahrner & Bjornsson, 2019). Early enrolment in speech, physical, behavioral, and occupational therapies is critical to optimize synaptic plasticity (Harris et al., 2020). Psychiatric comorbidities like severe anxiety, ADHD, and epilepsy are managed using standard psychopharmacology, though response rates vary due to high syndromic heterogeneity (Butcher et al., 2021).

Drug tolerability is highly syndrome-specific. For instance, higher-dose olanzapine has demonstrated clinical efficacy in reversing severe neurodevelopmental regression and sleep disruption in Kleefstra syndrome by mitigating astrocyte-driven neuronal network hyperactivity (de Boer et al., 2023). Conversely, patients presenting with *ARID1B*-related Coffin-Siris syndrome frequently exhibit poor tolerability to alternative low-dose sedatives like clonazepam (Vals & Öunap, 2014). Routine monitoring is essential for structural complications. Standard interventions include the surgical correction of congenital heart defects, orthopedic bracing for progressive scoliosis, and aggressive nutritional support (e.g., gastrostomy tubes) to counteract severe postnatal growth failure, feeding difficulties, and potential malignancy risks (Bogers et al., 2022). In cohorts exhibiting profound hypogammaglobulinemia, memory B-cell deficiencies, and recurrent respiratory infections (such as Kabuki or ICF syndromes), prophylactic antibiotic regimens and regular intravenous or subcutaneous immunoglobulin (IVIG/SCIG) infusions are widely utilized to prevent chronic pulmonary infections (Hoffman et al., 2018; Margot et al., 2020).

The underlying chromatin topology, histone marks and DNA methylation pattern is not fixed in contrast to classical genetic diseases due to permanent structural DNA errors, but still can be altered throughout the life (Bjornsson, 2015). This remarkable postnatal malleability can be targeted chemically to restore global transcriptional balance and baseline chromatin accessibility (Gabrielli et al., 2022). Also, HDACis, which are the leading experimental approach to address highly restricted chromatin states, is listed (Graff & Tsai, 2013).

Preclinical mouse models of Rubinstein-Taybi syndrome (*CREBBP/EP300* deficiency) and Kabuki syndrome type 1 (*KMT2D* deficiency) demonstrate that structural memory deficits, aberrant DNA methylation balances, and impaired hippocampal neurogenesis can be rescued postnatally (Alarcón et al., 2004; Bjornsson et al., 2014). Small-molecule inhibitors such as AR-42 and vorinostat block the enzymatic removal of acetyl groups, successfully compensating for defective intrinsic acetyltransferase or methyltransferase machinery (Kerkhof, Levy, et al., 2021).

In KMT2D mouse models, the administration of TAK-418-a highly selective, brain-penetrant lysine-specific demethylase 1A (KDM1A/LSD1) inhibitor-successfully normalized spatial memory deficits and adult neurogenesis without inducing hematological toxicity, establishing a vital template for resetting aberrant histone methylation profiles (Carosso et al., 2019; Miyamoto et al., 2022). Additional frameworks are actively investigating bromodomain and extra-terminal (BET) domain inhibitors as well as direct histone acetyltransferase (HAT) targeting (Arrowsmith et al., 2012). Existing drugs that target the action of the DNA modifiers may be repurposed for the treatment of certain chromatinopathies. Currently, the low-molecular-weight small molecules azacitidine and decitabine, developed as cancer drugs, are currently being tested in clinical trials for the treatment of some chromatinopathies due to abnormal promoter hypermethylation or disruption of DNA modifier enzymes (Jones et al., 2016). Chromatinopathy-specific strategies may also include next-generation approaches for complex chromatinopathies in the SWI/SNF (BAF) complex, exemplified by CRS (St. Pierre & Kadoch, 2017). When the mutated complex possesses residual activity, these strategies are being developed to inhibit selectively the aberrant downstream transcription of the pathogenic complexes, using small molecules or paralogue-specific inhibitors that are entering clinical trials (Schick et al., 2021).

To bypass the low target specificity and metabolic off-target profiles frequently associated with conventional catalytic small-molecule inhibitors, the translational field is rapidly pivoting toward precision molecular technologies (Pandelakis et al., 2020). Toolsets enable precise local control of epigenetics without permanent double-stranded DNA cleaving.

These systems utilize engineered zinc fingers (ZFs), transcription activator-like effectors (TALEs), or catalytically inactive Cas9 (dCas9) systems fused to specific chromatin-modifying enzymes or complex secondary configuration arrays, such as MS2, Casilio, SunTag, or SAM systems (Gjaltema & Rots, 2020; Hilton et al., 2015). These chimeric platforms can fine-tune either up- or downregulate expression of individual dosage sensitive loci in order to bring disease-specific episignatures back to normal (Luo et al., 2021). These technologies offer profound mechanistic advantages over traditional catalytic pocket blockades. In contrast, PROTACs can recruit endogenous E3 ubiquitin ligases to the target engaged protein scaffold for ubiquitin-dependent proteasomal degradation of the entire copy of the protein scaffold, thereby 'obliterating' pathological protein-protein interaction complexes that cannot be prevented by traditional inhibitor approaches (Schapira et al., 2019).

Over the past ten years, gene and protein replacement therapies, induced pluripotent stem cell (iPSC) technologies for tissue replacement, and direct genome editing methods have expanded, indicating that innovative therapies for monogenetic disorders affecting single organs or tissues are on the horizon. Additionally, emerging applications are evaluating the efficacy of antisense oligonucleotides (ASOs) as direct molecular and genetic interventions to modulate disease expression (Rinaldi & Wood, 2018).

Acknowledging that epigenetic enzymes rely heavily on primary metabolic cofactors, modulating structural chromatin intermediates (e.g., acetyl-CoA or α-ketoglutarate) represents a non-invasive therapeutic frontier (Su et al., 2016). In KMT2D models, dietary interventions-such as a ketogenic diet or the direct administration of the ketone body beta-hydroxybutyrate-elevate endogenous histone deacetylase inhibition (Benjamin et al., 2017). This metabolic shift drives the increase in H3ac, and the increase in H3K4me3 open chromatin marks, in the dentate gyrus, thereby rescuing neurogenesis and intellectual deficits and translating into clinical cognitive phenotypes (Benjamin et al., 2017).

Limitations

Since neurodevelopmental delay is the main contributor to disease burden, disease-modifying small molecules and bulky CRISPR vectors will need to access the brain, overcoming the blood-brain barrier (Moutinho et al., 2021).Consequently, advanced drug delivery design is heavily pivoting toward engineered lipid nanoparticles (LNPs), specialized polymeric carriers, and engineered extracellular vesicles to optimize safety, central nervous system delivery, and tissue-specific bioavailability (Terstappen et al., 2021). Finally, a critical milestone for future clinical frameworks involves translating newly identified episignature biomarkers into valid, personalized therapeutic monitoring tools (Aref-Eshghi et al., 2020). Nonetheless, due to the baseline rarity of these Mendelian conditions (Kaufmann et al., 2018), developing well-powered clinical trial designs is a systemic challenge. The database search could have excluded few reviews and literature. The authors agreed there could be bias on the inclusion of diseases and literature. Our aim was to provide insights into the role of chromatin and episigantures and their roles in development and disease, hence few sections appear lengthy and narrative.

7. DISCUSSION

Chromatinopathies are a genetically and clinically heterogeneous group of NDDs due to pathogenic variants in chromatin structure and function regulatory genes (Wojcik & Fahrner, 2024). The considerable phenotypic overlap and genes heterogeneity among these conditions constitute an important challenge for diagnosis, as a significant proportion of cases remain unresolved (VUS). Chromatinopathies constitute a homogenous class of disorders with a common molecular mechanism (altered chromatin structure and epigenetic regulation) underlying the disease (Sadikovic et al., 2023).

NDDs caused by mutations affecting different chromatin regulators comprise more than 100 disorders (Sadikovic et al., 2020). Chromatin architecture holds and packages a vast amount of DNA in an organized system within the cell, this is the role of chromatin. Chromatin can be distinguished as heterochromatin, characterized as a highly condensed and transcriptionally inert state, or as euchromatin, a loosely packaged DNA arrangement easily accessible by transcription factors and the transcription machinery (Levy et al., 2022). These states are largely determined by covalent modifications of the histone proteins contained within chromatin and by DNA methylation.

The cell's DNA methylation “signature” provides explicit instructions for directing genomic functions (Sadikovic et al., 2020). Thus, DNA methylation and the proteins associated with writing (DNMTs) and reading (MBDs) this mark provide a robust mechanism for the regulation of transcriptional activity (Sadikovic et al., 2023). Further, the stability of DNA methylation as a covalent modification and the replicable nature of DNA methylation marks facilitate the inheritance of epigenetic information during several important cellular processes, such as X chromosome inactivation, imprinting, silencing of repetitive elements, transposable elements, pericentromeric repeats, and developmental gene regulation (Sadikovic et al., 2023).

Mutations that alter the epigenotype will become increasingly recognized as mutational mechanisms that cause a variety of human disorders (Wojcik & Fahrner, 2024). Traditionally, the identification of disease-causing genes has focused on disorders in which familial cases or patients with chromosomal abnormalities facilitated the positional cloning of the responsible gene. At this time, we

are challenged as we attempt to discover the mutational bases for rare disorders. Even single-gene disorders, such as AS, BWS, and SRS, can be caused either by genomic mutations or mutations that affect the epigenotype, and can be either inherited or de novo, thus demonstrating the importance of epigenetics in diseases. Research data demonstrate that the levels of several proteins involved in epigenetic regulation are tightly regulated. Perturbations of such levels, either through loss-of-function mutations or duplications, cause human disorders, suggesting that epigenetic mutations that affect transcription, RNA splicing, or protein modifications are also likely to cause disease (Levy et al., 2022).

Evolutionary theory posits that originally DNA methylation may have been evolutionarily acquired to defend against genomic disruption by parasitic insertional element translocations in eukaryotic genomes (Sadikovic et al., 2020). Subsequently, functionality for DNA methylation in other modes of genomic stability may have been co-opted; this idea has become widely supported through research. Epigenetic determination also allows for adaptive karyotypic evolution and may provide an important mechanistic means for speciation (Sadikovic et al., 2023).

While next-generation genomic sequencing via whole-exome sequencing (WES) or whole-genome sequencing (WGS) is the standard that bypasses older cytogenetic arrays, sequence analysis alone frequently surfaces a high volume of variants of uncertain significance (VUS). The diagnostic landscape has moved to genome-wide DNA methylation episignatures for classifying overlapping complex phenotypes (Sadikovic et al., 2020; Levy et al., 2022). Computational approaches that leverage methylation classifiers driven by machine learning can provide an unbiased functional readout of a given sequence variant to establish whether or not it is pathogenic (Sadikovic et al., 2020). Supervised learning platforms, such as support vector machines (SVM), generate a Methylation Variant Pathogenicity (MVP) score (Sadikovic et al., 2020).

This approach provides functional resolution for up to 35.3% of ambiguous VUS findings and helps resolve complex clinical presentations resulting from pathogenic copy number variants and microdeletions involving epigenetic regulators (Levy et al., 2022). Alternatively, without a known signature, the decreased probability of a disease-causing molecule is not absolute. Hypomorphic variants, somatic mosaicism, or an expression in tissues other than the blood can complicate the peripheral blood signature detection (Sadikovic et al., 2023). Charting the expression of certain epigenetic signatures with broad-spectrum or overlapping severities may change the screening outlook from a sequence-guided interpretation to a function and systems-biology interpretation (Sadikovic et al., 2023).

Not only diagnostic, our approach also exemplifies a fundamental biological difference: Follow up chromatin changes, in contrast to structural genetic mutations, are reversibly programmable (Wojcik & Fahrner, 2024). With the advent of clinical epigenomics, DNA methylation episignatures have emerged as practically reliable and highly specific biomarkers for an increasing number of rare neurodevelopmental disorders. Episignatures describe disease-specific methylation signatures detectable in peripheral blood and are instrumental when previous genomic tests proved uninformative. It is envisaged that the field of rare disorders will benefit from these developments.

Declaration

No human subjects were involved in the study; the review article is based on previous findings.

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Table-1 Genes with epigenetic functions and their role in chromatinopathies

Genes	Class	Functions	Reference
ARID1B,ASH1L,ATR, BRCA2,CHUK,CREBBP, CULB4, DDB1, EP300, HUWE1,KAT5, KAT6B,	Histone modification writers	Histone acetylases; proteins add acetyl groups to histone	Bukowska-Olech et al., 2024
KMT2A,KMT2C, KMT2D,KMT5B, MAP3K7,NEK9, NSD1,NSD2,OGT, PPP2CA,PRMT7, RAG1,RNF168, SETD1A,SETD1B, SETD2,SETD5,TAF1, TLK2		Histone methyltransferases; proteins add methyl groups	
BAP1,EYA1,HDAC4, HDAC8,KDM1A, KDM3B,KDM5B, KDM5C,KDM6A, KDM6B,MYSM1, PHF8	Histone modification erasers	a) Histone deacetylases; proteins remove acetyl groups from histones (b) Histone demethylases; proteins remove methyl groups	
ASXL2,GATAD2B, CRB2, MSH6, MSL3, PHIP, POGZ, RAG2, SMARCA4, SMARCB1, SUPT16H, ZMYND11	Histone modification readers	Proteins capable of identifying histone post-translational modifications	
ATRX, BPTF, CDC6, CHD1, CHD2, CHD3, CHD4,CHD7, CTBP1, CTCF, DPF2, ERCC6, HCFC1,HELLS, MBD5,MYSM1, PCNA,RAI1, SMARCAD1, SMARCD1, SRCAP	Chromatin remodelers	Proteins capable of catalyzing a broad range of chromatin changing reactions including sliding of an octamer across the DNA (nucleosome sliding), changing the conformation of nucleosomal DNA and altering the composition of the octamers (histone variant exchange)	
TAF6	Histone chaperones	Histone-binding proteins that influence chromatin dynamics in an ATP-independent manner	
ASXL3,ELP1, EXOSC2	Scaffold protein	Proteins capable of bringing together two or more proteins in a relatively stable configuration	
AICDA,DNMT1, DNMT3A, DNMT3B, TET3, USP7	DNA modifiers	Proteins capable of regulating DNA structure	
ASXL1, ASXL3, BAP1, BCOR, EED, EZH2, PCGF2, SUZ12	Polycomb group proteins	Proteins enable genes silencing	
AIRE, BRCA1, CTCF, FOXP1,FOXP2, FOXP,MECP2, SIN3A,SMARCA2, SMARCA4,SUZ12, TAF2,TP53, VDR, YY1	Transcription factors	Proteins enable gene expression regulations	
BRCA1,CDC73, KANSL1,LAS1L, MECP2,MEN1, PRKAG2,	Cofactors for histone writers	Histone writers accessory protein	

RPS6KA3, TP53, TRRAP, WAC			
ATN1,BCORL1, SIN3A, SNAI2, NIPBL, PHF21A,RLIM, ZNF11	Cofactors for histone erasers	Histone erasers accessory proteins	

Table 2- Genetic disorders affecting chromatin structure in cis and trans

Disorder	Gene	Function	Reference
Coffin–Siris syndrome, intellectual disability	*ARID1A*	Component of the BRG1-associated factor complex	Zoghbi and Beaudet 2016
Rubinstein–Taybi syndrome	*CREBBP*	Histone acetyltransferase	
Immunodeficiency-centromeric instability-facial anomalies syndrome 2 (ICF2) and intellectual disability	*ZBTB24*	DNA methylation	
Intellectual disability, seizures, dysmorphism; Kleefstra syndrome	*EHMT1/ KMT1D*	Histone methyltransferase	
Intellectual disability, cleft lip/palate Siderius syndrome	*PHF8*	Histone H4K20me1 demethylase	
Immune defects, nephritis, skeletal abnormalities, Schimke immuno-osseous dysplasia	*SMARCAL1*	SNF2-like family, DNA-dependent ATPase activity	
gdb- and dbthalassemia		Deletion of LCR causes decreased globin expression	
Fragile-X syndrome	*FMR1*	Expansion of CCG repeat leads to abnormal methylation and silencing	
Multiple cancers	*MLH1*	Germline epimutation	

Table-3. Chromatinopathies syndromes and linked epigenes

Chromatinopathy syndrome	Epigene implicated	OMIM	Inheritance	Reference
Alazami-Yuan syndrome	*TAF6*	617126	AR	Bukowska-Olech et al., 2024
Arboleda-Tham syndrome	*KAT6A*	616268	AD	
Autoimmune lymphoproliferative syndrome type III	*PRKCD*	615559	AR	
Bainbridge-Ropers syndrome	*ASXL3*	615485	AD	
Beck-Fahrner syndrome	*TET3*	618798	AD/AR	
Cerebrooculofacioskeletal syndrome 1	*ERCC6*	214150	AR	
Chung-Jansen syndrome	*PHIP*	617991	AD	
Desanto-Shinawi syndrome	*WAC*	616708	AD	
Diets-Jongmans syndrome	*KDM3B*	618846	AD	
Fetal encasement syndrome	*CHUK*	613630	AR	
Focal segmental glomerulosclerosis 9	*CRB2*	616220	AR	
Genitopatellar syndrome	*KAT6B*	606170	AD	
Hao-Fountain syndrome	*USP7*	616863	AD	
Huriez syndrome	*SMARCAD1*	181600	AD	
Imagawa-Matsumoto syndrome	*SUZ12*	618786	AD	

Intellectual developmental disorder X-linked, syndromic, Lubs type	*MECP2*	300260	XLR	
Intellectual developmental disorder, X-linked 33	*TAF1*	300966	XLR	
Kohlschutter-Tonz syndrome-like	*ROGDI*	226750	AR	
Li-Fraumeni syndrome	*TP53*	151623	AD	
Meier-Gorlin syndrome 5	*CDC6*	613805	AR	
Nabais Sa-de Vries syndrome type 2	*SPOP*	618829	AD	
Neuropathy, hereditary sensory, and autonomic type III	*ELP1*	223900	AR	
Nijmegen breakage syndrome	*NBN*	251260	AR	
Omenn syndrome	*RAG1, RAG2*	603554	AR	
Pilarowski-Bjornsson syndrome	*CHD1*	617682	AD	
Riddle syndrome	*RNF1*	611943	AR	
Shashi-Pena syndrome	*ASXL2*	617190	AD	
Tatton-Brown-Rahman syndrome	*DNMT3A*	618724	AD	
UV-sensitive syndrome 1	*ERCC6*	600630	AR	
Ventriculomegaly with cystic kidney disease	*CRB2*	219730	AR	
White-Kernohan syndrome	*DDB1*	619426	AD	
X-linked intellectual developmental disorder 19	*RPS6KA 3*	300844	XLD	

AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant; XLR, X-linked recessive

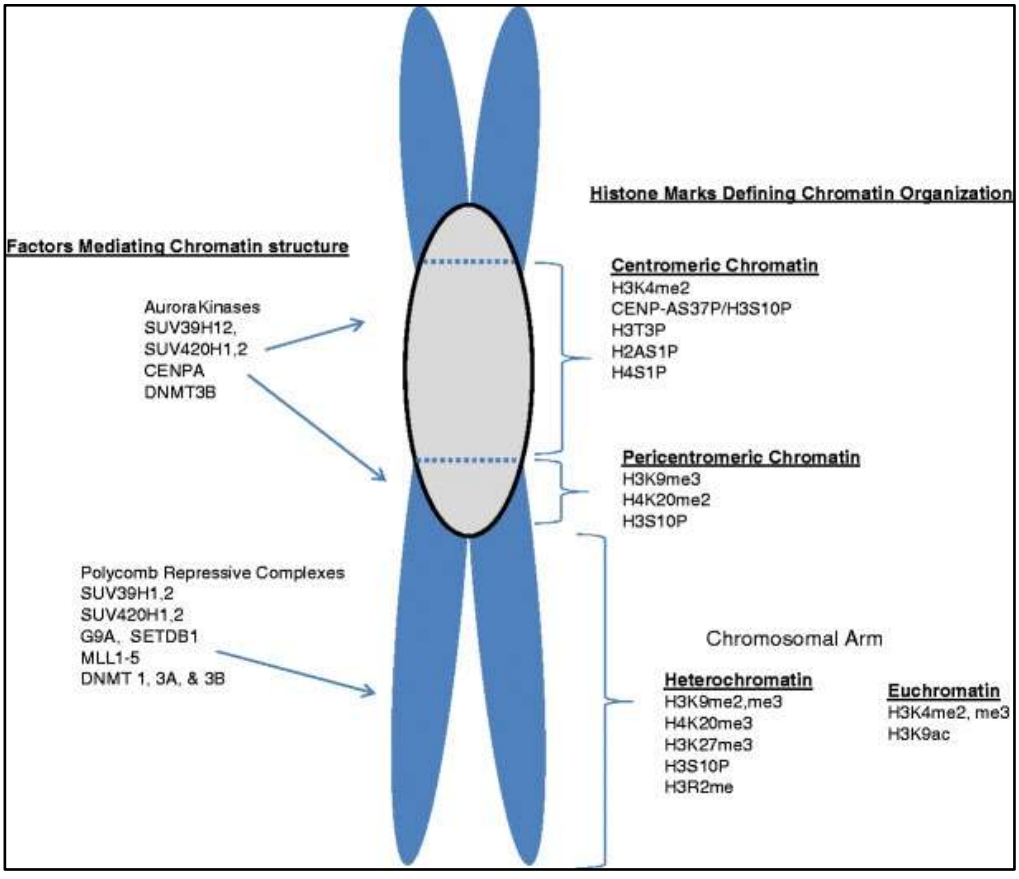


Figure: 1 Factors mediating chromatin structure and histone marks.

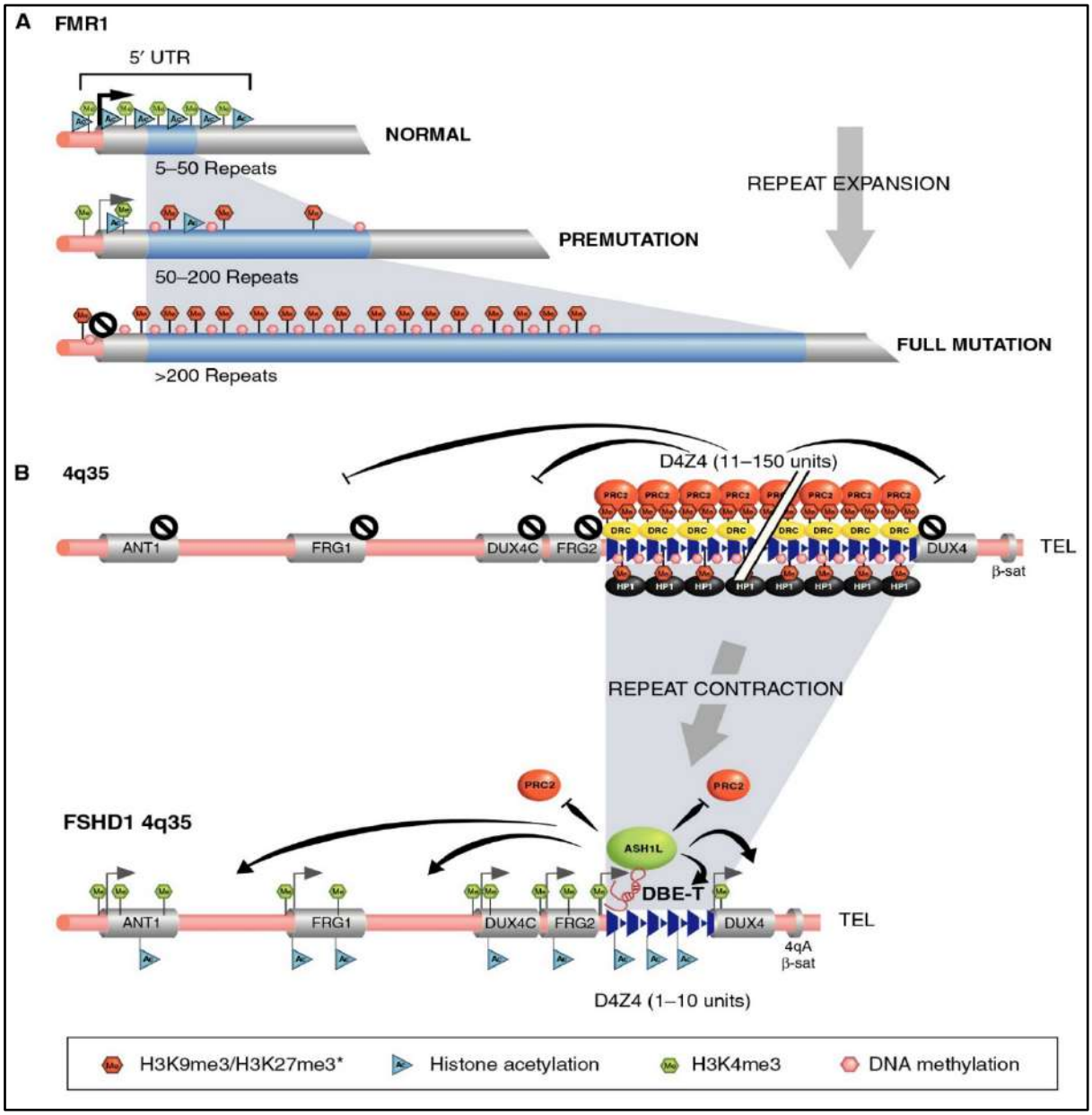


Figure: 2 Genetic alterations in regions with triple repeats in FMR1 and FSHD1 gene in the form of repeat expansion or contraction, with consequential in cis chromatin structural changes.