Epigenetic Aspects of Rare Diseases

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Epigenetics plays an important role in pathogenicity since it regulates basic cellular functions, such as gene expression, DNA damage, chromatin topology, and chromosomal organization. Rare diseases affect more than 300 million people worldwide.

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1. Introduction

Epigenetics plays an important role in pathogenicity since it regulates basic cellular functions, such as gene expression, DNA damage, chromatin topology, and chromosomal organization. DNA in the eukaryotic cell nucleus is wrapped around two copies of each of the core histones (H2A, H2B, H3, and H4) to form chromatin. Among other epigenetic mechanisms, modifications of DNA and histones play critical roles in gene expression regulation. The level of chromatin compaction has important consequences for gene transcription as it influences the accessibility of DNA sequences to transcription factors and other regulatory proteins. Modifications of DNA and histones regulate the level of chromatin compaction, either directly or by facilitating the binding of remodeling proteins that recognize modified sites.

Genetic alterations can have an important impact on epigenetic regulation. Mutations might affect the function of genes involved in histone or DNA modifications or even affect histone genes. These alterations typically have a broad impact on gene expression. Alternatively, mutations can be located in regulatory elements or alter the conformation of chromatin affecting the expression of particular genes.

A disease is considered rare if it affects fewer than 1 in 2000 people [1]. Despite the low individual incidence, rare diseases affect altogether 350 million people in the world [2]. More than 8000 rare diseases have been described [3]. The large variabilities and complexities of symptoms often complicate their diagnoses, which can take up to several years for some patients [4]. Many rare diseases are associated with epigenetic alterations that cause changes in gene expression and can be used to aid diagnosis [5].

2. Epigenetic Aspects of Rare Diseases

Alterations in chromatin properties and structure are common in rare diseases and can be used as diagnostic tools. These alterations can be caused directly by mutations in genes that encode proteins involved in the regulation of chromatin. In addition, other alterations not involving epigenetic factors directly can affect the epigenome. For example, chromatin-related factors are very often recruited to chromatin through transcription factors and, therefore, mutations in transcription factors, their binding sites, or components of signal transduction pathways that control their activity can also lead to alterations in the cellular epigenetic landscape (**Figure 1**).

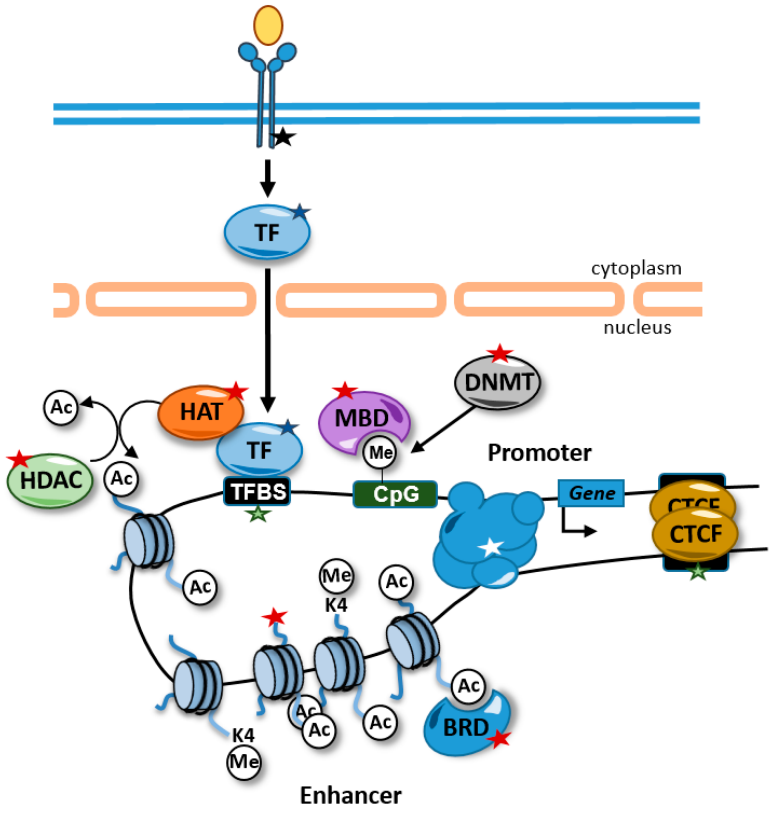

Figure 1. Alterations causing rare diseases that disrupt the epigenome and affect gene expression. Alterations in signal transduction pathways that regulate transcription factor activity (black star), transcription factors (blue star), transcription factor binding sites (green stars), chromatin-related activities (red stars), and promoter–enhancer interactions (white star) can affect gene expression. Some alterations, such as mutations in transcription factor binding sites, are likely to affect the expression of one gene, but other alterations, such as alterations in transcription factors and histone modifying enzymes, are predicted to have genome-wide impacts on the epigenome and in the expression of genes. For example, disruptions of transcription factor activity might interfere with the recruitment of HATs to the chromatin and maintain the proper levels of histone acetylation at enhancers. TFBS, transcription factor binding site; HDAC, histone deacetylases; HAT, histone acetyltransferases; BRD, bromodomain-containing protein; MBD, methyl CpG binding protein; DNMT, DNA methyltransferase; TF, transcription factor; Ac, acetylated residue; Me, methylated cytosine.

Haploinsufficiency in chromatin-related factors frequently causes neurodevelopmental syndromes. Although most of these proteins are ubiquitously expressed, the nervous system appears to be particularly vulnerable to the alteration of their activities. Next, critical aspects of epigenetic regulation and its alterations are reviewed (**Table 1**).

Table 1. DNA methylation-related genes known to cause rare diseases according to OMIM (https://www.omim.org/ accessed on 25 June 2022).

Function	Gene Symbol	Disease	MIM Phenotype
DNMT	*DNMT1*	Cerebellar ataxia, deafness, narcolepsy, autosomal dominant	604121
		Neuropathy, hereditary sensory, type IE	614116
	DNMT3A	Heyn–Sproul–Jackson syndrome	618724
		Tatton–Brown–Rahman syndrome	615879
	DNMT3B	Facioscapulohumeral muscular dystrophy 4, digenic	619478
		Immunodeficiency–centromeric instability–facial anomalies syndrome 1	242860
MBD-containing protein	*MECP2*	Rett syndrome	312750
	MBD5	Intellectual developmental disorder, autosomal dominant 1	156200
	GATAD2B	GAND syndrome	615074

2.1. DNA Methylation

DNA methylation is catalyzed by DNA methyltransferases (DNMTs), typically at cytosines (5mC) [6]. Despite being a relatively stable mark, it can be reversed by the action of ten-eleven translocation (TET) enzymes that oxidize the methyl group of 5mC to yield 5-hydroxymethylcytosine (5hmC) [7]. DNA methylation is essential for normal development and is associated with a number of key processes, including genomic imprinting, X-chromosome inactivation, and gene repression. In particular, methylation of CpG islands, 500–2000 bp CpG-rich areas typically found near the transcription start site of genes, is an important mechanism for gene silencing [6]. The 5hmC residues are found in active genes and are emerging as regulators of gene activation and cellular differentiation during embryonic development and brain maturation [8].

The DNA-methyltransferase enzymes (DNMT1, DNMT3A, and DNMT3B) maintain normal patterns of DNA methylation. In addition, 5mC and 5hmC can be recognized by methyl binding proteins (MECP2, MBD1, MBD2, MBD3, MBD4, MBD5, and MBD6) that possess a methyl-binding domain (MBD) and act as methylation-sensitive transcriptional repressors. Both mutations in DNMTs and methyl binding proteins can cause rare syndromes (**Table 1**). Mutations in *DNMT1* are associated with neuropathies, mutations in *DNMT3A* cause overgrowth syndromes with intellectual disability, and *DNMT3B* mutations are involved in immunodeficiency and intellectual disability [9]. Loss-of-function mutations in *MECP2* cause Rett syndrome, a rare neurodevelopmental disorder, and alterations in other MBD-containing proteins have been described in autism spectrum disorders [10]. Since all these factors are involved in gene repression, it is expected that their loss-of-function results in the overexpression of certain genes that likely contribute to the disease. However, how the induction of genes contributes to the phenotype is not completely understood. In addition, other chromatin functionalities might be compromised. For example, mutations in *DNMT3B* cause centromeric instability and increased frequency of somatic recombination [11].

Mutations in factors controlling DNA methylation can also be involved in imprinting disorders. In humans, around 100 autosomal genes are preferentially expressed from only one of the two parental chromosomes as a result of differential DNA methylation during gametogenesis in the male and female germ lines [12]. Alterations in the methylation status of these genes, most commonly loss but also acquirement of DNA methylation at the non-imprinted locus, might be driven by genetic changes in a cis-acting element or trans-acting factor involved in the establishment or maintenance of imprinted methylation [13]. A number of alterations may also be caused by random environment-driven errors [13]. Most individuals with imprinting disorders exhibit altered DNA methylation at several imprinted loci, a condition that is referred to as multilocus imprinting disturbance (MLID). The molecular basis of these disorders is complex with few pathological variants likely involved in the establishment and maintenance of imprinting identified [14]. Genetic alterations that affect cis-acting elements might include deletions, duplications, and translocations, but perhaps are more common cases of uniparental disomy in which two copies of a given imprinted region are from one progenitor. Due to the dynamic regulation of DNA methylation in cells, it is relatively common for patients to show mosaicisms with variable levels of DNA methylation at imprinted regions between or within tissues, which might complicate the diagnosis. Emerging new technologies now allow the detection of allele-specific expression in single cells and are contributing to improving the understanding of how DNA methylation and epigenetics in general contribute to mosaicisms in rare diseases [15].

2.2. Histone Modifications

Dysregulation of histone methylation and acetylation have been involved in rare diseases [16]. Histone lysine methylation plays an essential role in gene expression and its deregulation has been linked to different neurodevelopmental conditions. Lysine methylation is a complex modification that affects gene expression in different ways depending on the modified residue [17]. Lysine methylation occurring at residues 4 and 36 of histone H3 is generally associated with active chromatin. Tri-methylation of histone H3 at lysine 4 (H3K4me3) is usually located at the transcription start sites (TSS) of actively transcribed genes while tri-methylation of histone H3 at lysine 36 (H3K36me3) is usually found at the gene bodies. Tri-methylation at lysine 9 and 27 of histone H3 (H3K9me3 and H3K27me3), and lysine 20 of histone H4 (H4K20me3) are typically associated with inactive or repressed chromatin. H3K27me3 is mediated by the polycomb repressive complex and is generally associated with facultative heterochromatin, while H3K9me3 marks constitutive heterochromatin. The levels of histone lysine methylation at a particular genomic location are dynamically controlled by the actions of histone lysine methyltransferases (KMTs) and demethylases (KDMs). Haploinsufficiency of KMTs or KDMs manifests in numerous neurodevelopmental disorders (**Table 2**) [18]. The overlap of symptoms caused by mutations in diverse histone modifiers and distinct symptoms caused by genes belonging to the same family of proteins suggests the existence of a complex network of gene expression regulation in the brain. The Kabuki syndrome can be caused by the loss of function of *KMT2D* (also called *MLL2*) or *KDM6A* (also called *UTX*). This overlap might be explained by the participation of both factors in the activation of the same genes, KDM2D by mediating H3K4 methylation and KDM6A by

removing the repressive H3K27me mark. More striking, patients with characteristics of Kleefstra syndrome harbor alterations in *EHMT1* or *KMT2C* genes, involved in gene repression and gene activation, respectively. In a similar way, mutations in *NSD1* or *EZH2* cause overgrowth syndromes. This overlap in phenotype is in contrast with alterations in the different members of the MLL family of H3K4 methyltransferases (*KMT2A-D, SET1A*, and *SET1B*) that cause different symptoms, suggesting that they play crucial yet non-redundant roles in the brain. Finally, both gain and loss-of-function mutations in *NSD2* have been found in patients with intellectual disabilities [19].

Table 2. Genes involved in histone methylation known to cause rare diseases according to OMIM (https://www.omim.org/ accessed on 25 June 2022).

Function	Gene Symbol	Disease	MIM Phenotype
H3K4 KMT	*KMT2A*	Wiedemann–Steiner syndrome	605130
	KMT2D	Kabuki syndrome type 1	147920
	KMT2C	Kleefstra syndrome 2	617768
	KMT2B	Dystonia 28, childhood-onset	617284
	SET1A	Epilepsy, early-onset, with or without developmental delay	618832
		Neurodevelopmental disorder with speech impairment and dysmorphic facies	619056
	SET1B	Intellectual developmental disorder with seizures and language delay	619000
	ASH1L	Intellectual developmental disorder, autosomal dominant 52	617796
H3K9 KMT	*EHMT1*	Kleefstra syndrome 1	610253
H3K27 KMT	*EZH2*	Weaver syndrome	277590
H3K36 KMT	*NSD1*	Sotos syndrome	117550
	NSD2	Rauch–Steindl syndrome	619695
	SETD2	Luscan–Lumish	616831
H4K20 KMT	*KMT5B*	Intellectual developmental disorder, autosomal dominant 51	617788
H3K4 KDM	*KDM1A*	Cleft palate, psychomotor retardation, and distinctive facial features	616728
	KDM5C	Intellectual developmental disorder, X-linked syndromic, Claes–Jensen type	300534
H3K27 KDM	*KDM6A*	Kabuki syndrome type 2	300867
H3K9 KDM	*PHF8*	Intellectual developmental disorder, X-linked, syndromic, Siderius type	300263

Histone acetylation is involved in transcriptional activation, and it is controlled by the action of histone acetyltransferases (HATs) and histone deacetylases (HDACs). The acetylated lysine residues of histones are recognized by bromodomain (BRD)-containing proteins that function as effectors of the acetylation signal through the recruitment of factors that mediate transcription. Alterations in activities related to histone acetylation also cause neurodevelopmental disorders, including the loss of function of HATs, HDACs, BRD-containing proteins, and structural components of HAT complexes (**Table 3**) [16]. Similar to KMTs and despite the fact that multiple HATs seem to acetylate the same residues in histone tails, some non-overlapping symptoms have been described, suggesting that their functions are non-redundant. In addition, it is important to take into account that histone-modifying enzymes might also modify non-histone proteins, such as transcription factors that impact the epigenome.

Table 3. Genes involved in histone acetylation known to cause rare diseases according to OMIM (https://www.omim.org/ accessed on 25 June 2022).

Function	Gene Symbol	Disease	MIM Phenotype
HATs	*KAT6A*	Arboleda–Tham syndrome	616268
	KAT6B	Genitopatellar syndrome	606170
		SBBYSS syndrome	603736
	CREBBP/ EP300	Rubinstein–Taybi syndrome	180849
		Menke–Hennekam syndrome 2	618333
BRD-containing protein	*BRPF1*	Intellectual developmental disorder with dysmorphic facies and ptosis	617333
HDAC	*HDAC4*	Neurodevelopmental disorder with central hypotonia and dysmorphic facies	619797
	HDAC8	Cornelia de Lange syndrome 5	300882
BRAF complex subunit	*PHF21A*	Intellectual developmental disorder with behavioral abnormalities and craniofacial dysmorphism with or without seizures	618725
HAT complex subunit	*TRRAP*	Developmental delay with or without dysmorphic facies and autism	618454

In addition to histone modifications and its effector readers, gene expression and repression entail the remodeling of chromatin, making it more or less accessible to transcription factors and the transcriptional machinery. Chromatin remodelers utilize energy from ATP hydrolysis to alter nucleosome spacing/density or to facilitate histone variant exchange. Several activities with ATP-remodeling activity or that are components of ATP remodeling complexes have been identified in patients with rare diseases, the most well-known being the Coffin–Siris syndrome caused by loss-of-function mutations of different subunits of the SWI/SNF chromatin remodeling complex involved in transcriptional activation (**Table 4**).

Table 4. Genes involved in chromatin remodeling known to cause rare diseases according to OMIM (https://www.omim.org/ accessed on 25 June 2022).

Function	Gene Symbol	Disease	MIM Phenotype
SWI/SNF complex	*ARID1A*	Coffin–Siris syndrome 2	614607
	ARID1B	Coffin–Siris syndrome 1	135900
	ARID2	Coffin–Siris syndrome 6	617808
	SMARCB1	Coffin–Siris syndrome 3	614608
	SMARCA4	Coffin–Siris syndrome 4	614609
	SMARCE1	Coffin–Siris syndrome 5	616938
	ARID2	Coffin–Siris syndrome 6	617808
	DPF2	Coffin–Siris syndrome 7	618027
	SMARCC2	Coffin–Siris syndrome 8	618362
	SMARCD1	Coffin–Siris syndrome 11	618779
	SMARCD2	Specific granule deficiency 2	617475
	ATRX	Alpha-thalassemia/mental retardation syndrome	301040
		Intellectual disability-hypotonic facies syndrome, X-linked	309580
ISWI complex	BPTF	Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies	617755

Function	Gene Symbol	Disease	MIM Phenotype
CHD family	*CHD2*	Developmental and epileptic encephalopathy 94	615369
	CHD7	CHARGE syndrome	214800
		Hypogonadotropic hypogonadism 5 with or without anosmia	612370
	CHD8	Intellectual developmental disorder with autism and macrocephaly	615032
	CHD5	Parenti–Mignot neurodevelopmental syndrome	610771
	CHD1	Pilarowski–Bjornsson syndrome	617682
	CHD3	Snijders Blok–Campeau syndrome	618205
	CHD4	Sifrim–Hitz–Weiss syndrome	617159

Recently, it has been described that mutations in histone H3 tails can also contribute to rare neurologic dysfunctions and congenital anomalies. These mutations likely cause disruptions of H3 interactions with DNA, other histones, and histone chaperone proteins, and result in altered histone modification patterns [20].

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