Chromatin remodelers: We are the drivers!!

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ABSTRACT
Chromatin is a highly dynamic structure that imparts structural organization to the genome and regulates the gene expression underneath. The decade long research in deciphering the significance of epigenetics in maintaining cellular integrity has embarks the focus on chromatin remodeling enzymes. These drivers have been categorized as readers, writers and erasers with each having significance of their own. Largely, on the basis of structure, ATP dependent chromatin remodelers have been grouped into 4 families; SWI/SNF, ISWI, INO80 and CHD. It is still unclear to what degree these enzymes are swayed by local DNA sequences when shifting a nucleosome to different positions. The ability of regulating active and repressive transcriptional state via open and close chromatin architecture has been well studied however, the significance of chromatin remodelers in regulating transcription at each step i.e. initiation, elongation and termination require further attention. The authors have highlighted the significance and role of different chromatin remodelers in transcription, DNA repair and histone variant deposition.

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Introduction: Chromatin and remodelers
The term chromatin was coined by Walther Flemming for the unique stainable fibrous structures observed in nucleus. Chromatin exists in a highly condensed form and is composed of nucleosomes possessing an octamer of histones H2A, H2B, H3 and H4, wrapped by 146bp of DNA and a linker histone H1. The distinction between condensed heterochromatin and open euchromatin structures were reported by Emil Heitz. Structural alteration in chromatin structure facilitates the downstream gene expression specific to cellular demand and thereby hold significant importance in gene regulatory network.1

Chromatin is highly dynamic structure and its plasticity is provided by (a) remodeling of nucleosomes, (b) chemical modification of histones or incorporation of variants, (c) non-histone DNA binding proteins and (d) non-coding RNAs. The affinity of histones for DNA and DNA-associated proteins is governed by combination of histone variants and post-transcriptional modifications (PTMs) of histones that further regulate the transcriptional activity and the accessibility of DNA for recombination, replication and repair. These alterations in chromatin structure are brought about by distinct class of remodeling enzymes, specified as chromatin remodelers.2

Molecular mechanisms of remodeler actions
Chromatin remodelers are versatile tools that catalyze 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).3 On the basis of their mode of action, these evolutionary conserved remodeling enzymes have been grouped in 2 categories: (a) mediates histone post-translational modifications on histone and (b) alter histone-DNA contact within the nucleosome through ATP hydrolysis.4

In order to restructure nucleosomes, ATP-dependent chromatin remodelers utilize energy from ATP hydrolysis (~7.3 kcal/mole) to disrupt the contacts between histones and DNA, and thus regulates the dynamic access to the packaged DNA.5 A conserved core ATPase is shared by all remodelers belonging to the superfamily 2 (SF2) of DEAD/H-box helicases.6 The Snf2 ATPase which is bilobed and consists of 2 tandem RecA-like folds (DEXX...
and HELIC), uses ATP that guides toward translocation down the DNA minor groove. On the contrary to usual helicases, remodeler ATPases lack the “pin” motif (wedge domain), that is essential for strand separation and therefore only act as DNA translocases.

Classification of chromatin remodelers

ATP-dependent chromatin remodelers are classified into 4 distinct families (Table 1): SWI/SNF (switch/sucrose-non-fermenting), ISWI (imitation switch), CHD (chromodomain-helicase-DNA binding) and INO80 (inositol requiring 80). SNF2-family ATPase domain present in all remodeler families is split in 2 parts; DExx and HELIC. The ATPase domain of the SWI/SNF, ISWI, and CHD remodeler families possesses a short insertion, whereas remodelers of the INO80 family consist of a long insertion. The exclusive domains reside adjacent to the ATPase domain. SWI/SNF remodelers contain bromodomains; ISWI remodelers - SANT-SLIDE modules; CHD remodelers - tandem chromodomains and members of INO80 family possess HAS (helicase SANT) domains (Fig. 1). Each of these domains plays role in remodeler recruitment to chromatin or interacting to specific histone modifications and/or they are involved in the regulation of the ATPase activity of the remodeler.

SWI/SNF

The yeast SWI/SNF complex was the first ATP-dependent chromatin remodeler described. Different subunits of SWI/SNF complex were encoded by 2 independent genetic screens for altered gene expression involved in regulating mating type switching (SWI) and sucrose fermentation in yeast (Sucrose Non-Fermenting). The SWI/SNF subunits are 1-2 MDa in size and consist of 9-12 subunits containing Brg1/Brm and their associated factors (BAFs). The complex is targeted to acetylated histone tails through bromodomain subunit within the ATPases. An additional feature of SWI/SNF complexes is the presence of actin and/or actin related proteins (Arps). It has been hypothesized that actin and Arps modulate binding of the remodeling complex to chromatin, stimulate the DNA-dependent ATPase activity, facilitates complex assembly and stability, binding of histone, or remodeling and translocation. Yeast contains 2 SWI/SNF ATPases (Swi2/Snf2 and Sth1) that constitute 2 complexes; ySWI/SNF and RSC, respectively. Corresponding to yeast in Drosophila occurs a single protein Swi2/Snf2, called Brahma (BRM), which is present in 2 complexes – BAP and PBAF. In humans, 2 discrete Swi2/Snf2-like ATPase subunits, named hBRM (human Brahma) and BRG1 (Brahma-Related Gene 1), constitutes the subunits of BAF and PBAF complexes. In mammals, the presence of unique compositions of BAF complexes in embryonic stem cells and during developmental transitions suggests their potential role in guiding cell fate decisions.

Diverse functions of SWI/SNF-like complexes have been studied so far. The majority of the studies have implicated SWI/SNF complexes in active gene transcriptional regulation. The cooperative association of ySWI/SNF with histone acetyltransferase complexes results in activation of gene transcription. On contrary, literature also suggests role of the SWI/SNF complexes in gene repression. In Drosophila, BRM has been reported to be involved in transcription regulation of majority of the genes and is largely associated with transcriptionally active sites on polytene chromosomes. In addition to playing significant role in gene transcription reports also suggests that most of SWI/SNF-family have a direct involvement in other processes such as DNA replication or DNA repair. In yeast, the role of ySWI/SNF in promoting replication initiation and nucleotide excision repair on reconstituted nucleosomal substrates in vitro has been reported.

Imaging studies of SWI/SNF complex using electron microscopy directs that these complexes form multilobed C-shaped assemblies that mount the nucleosome in a central cavity with the entry and exit sites of DNA exposed. Cross-linking and DNA footprinting experiments proposed that the ATPases localize sites at which DNA-histone binding is fragile, such that the torsional strain generated may be endured for loop preparation. For the SWI/SNF complex, it has been specifically hypothesized that the ATPase protein binds to a specific site on the nucleosome and subsequently hires 3’ translocase activity to draw DNA from one entry/exit location and extend it to the other in a directional movement. Even in the absence of ATP hydrolysis, chromatin remodeler complexes binding to their site of nucleosome attachment generates significant repositioning of DNA relative to the histone octamer, which is believed to assist the formation of a DNA loop necessary for ATP-dependent translocation.
| Chromatin Remodeller | Species | Interacting partner/partners | Function | Disease |
|----------------------|---------|-----------------------------|----------|---------|
| **SWI/SNF (switching defective) Family** | | | | |
| Complex | Yeast | Swi2/Snf2 | Transcriptional activation / repression | Coffin-Siris syndrome and Nicolaides-Baraitser syndrome, congenital heart disease, cardiac hypertrophy, malignant rhabdoid tumors, such as choroid plexus carcinoma, medulloblastoma |
| | Drosophila | BAP (Brahma Associated Protein) | | |
| | | PBAP (Polybromo-associated BAP) | | |
| | | BAF (BRG1-associated factors) | | |
| | | PBAF (Polybromo-associated BAF) | | |
| **ISWI (imitation switch) family** | | | | |
| Complex | Yeast | NURF | Nucleosome spacing, DNA damage repair, transcriptional repression. | Williams' syndrome, Melanomictumour, anencephaly |
| | | ACF, CHRAC | | |
| | | ISW1, ISW2 | | |
| | | NURF | | |
| | | ACF, CHRAC, NoRC, RSF, WICH | | |
| **CHD (Chromodomain-Helicase-DNA binding) family** | | | | |
| Subfamily 1 | | | | |
| Chd2 | A+T-rich DNA | SSRP1 protein H3K4me | ATPase activity and relocates nucleosomes. HDAC activity. | Prostate cancer, Hereditary diffuse gastric cancer (HDGC), Ehlers-Danlos syndrome |
| | | | | |
| Subfamily 2 | | | | |
| Chd3 | H3K36, HDAC1, HDA2, ATR, TRIM27 | HDAC activity | Dermatomyositis, Hodgkin’s lymphoma |
| Chd4 | HDAC1, HDAC2, TRIM28 | DNA dependent ATPase activity, Epigenetic transcriptional repression | Dermatomyositis |
| Chd5 | Unmodified Histone, H3K27me3, | | Expressed in neuronal cells, forms nucleosome remodeling and deacetylation complex | Neuroblastoma |
| Subfamily 3 | | | | |
| Chd6 | RNA Polymerase II, NRF2, NQO1 | Transcriptional activation, Role in redox homeostasis | Pitt-Hopkin syndrome |
| Chd7 | Chromatin | Development of neural crest cells | CHARGE syndrome |
| Chd8 | CTCF, Duplin | Transcriptional repressor, developmental regulation | Autism spectrum disorder (ASD) |
| Chd9 | PPAR1α, CBF1, osteocalcin, myosin | Transcriptional and developmental regulation, Nuclear receptor activation | osteogenic differentiation |
| **INO80 (inositol requiring 80) Complex** | | | | |
| INO 80 | | | DNA helicase activity, DNA repair and replication | Aortic hypoplasia, premature atherosclerosis, Immunoglobulin class-switch recombination defects (CSR-D) |
| Swr 1 | | | | |
ISWI ATPase encoding gene was first identified in *Drosophila* homologous to yeast Swi2/Snf2 gene exclusively at the region of the ATPase domain and consequently it was named as imitation switch (ISWI). Among eukaryotes ISWI family chromatin remodelers are highly conserved and play a critical role in nucleosome assembly and spacing as well as in the organization of chromatin at a greater level in the cell. ISWI complexes, compared to SWI/SNF remodelers are smaller and composed of 2 to 4 subunits; each having the nucleosome-dependent ATPase ISWI. ISWI possess highly conserved SWI2/SNF2 family ATPase domain that provides the motor for chromatin remodeling and a characteristic HANDSANT-SLIDE domains with DNA binding activity. By means of DNA-dependent ATPase activity, ISWI remodelers alter nucleosome positioning to promote chromatin assembly, resulting into the transcription suppression. Similarly to primary histone chaperones they are also involved in facilitating the de novo assembly of nucleosomes.

Variability exists within the complex of different species, such as; yeast possesses 2 ISWI ATPases – Isw1 and Isw2, which exist in 4 different complexes. The two different ISWI variants (Isw1 and Isw2) in *Saccharomyces cerevisiae* in combination with different subunits, form a total of 4 diverse complexes. Along with Ioc3 subunit, ISWI (Isw1) forms Isw1a complex and binds to Pol4 II promoters which rejects the basal Pol II transcription machinery, thus inhibiting transcription initiation. On the other hand, Isw1 association with Ioc2 and Ioc4 subunits results in the formation of Isw1b complex, which possess regulatory role in Pol II transcription elongation and termination. Whereas, *Drosophila* contains only one ISWI ATPase, which is a constituent of 3 complexes: dNURF (Nucleosome Remodeling Factor), dACF (ATP utilizing chromatin assembly and remodeling factor) and dCHRAC (chromatin accessibility complex). Six diverse functional ISWI complexes have been identified in *Drosophila melanogaster*, which include CHRAC, ACF, NURF, RSF, ToRC, and NoRC, each comprising ISWI bound to varied combinations of 9 different subunits. In general, the CHRAC and ACF complexes seem to function in assisting nucleosome sliding. NURF acts particularly in the epigenetic regulation of stem cells within the testis and RSF, in addition to chromatin remodeling activities plays a crucial role in chromatin assembly through the replacement of histone variants.

In mammals there exists a huge complex with 2 ISWI ATPases: SNF2H and SNF2L that reside in at least 8 different complexes. The characteristic of

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**Figure 1.** Diagrammatic representation of chromatin remodeler family highlighting the conserved domain with each family member. The DEX and HELICc domains are conserved throughout the family. However, HAND, SANT and SLIDE domains are specific to ISWI family, whereas BROMO domain distinguishes the SWI/SNF family. The presence of CHROMO domains is characteristic of CHD family.
ISWI complex is the presence of a SANT domain (structurally related to the c-Myb DNA-binding domains) which interacts with the unmodified histone tails, a SLIDE (SANT like ISWI domain) domain that binds with the nucleosomal DNA near the dyad axis, and a HAND domain occupied in both histone and DNA binding/recognition. Other specialized subunits constitute supplementary domains to the complexes, that include DNA-binding histone fold motifs (in hCHRAC), plant homeodomain zinc fingers (PHD fingers), bromodomains (hBPTF and hACF1), and extra DNA-binding motifs (HMGI(Y), for dNURF301).

ISWI association with transcription activation was confirmed experimentally in vitro where dNURF directly facilitated GAL4-mediated transcription from chromatin templates. Consequently, the interaction was reported with other sequence-specific transcriptional regulators, including dGAF and dHSF in vivo, thereby facilitating gene expression. Further, the transcription repressive role of ISWI remodelers was shown in the transcription of yeast meiotic genes during mitotic growth that was repressed by Isw2. In corroborations, the nuclease digestion analysis revealed that Isw2 complex generates nuclease protected chromatin structure near these genes promoters. Interestingly, the Isw2 mutant analysis in nucleosome mapping on a genome wide scale showed the role of Isw2 in prevention of antisense transcription from intergenic region and from cryptic initiation sites.

Significant implications of ISWI in maintaining higher order chromatin structure came from studies on the polytene chromosomes from 3rd instar Drosophila larvae where the loss of zygotic ISWI in larval salivary glands leads to extensive decondensation of the X chromosome. Moreover, human hSNF2h complex was shown to interact with cohesins. Human ISWI complexes participate in nucleosome positioning over several kilobases and thereby regulate chromatin folding into loop domains. In addition, it helps to promote replication fork progression as it gets enriched at the sites of active replication. In human cells, hSNF2h, in concert with ACF1, is essential for facilitating DNA replication through highly condensed heterochromatin.

INO80

This family of remodeler was first discovered in S. cerevisiae, the yeast Ino80 gene product is responsible for regulation of inositol-responsive gene expression. The homologous proteins exist in Drosophila as well as humans. The chromatin remodeling enzymes of the INO80 family are: Ino80 and Swr1 in S. cerevisiae; INO80, and p400 in Drosophila melanogaster and in mammals, as Snf2-related CBP activator protein (SRCAP) and p400. The individual complex is highly conserved and composed of 14 to 15 subunits. The unique proteins for INO80 and SWR1 complexes, are RuvB-like helicases that are functionally related to the bacterial RuvB helicase, involved in DNA repair.

The family has been reported to have the ability to perform unique and specialized functions by binding to the replication forks and Holliday junctions. They also bind to the histone variants of H2A; H2A.X and H2A.Z. In vivo INO80 complex influences nucleosome eviction, however the replacement of a canonical H2A-H2B dimer with an H2AZ-H2B variant dimer is catalyzed by SWR1 complex. INO80 complexes in Drosophila and mammals contain a YY1 subunit, a zinc finger containing Polycomb group transcription factor associated with growth and development regulatory genes.

The ATPase subunits of the INO80 family are distinguished from other ATPases in the SNF2 helicases by the presence of a long spacer region that splits the conserved ATPase domain. This region was shown to be bound by RuVB-like subunits and Arps. The motor subunits of INO80 protein also contain a HAS domain (Helicase-Sant domain) which is required for Arps and actin components binding. The presence of RuVB-like helicases in INO80 complexes suggested an involvement in DNA repair. Indeed, INO80 complex associates with γ-H2AX at sites of DSB and participates in eviction of nucleosomes surrounding DSBs. Conversely, it was suggested that SWR1 complex can exchange γ-H2AX for H2A.Z around DSBs. Ultimately, deletion of histone H2A.Z (HTZ1) in yeast, results in changes in chromatin structure at DSBs which consequently leads to reduced association of DNA repair and check point factors. The proposal based on above findings suggest antagonistic function of both complexes at chromatin neighboring a DSB site, and that they regulate the incorporation of different histone H2A variants that subsequently can either promote or block cell cycle checkpoint adaptation. In addition, both complexes have been shown in genetic screens in yeast to be involved in telomere regulation and proper chromosome segregation.
CHD

The characteristic feature of CHD family (Chromodomain - Helicase - DNA binding) is the presence of 2 signature sequence motifs: tandem chromodomains are located at the N terminal region, and the SNF2-like ATPase domain positioned in the central region of the protein. Subsequently, several proteins belonging to this highly conserved family have been identified in Drosophila, yeast and other species.70,71 A large group of ATP-dependent chromatin remodelers is constituted by the CHD family, that is further divided into 3 subfamilies based on the presence or absence of additional domains.72,73

The founding member of the CHD family, CHD1, was identified as a murine nuclear protein that interacts immunoglobulin promoter DNA sequences.74 Chd1 (yChd1) is the only CHD family member present in S. cerevisiae, and Hrp1 and Hrp3 in S. pombe. At their C-terminal region Chd1 and Chd2 proteins contain a DNA-binding domain that preferentially binds to AT-rich DNA motifs though, the function of this interaction remains elusive.74,75 The CHD3 and CHD4 (called also Mi-2α and Mi-2β respectively) belong to the second subfamily that lacks the standard DNA binding domain in the C-terminus. Instead, at the N-terminal region they harbour a pair of PHD Zn-finger-like domains. The third subfamily comprises proteins from CHD6 to CHD9. This subfamily is highly variable as it is defined by additional functional motifs in the C-terminal region, like SANT domain or BRK domains.72,73 CHD5 possess both the PHD fingers and a SANT domain, hence there is a discrepancy in protein classification of CHD5.

The CHD family is defined by the presence of tandem chromodomains as the signature motifs (Fig. 2). It was at first characterized in Drosophila HP1 and Polycomb proteins, where it contributes in binding to histone methylated marks, H3K9me3 and H3K27me3, respectively.76,77 The typical chromodomain module was refined to encompass ~50 amino acids and it folds into 3-stranded anti-parallel β-sheets and one α-helice.78 Human CHD1 chromodomains have been shown to bind H3K4me2/3.79 Additionally, the PHD Zn-finger-like domains are found in various nuclear proteins involved in chromatin-based transcriptional regulation.80,81 The exact function of PHD fingers in CHD remodeler is yet unknown. In CHD3 and CHD4 the PHD fingers interact with histone deacetylase HDAC1 within NuRD.82 Further, studies revealed the association of the second PHD finger of CHD4 with the N-terminus of histone H3 is facilitated by acetylation or methylation of Lys9 (H3K9ac and H3K9me respectively) and inhibited by methylation of Lys4 (H3K4me).83 However, functional correlation between PHD fingers and these interactions needs to be further addressed.

Additional domains were mapped in the sequences of CHD remodelers. SANT domains, involved in

![Figure 2. Schematic representation of subfamilies of CHD family of chromatin remodelers. The CHD family is divided into 3 subfamilies, each subfamily is designated with specific set of domains (PHD, SANT, BRK).](image-url)
histone tail binding, were found in several CHD subfamily III members (for example CHD5). The BRK domain (Brahma and Kismet domain) present in several SWI/SNF complexes, was found in Kismet, CHD7, CHD8 and CHD9.72,73,84

**Cellular functions of chromatin remodelers: Transcription**

The majority of the chromatin remodelers have been studied in relation to transcriptional regulation, both as activators and repressors (Fig. 3). The transcription stage (transcription initiation, elongation and termination) specific involvement of CHD chromatin remodelers has been reported. The only chromatin remodeling complex purified so far is the NuRD complex that couples ATP dependent nucleosome remodeling with histone deacetylation. The transcription repressive ability of the complex has been studied in various genes involved in differentiation and development of *C. elegans, D. melanogaster* and mammals.85,86 However, not much is known about the mechanism of gene repression by NuRD. In the presence of ATP, purified NuRD disrupts nucleosomes and recombinant Mi-2 slides mononucleosomes *in vitro*.82,87 On contrary, the disruption in deacteylase activity of NuRD complex does not affect nucleosome remodeling. However, reports do suggest that NuRD along with different gene specific transcription factors get recruited on the target gene promoter and allow histone tails accessibility for deacetylation. Consequently, the recruitment results in generation of more compacted chromatinin structure and thus subsequent gene repression.88

**Transcription initiation**

ATP-dependent chromatin remodelers SWI/SNF complexes have been extensively studied in relation to transcription initiation and subsequent assembly of transcription machinery. However, CHD remodelers and their role in transcription initiation are not studied in depth so far. Genome-wide studies on CHD1 homolog of *S. pombe*, i.e., Hpr1 and Hpr3, suggested their role in nucleosome disassembly at gene promoters.89 Hpr1 and Hpr3 localized at the promoters and to a lesser extent in the ORFs of various *S. pombe* genes. Hpr1/3 prefer nucleosome dense promoter region. Loss of these remodelers resulted in enhanced H3 density at the promoter regions genome wide, thus indicating their role in nucleosomal disassembly. Further the co purification studies have shown their association with a histone chaperone Nap1, that is linked to nucleosome assembly and disassembly in concert with remodeling complexes.90,91

Numerous studies have implicated CHD remodelers in facilitating transcription activation via binding to enhancers. In particular, human CHD7 genome wide enhancer occupancy has been shown to further overlap with the binding at DNAse I hypersensitive sites enriched in H3K4me1, a hallmark of enhancers. Moreover, CHD7 strongly binds to actively transcribed regions reinforcing its role in gene activation.92 Indeed, another study in *Xenopus* showed CHD7 mediated direct transcription regulation of core neural crest transcription factors. CHD7 has been shown to interact with BRG1-like complexes, BAF/PBAF and both CHD7 and BRG1 reside in distal regulatory elements of their target genes.93 A weak signal of CHD7 detected at nearby promoters suggests the existence of a looping mechanism.92 Nevertheless, the mechanism of gene activation by CHD7 remains to be elucidated. The enhancer element of an androgen receptor (AR) responsive gene in prostate cancer cells were shown to be occupied by CHD8 in an induction independent manner. CHD8 knockdown studies suggested their plausible involvement in chromatin remodeling at this...
enhancer and consequently results in gene repression. In addition, Mi-2β (CHD4) facilitates enhancer element binding at the CD4 gene during T-cell development. Moreover, Mi-2β was shown to assist recruitment of transcription factor HEB and a histone acetyltransferase, p300, to the CD4 enhancer element, facilitating open chromatin formation and gene activation. Mi-2β remodeler might be implicated in active transcription outside of the NuRD complex since it has been shown to interact with factors in an HDAC independent manner.

**Transcription elongation**

Transcription elongation is a highly controlled mechanism and recent studies indicate the significance of chromatin structure in its regulation. The state of transcription elongation to a large extent is defined by the phosphorylation status of the C-terminal domain of the largest subunit of RNAP II (CTD). CHD remodeler Kismet (KisL) has been suggested to be involved in an early elongation step. The study have shown the localization of KisL at transcriptionally active sites on polytene chromosomes. KisL binding pattern highly overlapped with RNAP II phosphorylated at Ser5 and Ser2, Brahma and dCHD1. However, the levels of elongating RNAP II (Ser2) in kisL mutants were drastically reduced, whereas RNAP II phosphorylation at Ser5 remains unaffected. Consequently, chromatin association of the elongation factors Spt6 and dCHD1 was considerably reduced. Further studies on KisL mutant showed decrease in association of H3K4 methyltransferases ASH1 and TRX with chromosomes. Additionally, the enhanced H3K27me3 that is essential for Pc function was observed in kisL as well as ash1 and trx mutants. In corroboration with above findings, the human homolog of KisL, CHD8, associates with subunits of MLL, a histone H3K4 methyltransferase Ash2L containing complex. CHD8 has been implicated in early transcription elongation or activation of cyclin E2 gene in G1/S cell cycle transition. Interestingly, CHD8 depleted cells were more sensitive toward inhibitors of transcription elongation, like DRB and flavopiridol. Though, further studies are required to elucidate the exact functions of CHD8 remodelers in transcription elongation.

CHD1 remodeler also participates in transcription elongation as shown in studies performed on Drosophila where dCHD1 is recruited at the transcription active sites on polytene chromosomes. Consequently, studies in yeast revealed the interaction of yChd1 with Spt4-Spt5 and Spt16-Pob3 (FACT) and PAF complexes that are exclusively involved in transcription elongation. In addition to this, dCHD1 participates in deposition of H3.3 variants, nucleosomes spacing and assembly in vivo. Collectively, the experiments suggest a role of CHD1 in nucleosome reassembly over elongating RNAP II and in re-establishing of a repressive chromatin structure. However, the function of CHD1 in transcription dependent chromatin assembly demands further investigation.

**Transcription termination**

The last phase of transcription cycle is transcription termination, which involves the dissociation of the transcription complex from the DNA template and release of the RNA transcript. A homolog of yChd1 in S. pombe, identified as Hrp1A is involved in transcription termination by RNAP II. Run on assays on several genes from both hrp1 and chd1 deletion strains showed failure in transcription termination. The chromatin structure analysis indicated alteration in termination region of 800bp that extends ahead of the 3’ end of the gene. Similar changes in both induced and uninduced gene states suggest a role of yChd1 in establishment of chromatin structure in the termination regions of yeast ORFs. Furthermore, rDNA (rDNA) genes the transcription termination of RNA Pol I is achieved by yChd1 in combination with Isw1/2. However, in the mutants no effect was observed in the levels of rRNA, thus suggesting that the termination defects were not due to transcription elongation.

**Other cellular function of chromatin remodelers**

Chromatin remodelers are also associated with other cellular functions, chromatin compaction/accessibility, replication, histone variant deposition, DNA repair and chromatin maintenance etc.

**Histone variant deposition**

Different variants of histone proteins exist, having specialized cellular functions along with their fundamental role in DNA structural organization. H3.3 variant of H3 has been largely associated with transcriptional activation and CHD1 might be associated with its deposition.
and nucleosome assembly during transcription elongation. However, deposition of H3.3 variant outside transcription has been reported in early *Drosophila* development accomplished by dCHD1 within the paternal pronucleus. Additionally, in mammalian cell lines CHD1 has been associated with centromere function. Moreover, knockdown studies on CHD1 reported marked decrease in CENP-A binding to the centromers, which suggest the plausible role of CHD1 in centromeric histone variant deposition. However, this function of CHD1 is not necessarily conserved, as in *Drosophila* this remodeler is not required for CENP-A deposition.

**DNA repair**

INO80 complexes in the context of DNA break repair in yeast has been well studied, however its role in ATP-dependent chromatin remodeling at damaged sites within the human genome remains yet to be deciphered. CHD4 association with ataxia telangiectasia mutated serine protein (ATR) kinase and also as a target of the ATM/ATR pathway in a proteomic screen suggested its potential role in DNA repair. Despite few ambiguities in the results of various studies, the outcome ascertained that CHD4 depleted cells displayed sensitivity toward ionizing radiation, lacking in double strand break (DSB) repair ability and they exhibit extended persistence of the phosphorylated H2AX (γH2AX). In addition, CHD4 knockdown studies have reported delay in cell cycle progression and apoptosis activation via the p53/p21 pathway. This, suggests the possible role of CHD4 in regulating deacetylation of p53, thereby controlling G1/S cell cycle transition. Interestingly, other studies in CHD4 depleted cells have shown decreased accumulation of ubiquitination at the DSB sites. Notably, CHD4 knockdown leads to a significant decrease in histone ubiquitin ligases, RNF168 and BRCA1 accumulation at the DSB sites. Collectively, these results signify multifaceted and probably mutually dependent roles of CHD4 in DNA damage response and cell cycle progression. Consequently, a more widespread role of CHD4 in chromatin maintenance has been suggested.

**Chromatin remodelers association in disease**

Chromatin remodeling is an ill-defined multistep process that requires communication, cooperation between the ATPase and auxiliary domains; and their interaction with chromatin. Histone (PTM) and chromatin remodeling in concert play an essential role in embryonic development and disease by altering gene expression profile. Therefore, mutations or alterations affecting the function and targeting of chromatin-remodeling complexes cause several types of cancers, other syndromes and multi-system developmental disorders. Studies have shown temporal and tissue specific function of chromatin remodelers during heart development and thereby any mutation leads to the advancement of many cardiovascular tissues.

SWI/SNF complexes recently have gained more attention because of their unusual frequency of mutation in a varied range of human cancers as well as neurodevelopmental disorders. SWI/SNF gene mutations occur in a broad spectrum of tumors ranging from early stage stem cell-like cancer to later stage adult cancers such as lung cancers. Mutations in SWI/SNF component are reported in huge spectrum of cancers at a frequency of around 19%. Malignant rhabdoid tumor (MRT) are a highly aggressive group of tumors that usually occur in early childhood in various locations, including the kidney, lung, soft tissue and brain. They are mostly found in children is characterized by biallelic loss of the SWI/SNF core component. The SNF5 gene is found to have undergone bi-allelic loss in the majority of human malignant rhabdoid tumors (MRTs), and some 'proximal-type' epithelioid sarcomas. Mammalian SWI/SNF complexes play significant role in cell cycle progression and facilitate double strand break (DSB) repair via H2A.X phosphorylation. SWI/SNF complexes contribute to the development of T cells, hepatoocytes, oligodendrocytes, and embryonic stem cell self-renewal and pluripotency.

Also, mutations in other complexes like CHD1, CHD4, CHD5, CHD7, ATRX leads to a variety of disorders and genomic instability. There are many human developmental disorders that are a result of mutation in remodeling genes. Loss of CHD5 leads to microcephaly and features as seen in 1p36 Syndrome. Williams Beuren Syndrome is also the result of deletion of WSTF along with several critical genes required for proper development. CHD7 mutation leads to CHARGE Syndrome. Mutation in ATRX gene leads to α thalassemia X-linked mental retardation syndrome ATRX Syndrome.

The disorders related to dysregulation of chromatin remodeling complexes are as:
**ATRX syndrome**
The cytogenetic location of ATR gene is Xq21.1. It encodes for a protein that plays role in normal development. Studies have shown ATRX regulating the expression of HBA1 and HBA2 genes that are crucial for hemoglobin production in RBC and this leads to a blood disorder called *α thalassemia*. It is the only gene found to be mutated in ATRX Syndrome. Patients with this syndrome are reported with intellectual disability, somatic abnormalities, hypotonia and abnormal hemoglobin synthesis.118

**CHARGE syndrome**
CHARGE syndrome is a multiple organ disorder that stands for Coloboma of eye, heart defects, atresia choanae, retarded growth, genital abnormality and ear abnormality.119 It occurs in approximately 1 in 8500 or 10,000 individuals. Mutations (frameshift and deletion) in CHD7 gene (located on chromosome 8), leads to the production of nonfunctional protein that interrupts chromatin remodeling of other genes involved in normal development and thus leads to the disorder. The identification of 7 heterozygous CHD7 stop-codon mutations and 2 single-copy 8q12 deletions of CHD7 gene designate that haploinsufficiency of this gene could account for most cases of CHARGE syndrome. CHARGE syndrome might also have a genetically heterogeneous etiology, as different genomic abnormalities have been identified in affected individuals.

**Neuroblastoma**
Neuroblastoma is a tumor of the sympathetic nervous system. It is the most common childhood extracranial solid tumor, accounting for 8%–10% of childhood cancers and 15% of childhood cancer deaths.120 Neuroblastomas demonstrate clinical heterogeneity, from spontaneous regression to relentless progression. Chromo domain helicase DNA binding protein 5 (CHD5) is the strongest candidate tumor suppressor gene that is deleted from 1p36.31 in neuroblastomas, and inactivation of the second allele may occur by an epigenetic mechanism. It is assumed that it functions by forming a nucleosome remodeling and deacetylation (NuRD) complex which regulates transcription of particular genes. CHD5 is mainly expressed in the nervous system and testis. On the basis of its position, pattern of expression, and function in neuroblastoma cells and xenografts, CHD5 was identified as a tumor suppressor gene (TSG). The chromatin remodeler CHD5 is expressed in neural tissue and is frequently deleted in aggressive neuroblastoma. Very few studies have been carried out about the function of CHD5 in the nervous system or its mechanism of action. CHD5 may also play an important role in the development of many other tissues besides the nervous system and testis. CHD5 also plays a major role as a tumor suppressor gene in gliomas and a variety of other tumor types, including breast, colon, lung, ovary, and prostate cancers.117

**Coffin-Siris syndrome**
It is an autosomal dominant disorder known to be caused by mutation in one of the 5 genes (*ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, and *SMARCE1*), but mostly de novo mutations are the main reason. Each of these genes codes for one of the subunit of multi-protein complex SWI/SNF. The mutation in one of the genes thus result in abnormal or deregulated chromatin remodeling followed by expression of several genes that are responsible for different signs and symptoms associated to the disease, which includes hypoplasia of the nail of the fifth digit (fifth digit syndrome), mild to severe intellectual and developmental disability (sitting and walking), distinctive facial features typically with wide nose and a flat nasal bridge.121

**COFS and COCKAYNE syndrome type II**
Mutations in yeast homolog Rad26, ERCC6 (excision repair cross complementing rodent repair deficiency, complementing group 6) that codes for a SWI/SNF related ATPase causes both COFS (cerebro-oculo-facio-skeletal) and Cockayne syndrome. It is inherited in an autosomal recessive manner. ERCC6 protein promotes transcriptional elongation by RNA Polymerase I,II,III and functions in transcription coupled DNA repair. COFS is a rare genetic progressive neurodegenerative disorder that affects mainly brain and spinal cord. It is said that COFS syndrome is prenatal extreme case of Cockayne Syndrome. The symptoms include postnatal growth failure, microcephaly, congenital cataracts, severe mental retardation, dysmorphic features, progressive skeletal defects, retinopathy. The most common symptom between the 2 syndromes is increased sensitivity to UV induced DNA damage and oxidative stress.4
**Williams Syndrome**  
An autosomal dominant disorder caused by deletion of specific genetic segment from chromosome 7 (7q11.2). The segment contains more than 25 genes and some of the genes that are deleted in this disorder includes CLIP2, ELN, GTF2I, GTF2IRD1, and LIMK1. It has been observed that deletion or loss of function of ELN gene leads to cardiovascular disabilities and connective tissues abnormalities. Studies report that gene deletion of CLIP2, GTF2I, GTF2IRD1, LIMK1 explains the characteristic visual-spatial difficulties, dysmorphism, aberrant vitamin D metabolism, hypercalcemia, behavioral imbalance and other cognitive disabilities in patients of Williams Syndrome. An indirect correlation exists between BRG1 and BRM associated chromatin remodeling complexes and in the pathogenesis of this syndrome.122

**Schimke immuno osseus dysplasia**  
An autosomal recessive multisystem disorder, caused by mutation in the SMARCAL1 gene (SWI/SNF-related matrix associated, actin-dependent regulator of chromatin, subfamily A-like protein 1) whose specific function is still unknown Being a pleiotropic disorder, it leads to a spectrum of symptoms that includes T-cell immunodeficiency, renal defects, spondyloepiphyseal dysplasia (SED) resulting in short stature, nephropathy, hyperpigmentation, lordosis (exaggerated curvature of the lower back) facial dysmorphism. It is also known to regulate several genes required for cellular proliferation. More is yet to be discovered about this gene and disorder.123

**Conclusion**  
In summary, chromatin remodelers have significant role in molecular and cellular function viz nucleosome sliding, eviction, histone exchange, histone post-translational modification, chromatin compaction, accessibility, transcription, replication, DNA repair etc. We can summarize that defect in chromatin remodelling complexes lead to a diverse spectrum of human disorders like cancer, developmental disorders and birth defects. These disease phenotypes depict the role of these complexes in DNA replication, regulation of gene expression and DNA repair. Chromatin remodelers have implications in gene regulation that associates with gene reprogramming and disease conditions like in cancer progression. Further study of chromatin remodelers is required to understand their mode of action and to help us in designing novel strategies for prevention and cure of cancer and other chromatin related diseases. Structural aspects of remodeler will be essential for defining precisely the molecular pathophysiology and scope of chromatin remodeling and epigenetics in human diseases. The field is an open platform to decipher the possible therapeutic potential of these chromatin modulation proteins in future.

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No potential conflicts of interest were disclosed.

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