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Architects of the genome: CHD dysfunction in cancer, developmental disorders and neurological syndromes

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Abstract

Chromatin is vital to normal cells, and its deregulation contributes to a spectrum of human ailments. An emerging concept is that aberrant chromatin regulation culminates in gene expression programs that set the stage for the seemingly diverse pathologies of cancer, developmental disorders and neurological syndromes. However, the mechanisms responsible for such common etiology have been elusive. Recent evidence has implicated lesions affecting chromatin-remodeling proteins in cancer, developmental disorders and neurological syndromes, suggesting a common source for these different pathologies. Here, we focus on the chromodomain helicase DNA binding chromatin-remodeling family and the recent evidence for its deregulation in diverse pathological conditions, providing a new perspective on the underlying mechanisms and their implications for these prevalent human diseases.

Keywords

cancer; CHD proteins; chromatin remodeling; copy number variation; developmental disorders; DNA damage; male infertility; mutation; neurological syndromes

In eukaryotic cells, DNA is packaged into chromatin, the fundamental unit of which is the nucleosome. Nucleosomes contain an octamer consisting of two copies of each core histone protein: H2A, H2B, H3 and H4, around which 146 base pairs of DNA is wrapped, with histone H1 being positioned on the DNA linkers between adjacent nucleosomes. During all DNA template-based cellular processes, chromatin undergoes dynamic remodeling to allow optimal states for efficient transcriptional regulation, DNA replication, DNA recombination and repair, as well as chromosome condensation and segregation. Such dynamic chromatin remodeling is enabled through the interplay of elaborate mechanisms including chromatin remodeling by ATP-dependent chromatin remodelers, covalent histone modifications, exchange of canonical histones with histone variants, DNA methylation and noncoding RNAs. In particular, chromatin remodelers perform critical roles in regulating DNA

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accessibility and chromatin structure through their ability to mobilize and restructure nucleosomes using the energy derived from ATP hydrolysis. ATP-dependent chromatin remodelers are highly conserved across organisms from yeast to humans, and share an ATPase domain similar to that of the SNF2 (sucrose nonfermenting 2) family of DNA translocases [1]. Based on the presence of additional functional domains, chromatin remodelers are classified into four families: SWI/SNF (switching defective/sucrose non-fermenting), ISWI (imitation SWI), INO80 (inositol requiring 80) and CHD (chromo domain helicase DNA binding) [1]. Members of these chromatin-remodeling families have been shown to play important roles in the regulation of gene transcription, DNA replication, DNA recombination, DNA repair, higher-order chromatin assembly and chromosome segregation, and their perturbations are linked to human diseases including cancer and developmental disorders [1,2]. In this review, we focus specifically on the CHD chromatin remodeler family [3,4], highlighting emerging evidence demonstrating the functional roles of CHD proteins in the pathogenesis of cancer, developmental disorders and neurological syndromes.

The CHD family of chromatin remodelers

The CHD family encompasses nine members (CHD1–9) [3,4] (Figure 1). CHD proteins are highly conserved from yeast to humans, being characterized by a SNF2-like helicase-ATPase domain located in the central region, and signature tandem chromodomains (chromatin organization modifier domains) located in the amino terminal region of the protein [3-6]. The SNF2-like domain confers the ATP-dependent enzymatic activity that enables CHD proteins to mobilize and restructure nucleosomes [4,7-11]. Chromodomains are evolutionarily conserved motifs that mediate interactions with chromatin by binding directly to DNA, RNA or methylated histones [12]. Interestingly, DNA-binding activity by chromodomains is important for the ATPase and transcriptional repression activities of CHD4 [7,13,14]. The two tandem chromodomains of CHD1 co-operate to bind to lysine 4-methylated histone H3 (H3K4me) [15]. The chromodomains of Chd5 directly bind to and are required for maintenance of H3K27me3 on Polycomb group-regulated target genes [16].

Besides these domains that are common to the nine CHD proteins, additional functional domains divide CHD proteins into three subfamilies [3,4] (Figure 1). Subfamily I members (CHD1, CHD2) contain a DNA-binding domain with a preference for binding AT-rich sequences [6]. Subfamily II members (CHD3, CHD4, CHD5) lack a defined DNA-binding domain, but harbor dual plant homeodomain (PHD) zinc finger motifs upstream of the chromodomains. PHD fingers are multifaceted readers of the N-terminal tail of histone H3, including the methylation state of Lys4 (H3K4me2/3 vs. H3K4me0), Arg2 (H3R2me0 vs. H3R2me2), Lys9 (H3K9me3) and Lys36 (H3K36me3), as well as the acetylation state of Lys9 (H3K9ac) and Lys14 (H3K14ac) [17,18]. For example, the two PHD fingers of CHD4 bind to H3 tails with unmodified H3K4 and/or trimethylated H3K9, but not trimethylated H3K4 [19,20]. Furthermore, the PHD fingers are required for the nucleosome remodeling and repressive functions of CHD4 [7,21]. Similarly, our lab discovered that the tandem PHD fingers of CHD5 bind to H3 tails with unmodified H3K4 and this interaction is required for CHD5's ability to regulate transcription [22]. Interestingly, PHD fingers are also implicated in binding to nonhistone domains such as RNA recognition motif (RRM) and homology

domain 1 (HD1) [17]. Subfamily III members (CHD6, CHD7, CHD8, CHD9) contain additional functional motifs in their C-terminal regions, including paired BRK (Brahma and Kismet) domains, a SANT-like (switching-defective protein 3, adaptor 2, nuclear receptor corepressor, transcription factor IIIB) domain, conserved region (CR) motifs and a less-defined DNA-binding domain. SANT domains are suggested to interact primarily with unmodified histone tails, and couple histone binding to ATP catalysis [28], whereas functions of BRK and CR domains are not well understood. The diverse functional domains of CHD proteins suggest that they could have multi-faceted roles as ATP-dependent chromatin remodelers, 'readers' of covalent histone modifications and DNA-binding factors, while the specific domains ascribed to different CHD family members could equip distinct CHD proteins with unique biological roles. Numerous studies have revealed roles for CHD proteins in cellular processes such as transcriptional regulation, chromatin assembly, nucleosome remodeling, DNA damage repair, RNA processing, ribosomal RNA biogenesis, cellular proliferation, senescence, apoptosis and differentiation [3,4,29-39]. Increasing evidence also links genomic lesions such as mutations, deletions, translocations and copy number variations (CNVs), in CHD family members to human disease syndromes [3,4].

CHD proteins in cancer

Recent studies have revealed that a number of CHD proteins are potent tumor suppressors and their deficiencies contribute to development of a variety of cancers. Our laboratory identified *CHD5* as a tumor suppressor gene mapping to human 1p36 [40], a genomic region frequently deleted in a broad range of cancers including neural, epithelial and hematopoietic malignancies [41]. Chd5 is a tumor suppressor that controls cellular proliferation, senescence and apoptosis by its ability to facilitate transcriptional activation of *Cdkn2a*, thereby inducing p16/Rb and p19/p53-mediated tumor-suppressive pathways [40]. In addition, Chd5 binds other regions of the genome, showing preferential binding to genomic loci lacking H3K4me3, and its interaction with H3 is crucial for Chd5-mediated transcriptional modulation of genes implicated in cancer, cell cycle control and chromatin regulation [22]. Chd5 binds unmodified H3 via its dual PHDs [22,42]. Mutation of specific conserved residues within the PHDs of Chd5 abrogate the Chd5-H3 interaction, and in contrast to wild-type Chd5, H3-binding defective Chd5 mutants are not able to suppress proliferation or to induce differentiation in cultured cells, and hence are not able to inhibit tumor growth *in vivo* [22]. In addition, the chromodomains of CHD5 bind H3 tails that are trimethylated at Lys27 (H3K27me3) and the interaction is required for maintenance of H3K27me3 at polycomb-repressive genes required for neuronal differentiation [16]. These findings suggest that CHD5 is capable of interacting with nucleosomes through multiple structural domains with preference for specific histone modifications and potentially via combinatorial recognition of multiple histone modifications.

Since the time that CHD5 was discovered as a tumor suppressor [40], a flurry of studies have reported tumor-suppressive functions for CHD5 and revealed a high frequency of *CHD5* lesions (including compromised expression, promoter hypermethylation, mutation and/or deletion) in diverse cancers including neuroblastoma [43-47], glioma [40,48,49], breast cancer [48,50], lung cancer [51], ovarian cancer [52], gastric cancer [53], gallbladder carcinoma [54], colorectal cancer [48,55,56], hepatocellular carcinoma [57], melanoma [58],

leukemia [59] and laryngeal squamous cell carcinoma [60]. A number of studies have also defined robust CHD5 expression as an independent prognostic marker for better survival for patients with neuroblastoma [44], glioma [49], ovarian cancer [52] and gallbladder carcinoma [54]. Notably, CHD5 expression has been primarily detected in brain and testis to date [47,61-65]. It is thus intriguing that CHD5 seems to exert tumor-suppressive functions in cell types where it is not normally detected. It is possible that Chd5 affects cell fate choices, such that its perturbation leads to unbridled expansion of a cell type in which Chd5 is not expressed, as recently proposed [66]. Another possibility is that Chd5 expression is induced in response to DNA-damage, but is not normally detected in those tissues, and therefore its loss leads to increased DNA damage and eventually tumorigenesis. In support of this idea, we found that DNA-damaging agents induce *Chd5* expression [64]. Another possibility is that Chd5 in an 'expressing' cell type has paracrine effects on cell types in which it is not expressed, for example, due to its ability to modulate cancer pathways and/or the DNA damage response [22,64]. Thus, whereas it is clear that CHD5 is a potent tumor suppressor, a better understanding of how it works in different cellular contexts and how its perturbation leads to diverse cancers is needed.

While CHD5 was the first CHD protein to be implicated in cancer [40], tumor-suppressive roles for additional CHD members have also been found. For the most part, these studies have been based on sequencing of human tumors. Kim *et al*. examined mutational status of *CHD1, CHD2, CHD3, CHD4, CHD7, CHD8* and *CHD9* in 28 gastric cancers (GCs) with high microsatellite instability (MSI-H), 45 GCs with low MSI (MSI-L), 35 colorectal cancers (CRCs) with MSI-H and 45 CRCs with MSI-L and assessed CHD4 and CHD8 expression in these tumors by immunohistochemistry. *CHD1, CHD2, CHD3, CHD4, CHD7, CHD8* and *CHD9* mutations were, respectively, found in 7.9% (5/63), 30.2% (19/63), 4.8% (3/63), 7.9% (5/63), 11.1% (7/63), 15.9% (10/63) and 11.1% (7/63) of the high MSI tumors (GC and CRC combined) [67]. Loss of CHD4 expression was observed in 56.4% of GCs and 55.7% of CRCs, and loss of CHD8 was observed in 35.7% of GCs and 28.6% of CRCs [67]. These findings suggest that mutations and deficiency of CHD proteins may be common in cancers of the stomach and colon, and that their disruption could contribute to tumorigenesis. Increasing genetic and functional evidence for individual CHD family members provides further support for this idea.

In addition to the frequent frameshift mutations of *CHD7* and *CHD8* in cancers of the stomach and colon discovered by Kim *et al*. [67], Tahara *et al*. also found that mutations of *CHD7* and *CHD8* occur in 42% (18/42) of CRCs with CpG island methylator phenotype 1, referred to as CIMP1 CRCs, making *CHD7* and *CHD8* the most commonly mutated genes in the study [68]. *CHD7* and *CHD8* mutations are also found in 9% (3/34) CIMP2 CRCs and 6% (2/34) CIMP-negative CRCs [68]. By analyzing expression of CHD8 in 101 cases of GCs and corresponding noncancerous tissues, Sawada *et al*. found that CHD8 expression is significantly compromised in GCs, and is an independent prognostic marker for biological aggressiveness of this tumor type [69]. Through gene set enrichment analysis, low *CHD8* expression was found to be significantly associated with components of the WNT/β-catenin signaling pathway and with cell cycle regulators, and *CHD8* knockdown in gastric cancer cells promotes proliferation [69]. These reports are consistent with previous studies showing

that CHD8 inhibits β-catenin-mediated gene expression through its direct interaction with β-catenin [9], and cyclin E2 expression through its interaction with RNA polymerase II during transcriptional elongation [70]. These genomic and functional findings indicate a tumor-suppressive role for CHD8 in gastric cancer, and implicate both CHD8 and CHD7 in CRCs.

In addition, Colbert *et al*. reported that CHD7 expression predicts favorable survival in patients with resected pancreatic ductal adenocarcinoma (PDAC) [71]. CHD7 depletion sensitizes PDAC cells to gemcitabine treatment and delays their growth in tumor xenografts. Immunohistochemical analysis of specimens from 59 patients with resected PDAC receiving adjuvant gemcitabine revealed that low CHD7 expression was associated with increased recurrence-free survival and overall survival [71]. In addition, Pleasance *et al*. identified rearrangements of the *CHD7* locus in three small-cell lung cancer cell lines, two carrying a *PVT1-CHD7* fusion gene in the setting of *MYC* amplification and one carrying a tandem duplication of exons 3–8 of *CHD7* [72,73]. These data imply roles for CHD7 in pancreatic and lung cancers.

A number of studies also identified *CHD1* as a tumor suppressor mapping to human 5q21, a region frequently deleted in prostate cancer [74-76]. Berger *et al*. identified splice site mutations and intragenic breakpoints of *CHD1* in 42.9% (3/7) of primary prostate tumors analyzed by whole-genome sequencing [77]. Grasso *et al*. identified focal deletions/mutations of *CHD1* in 8% (10/119) of prostate primary tumors analyzed through exome sequencing and array comparative genomic hybridization analysis [78]. Burkhardt *et al*. found that CHD1 is required for efficient recruitment of the androgen receptor (AR) to promoters of hormone-responsive genes, and that CHD1 regulates expression of AR-responsive tumor suppressor genes, including *NKX3–1 (NK3 homeobox 1), FOXO1 (Fork-head box 01)* and *PPAR-γ* [74]. Interestingly, Huang *et al*. and Liu *et al*. independently revealed that depletion of CHD1 in prostate cancer cells increases cell invasiveness without altering cellular proliferation [75,76]. Together, these findings strongly indicate tumor-suppressive functions for CHD1 in the prostate and suggest that CHD1 deficiency may contribute to prostate cancer metastasis.

Increasing evidence also reveals important roles for CHD4 in serous tumors and other cancers. By exon sequencing of 52 primary serous endometrial tumors, Le Gallo *et al*. identified somatic mutations of *CHD4* in 17% of the samples, significantly higher than the background mutation rate ($q \leq 0.0353$) [79]. Zhao *et al*. also identified somatic missense mutations in *CHD4*, many of which appear to impair CHD4 function, in 27.3% (6/22) uterine serous carcinomas analyzed, which was a significant increase in mutation burden than expected ($p < 2.4 \times 10^{-6}$) [80]. In addition, copy number gain and loss of the region of human chromosome 12 that harbors *CHD4* are found in 28% (7/25) and 12% (3/25), respectively, of serous carcinomas [80]. These genomic data provide strong support for a role of CHD4 perturbation in serous tumor development. Functionally, a number of studies have indicated that CHD4 is a key regulator of the DNA-damage response and genome maintenance [29,31,32,81], suggesting that CHD4 is critical for genomic integrity and that its disruption contributes to tumorigenesis. In addition, CHD3 and CHD4 are catalytic components of the NuRD (nucleosome remodeling histone deacetylase) complex, which has been associated with tumorigenesis, epithelial-to-mesenchymal transition and metastasis

[82]. For example, CHD4 and CHD3 bind ZGPAT (zinc finger, CCCH-type with G patch domain), a transcriptional repressor of genes encoding modulators of cellular proliferation, survival and migration, thereby inhibiting breast cancer development [83].

Some studies suggest roles for CHD6 in CRC and bladder cancer. Mouradov *et al*. identified *CHD6* mutations in 19.5% (8/41) of CRC cell lines studied [84]. Hassan *et al*. performed CNV profiling of 64 paired CRC-normal specimens from the same patient, and revealed significant gains of 20q12—a chromosomal region that encompasses *CHD6* and seven other genes—in 45.31% of the tumors [85]. In addition, Gui and colleagues detected missense mutations in *CHD6* in 7% (7/97) of transitional cell bladder carcinomas [86]. These genomic findings implicate a role for CHD6 in colorectal cancer and bladder cancer, although additional functional data are required to support this hypothesis. Similarly, genomic data for the prevalence of *CHD2* lesions in human cancer are currently limited. However, deficiency of Chd2 in mice has been shown to lead to lymphomagenesis [35]. *Chd2* mutant cells accumulate higher levels of γ-H2AX and exhibit a defect in repair of DNA damage after γ-irradiation, implying a role for Chd2 in the DNA damage response and maintenance of genomic stability [35]. In addition, cystic endometrial hyperplasia occurs in female mice that are heterozygous for a different *Chd2* mutant allele [87].

Together, this accumulating body of literature indicates important roles for CHD family members in a broad range of cancers. Particularly compelling evidence has been shown for the tumor-suppressive roles of CHD5 in a variety of cancers, CHD1 in prostate cancer, CHD4 in serous cancer and CHD8 in gastric cancer. Multiple CHD proteins including CHD2, CHD4, CHD5, CHD6, CHD7 and CHD8 are also implicated in tumorigenesis, particularly in CRCs. These findings imply that perturbation of CHD-mediated chromatin remodeling is a common theme in tumorigenesis, while individual CHD proteins could exert particular functions in specific cancer types. On the other hand, significant variations in mutation frequencies of *CHD* genes have been reported in different studies, which will require further analyses to clarify. More functional data are also needed to further demonstrate and elucidate the roles of CHD proteins such as CHD6 in cancer development.

CHD proteins in neurological syndromes

Increasing evidence reveals important roles for CHD proteins in neurological syndromes. A battery of independent studies discovered 13 *de novo* mutations of *CHD8* in patients with autism spectrum disorder (ASD) and consistently identified *CHD8* as one of the most significant risk genes for autism [88-91]. In addition, McCarthy *et al*. reported *de novo* mutations in *CHD8* in patients with schizophrenia through whole-exome sequencing of 57 parent–parent–offspring trios [92]. In addition to these recurrent *CHD8* mutations, lesions in other *CHDs* (*CHD1*, *CHD2*, *CHD3*, *CHD5* and *CHD7*) were identified in the same studies [88-91]. Of particular note, mutations in *CHD7* cause CHARGE syndrome, a genetic syndrome characterized by a constellation of developmental defects that often includes behavioral abnormalities [93-98]. A large percentage (28–42%) of CHARGE syndrome patients are reported to have autism-like behaviors [99-102], suggesting a role for CHD7 in the pathogenesis of ASD. Jiang and colleagues identified an inherited missense mutation in *CHD7* in a family with autism [103]. In addition, Pinto *et al*. reported distinct *de novo*

deletions within *CHD2* in two brothers with ASD, one with deletion of the first six exons of *CHD2*, and the other with an 83 kbp deletion within *CHD2* [104]. In addition, a *de novo* missense mutation in *CHD2* was reported in ASD [89], and a 15q26.1 microdeletion encompassing *CHD2* and the flanking gene *RGMA (repulsive guidance family molecule a)* was reported in a patient with autism-like behavior and epilepsy [105]. Together, these findings suggest that disruption in genes encoding CHD chromatin remodelers such as *CHD2, CHD7* and *CHD8* play important roles in the pathogenesis of ASD.

An increasing body of evidence also strongly implicates critical roles for CHD2 in epileptic encephalopathy. Targeted sequencing of 46 candidate genes in 500 individuals affected with epileptic encephalopathy—a severe form of epilepsy beginning in infancy—revealed six mutations in *CHD2*, representing 1.2% of the subjects and identifying *CHD2* as the most highly mutated gene [106]. Suls *et al*. performed whole-exome sequencing of proband–parent trios that included nine patients with Dravet syndrome, a severe form of epilepsy, and identified *de novo* mutations in *CHD2* in 33% (3/9) of the individuals [107]. The authors also showed that knockdown of *chd2* in zebrafish caused altered locomotor activity and epileptiform discharges similar to seizures described in affected persons [107]. Lund *et al*. found mutations in *CHD2* in 9% (2/22) of patients with Lennox–Gastaut syndrome, an epileptic encephalopathy with a heterogeneous etiology [108]. *De novo* mutations in *CHD2* in Lennox–Gastaut syndrome were found by exome sequencing of 109 probands and their parents [109]. In addition, a *de novo CHD2* frame shift mutation was reported in a patient with intellectual disability [110]. These findings indicate that *CHD2* is a risk gene for epileptic encephalopathy, and suggests that CHD2 perturbation may contribute to other neurological disorders as well.

Preliminary evidence also suggests potential roles for several other CHD family members in neurological dysfunctions. For example, several human ataxia syndromes have CNVs on chromosome 20q12 that encompass *CHD6* [112-114], and deletion of exon 12 of *Chd6* in mice impairs motor co-ordination [115]. A *de novo* balanced (4; 20)(q33; q12) translocation that disrupts *CHD6* and compromises its expression was also reported in a patient with severe mental retardation [111]. In addition, deletion of 1p36.32-p36.22, a chromosome region encompassing *CHD5* was reported in patients with developmental delay and intellectual disability [117,118]. We found that Chd5-compromised mice have severe behavioral phenotypes and aberrant dendritic arborization (Mills, unpublished). A *de novo* mutation in *CHD4* was reported in 1/109 patients with epileptic encephalopathy [109], and conditional disruption of *Chd4* specifically within Schwann cells leads to abnormal motor co-ordination and hind limb reflexes [116]. While more supporting human genetic data are needed, these functional data in model organisms and preliminary reports in humans suggest that perturbation of CHD4, CHD5 and CHD6 might also play important roles in neurological dysfunction.

Taken together, compelling evidence has established critical roles for CHD2, CHD7 and CHD8 in a number of neurological disorders, in particular ASD and epileptic encephalopathy, while preliminary data implicate roles for CHD4, CHD5 and CHD6 in neurological dysfunction, suggesting common roles for perturbation of CHD chromatin remodelers in the pathogenesis of neurological diseases.

CHD proteins in developmental disorders

CHD proteins are also implicated in development. Most notably, lesions in *CHD7* cause CHARGE syndrome, a developmental syndrome named by its constellation of birth defects including ocular coloboma, congenital heart defects, choanal atresia, retardation of growth and development, genital hypoplasia and ear anomalies associated with deafness [93-98]. The diverse developmental anomalies that clinically define CHARGE syndrome suggest that CHD7 plays pleiotropic roles in development, consistent with the fact that *CHD7* is expressed in a wide variety of tissues during embryogenesis and in the adult [98,119]. CHD7 binds to H3K4me3 at enhancer regions of numerous genes, and is bound to these regulatory elements in a cell type and stage-specific manner [120]. CHD7 is implicated in neurogenesis, ear morphogenesis, osteoblast formation and somitogenesis [119,121-123]. Nucleosome remodeling is believed to be a key function for CHD7 during development, as CHARGE syndrome mutations impair CHD7's chromatin-remodeling activity [8]. In addition to CHARGE syndrome, polymorphisms within *CHD7* are associated with susceptibility to idiopathic scoliosis, a progressive spine deformity that is often deadly [124].

In addition to CHD7, many studies imply diverse roles for other CHD members in development. Disruption of *Chd2* using a gene trap strategy leads to neonatal lethality in homozygous mice and partial lethality in heterozygotes [87]. Heterozygous mice that survive have developmental delay and are runted as adults, with extremely hypoplastic subcutaneous fat and pronounced lordokyphosis by 4 months of age [87]. A small proportion (2/15) of heterozygous mice have eye defects [87]. A distinct *Chd2* mutant mouse model with a mutation that abrogates the DNA-binding activity of Chd2 has delayed embryogenesis and perinatal lethality [125,126]. Surviving heterozygous mice have an enhanced susceptibility to damage in many primary organs, in particular the kidney and heart [125,126]. The diverse developmental defects exhibited by Chd2-deficient mice indicate that Chd2 plays important roles in the development of multiple tissues and organs. Human developmental disorders associated with *CHD2* dysfunction have not yet been reported, however, a *CHD2* breakpoint mutation was found in a patient with scoliosis, consistent with the lordokyphosis phenotype observed in *Chd2*-deficient mice [87]. In addition, Qin *et al*. reported an association between a genetic variant of *CHD2* and nonobstructive azoospermia [127]. We and others recently discovered that Chd5 is critical for sperm development [64,65]. We defined Chd5 as a master regulator of the histone-to-protamine replacement process during the post-meiotic phase of sperm development [64]. Inactivation of *Chd5* in mice results in deficient histone acetylation, nucleosome eviction and increased DNA damage during spermatid maturation, leading to deficient sperm production and defective sperm function, culminating in male infertility [64]. Consistent with the compromised fertility of Chd5-deficient mice, we also found that low *CHD5* expression is correlated with low human male fertility [64]. In addition, both our lab and others discovered that Chd5 is induced during neuronal development and is required for neurogenesis [16,63]. CHD5 binds a large cohort of genes and is required for the maintenance of H3K27me3 at these loci and activation of polycomb-repressed neuronal genes [16]. In addtion, Chd4 is essential for polycomb-mediated inhibition of astroglial

differentiation through its interaction with Ezh2 and suppression of genes that induce the astrogenic lineage [128]. Chd4 also interacts with Nab corepressors to direct Schwann cell mediated peripheral nerve myelination, and conditional ablation of Chd4 in Schwann cells leads to delayed myelination, radial sorting defects, hypomyelination and deregulation of promyelinating Schwann cells [116]. In addition, Chd4 is required for expression of CD4 (CD4 molecule) and T-cell development [129], and CHD4 forms a complex with GATA3 (GATA-binding protein 3) to simultaneously activate transcription of Th2 cytokines and to repress transcription of the Th1 cytokine IFNG (interferon, γ) to establish T helper 2 cell identity [130]. Chd4 is also required for the establishment of basal keratinocytes within the epidermis of the skin and for the morphogenesis of hair follicles [131]. Consistent with Chd4's role in skin development, autoantibodies against CHD3 and CHD4 are detected in 10–30% of patients with dermatomyositis [132]. Also, Chd8 is essential for mouse embryogenesis, as *Chd8*−/− embryos manifest growth retardation at embryonic day 5.5 (E5.5) and developmental arrest accompanied by massive apoptosis at E7.5 [133]. Furthermore, Chd8 recruits histone H1 to suppress p53-mediated apoptosis during early embryogenesis [134]. The *Xenopus laevis CHD8* ortholog *Duplin* encodes a negative regulator of Wnt/β-catenin signaling that inhibits axis formation during embryonic development [135]. Injection of mRNA encoding Duplin into the dorsal axis of the developing embryo leads to defective head development [135]. Mutation of *Chd1* causes abnormal wing development, male infertility and female subfertility in *Drosophila melanogaster*, indicating a multifaceted role for Chd1 during embryogenesis [136]. Chd1 plays a crucial role during ovarian follicle development in the silkmoth *Bombyx mori*, as it specifically binds and repositions nucleosomes located near promoters of genes encoding chorion proteins, allowing binding of CEBP (CCAAT/enhancer-binding protein) and TBP (TATA box-binding protein) and initiation of transcription [137]. In mouse, Chd1 is essential for maintaining an open chromatin conformation and for pluripotency of embryonic stem cells [138]. Altogether, these findings indicate that CHD proteins are widely implicated in developmental processes. Although human developmental disorders reported to be associated with lesions of *CHD* genes are currently limited (with the exception of *CHD7)*, the diverse roles demonstrated in development of mouse and other organisms suggest that dysfunction of CHD proteins could also bear severe consequences that contribute to a range of developmental anomalies and syndromes.

Connections

The roles of CHD proteins in cancer, neurological syndromes and developmental disorders not only suggests diverse functions for these chromatin remodelers, but also indicates shared risks and interconnections between the pathogenesis of these major human diseases. Increasing clinical and epidemiologic studies also suggest links between cancer, neurological diseases and developmental disorders. For example, Shavelle *et al*. analyzed the cause of death for 13,111 patients with autism that had been followed between 1983 and 1997, and found that there was a higher standardized mortality from cancer, ranging from 1.9 in subjects with no or mild intellectual disability, to 2.9 in subjects with moderate, severe or profound intellectual disability, although the absolute number of deaths in both categories was only 6 and 15, respectively [139]. Kao *et al*. analyzed the prevalence of autism in cancer

subjects that were diagnosed in the United States, and found significant correlations between the prevalence of autism and the incidence of *in situ* breast cancer, but no correlation with the other types of cancers analyzed [140]. Although more studies are needed to validate these findings and to exclude other factors such as environmental effects, these epidemiologic studies suggest a link between certain forms of cancer and autism.

Similarly, a recent study analyzed the medical records of 2,238 infertile men, 451 of whom had azoospermia (i.e., lack of sperm), and found that infertile men were 1.7-times more likely to develop cancer than the general population [141]. Furthermore, men with azoospermia had a 2.9-fold increased risk of developing cancer. This finding is in agreement with a previous study reporting a significant association between subfertility and increased risk of testicular cancer using meta-analysis of seven case–control studies that included 4,954 participants [142], suggesting a common etiology between cancer and male infertility. In line with this study, we discovered that deficiency of Chd5 leads to male infertility, cancer and behavioral anomalies, at least in mice [40,64]. We defined *CHD5* as a tumor suppressor mapping to human 1p36 [40], and a trove of later studies identified lesions in *CHD5* and demonstrated tumor-suppressive functions for CHD5 that when compromised lead to a variety of human cancers [43-46,48-55,58,60,143]. We discovered that CHD5 deficiency also correlates with male infertility in humans [64]. Together, these findings define perturbation of CHD5-mediated chromatin regulation as one potential common etiology for the three types of diseases. Similarly, *CHD8* is both a risk gene for ASD [88-91] and an independent prognostic factor for gastric cancer [69], while it is also essential for embryonic development including axis formation and head development [134,135]. CHD8 negatively regulates WNT/β-catenin signaling [135], which could be a common pathway affected by *CHD8* lesions in pathogenesis of all these diseases, as WNT/β-catenin signaling is implicated in neurological syndromes, tumorigenesis and development [144-146]. However, CHD8 also has WNT/β-catenin-independent functions [134], through which CHD8 could affect pathogenesis of the three disease categories. *CHD7* mutations are the main cause of CHARGE syndrome, a disease characterized by an array of developmental defects [93-98], with 28–42% of CHARGE syndrome patients having autism-like behaviors [99-102]. *CHD7* mutations are also found in ASD patients [103]. In addition, *CHD7* is highly mutated in CRCs with the CpG island methylator phenotype 1 [68] and is rearranged in small-cell lung cancer cell lines [72,73]. CHD7 expression also predicts a favorable survival outcome for patients with resected PDAC [71]. These observations indicate that CHD7 is involved in the pathogenesis of developmental and neurological syndromes as well as cancer. Similarly, CHD2 is implicated in pathogenesis of epilepsy and ASD [88-91,104-110], lymphoid cancers [35], as well as being essential for the development of the axial skeleton, kidney and other organs [87,126], suggesting a common role for *CHD2* lesions in pathogenesis of these diseases. *CHD4* is reported to be among the most frequently mutated gene in serous tumors [79,80], and is also essential for astroglial differentiation [128], T-cell development [129] and skin development [131]. Autoantibodies against CHD4 are detected in 10–30% of human patients with dermatomyositis [132]. While human genetic data implicating CHD4 alterations in neurologic diseases are currently limited, ablation of Chd4 in Schwann cells leads to abnormal motor co-ordination and hind limb reflexes [116], suggesting that CHD4 could affect development of all three types of diseases.

Altogether, these findings define deregulation of CHD proteins as a common culprit for three main categories of human diseases, and also indicate shared mechanisms underlying the pathogenesis for the different disease syndromes. In addition to CHD proteins, mutations in other chromatin remodelers, such as BAF250A, BAF250B, BRG1 and BRM, have also been identified and implicated in the pathogenesis of both cancer and neurodevelopmental syndromes, as recently reviewed by Ronan *et al*. [147], suggesting perturbation of chromatin remodeling as a common pathogenic mechanism.

At the molecular level, how could chromatin-remodeling proteins, more specifically CHD proteins, impact pathogenesis that impinges upon cancer, neurological syndromes and developmental disorders? These human ailments are each characterized by genomic lesions, including mutations and CNVs. Several CHD proteins play critical roles for the DNA damage response and for maintaining genome integrity [29-35]. For example, CHD4 is a critical factor that co-ordinates both checkpoint signaling and repair of DNA damage [29-32]. Depletion of CHD4 disrupts the DNA damage response at the chromatin level, leading to an increase in DNA breaks and rampant genomic instability [29-32]. CHD2 is also important for mediating DNA repair [34,35], and Chd2-deficient cells have a compromise in repair of DNA damage after ionizing or ultraviolet irradiation [34,35]. We also found that Chd5 is required for an efficient DNA damage response in the male germ line and that DNA damage induces *Chd5* expression [64]. Given the common roles for CHD proteins in repair of DNA damage and maintenance of genomic stability [29-35] and their shared functions in modulating chromatin structure and gene expression programs in diverse cellular processes [1], we speculate that a compromise in CHD proteins renders chromatin more susceptible to intrinsic and/or extrinsic damage, resulting in a higher extent of genomic lesions. The functional genomic elements jeopardized by these perturbations could have versatile roles in regulating cellular proliferation, tissue development and neural function, thereby culminating in cancer, developmental disorders and neurological syndromes in the same subject. Depending on the specific combination of functional genomic elements jeopardized by these lesions and the compounding consequences, these perturbations could also lead to a specific type of disease or make one disease more pronounced than the others.

Conclusions & future perspectives

The common implications for CHD proteins in cancer, neurological syndromes and developmental disorders and the potential underlying molecular mechanisms linking the pathogenesis of these diseases, exemplify the interconnections between these diseases and the converging roles of chromatin-remodeling proteins in the pathogenesis of multiple diseases. We expect future studies to add increasing evidence for the interconnections between cancer, neurological syndromes and developmental disorders, and to provide a clearer understanding of the underlying molecular mechanisms. Such insight will be valuable for developing better diagnosis, treatment and management for patients affected by these prevalent diseases (Table 1).

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- • of interest;
- •• of considerable interest

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Executive summary

- Chromatin-remodeling proteins are classified into four families (SWI/SNF, ISWI, INO80 and chromodomain helicase DNA binding [CHD]) and play important roles in diverse molecular and cellular processes.
- Nine CHD chromatin-remodeling proteins (CHD1–9) are divided into three subfamilies based on their distinct functional domains; these proteins share common ATPase domains and tandem chromodomains and are implicated in a number of biological processes and human diseases.
- Increasing evidence identifies important roles for CHD proteins in cancer and demonstrates CHD proteins as useful for predicting patient survival.
- Emerging evidence is establishing lesions in *CHD* genes as top risk factors for neurological diseases such as autism spectrum disorder and epileptic encephalopathy.
- CHD proteins are essential for diverse developmental processes, and mutations in *CHD* genes can lead to severe developmental disorders (e.g., *CHD7* mutations in CHARGE syndrome).
- The common roles for CHD perturbation in cancer, neurological diseases and developmental disorders indicate shared etiology among these diseases, which is supported by increasing epidemiological evidence.
- Critical roles of CHD proteins in the DNA damage response and the maintenance of genome integrity may underlie the pathogenesis of cancer, neurological diseases and developmental disorders.
- Future studies will add increasing evidence for the interconnections between cancer, neurological diseases and developmental disorders and provide a clearer understanding for the molecular mechanisms that are responsible.

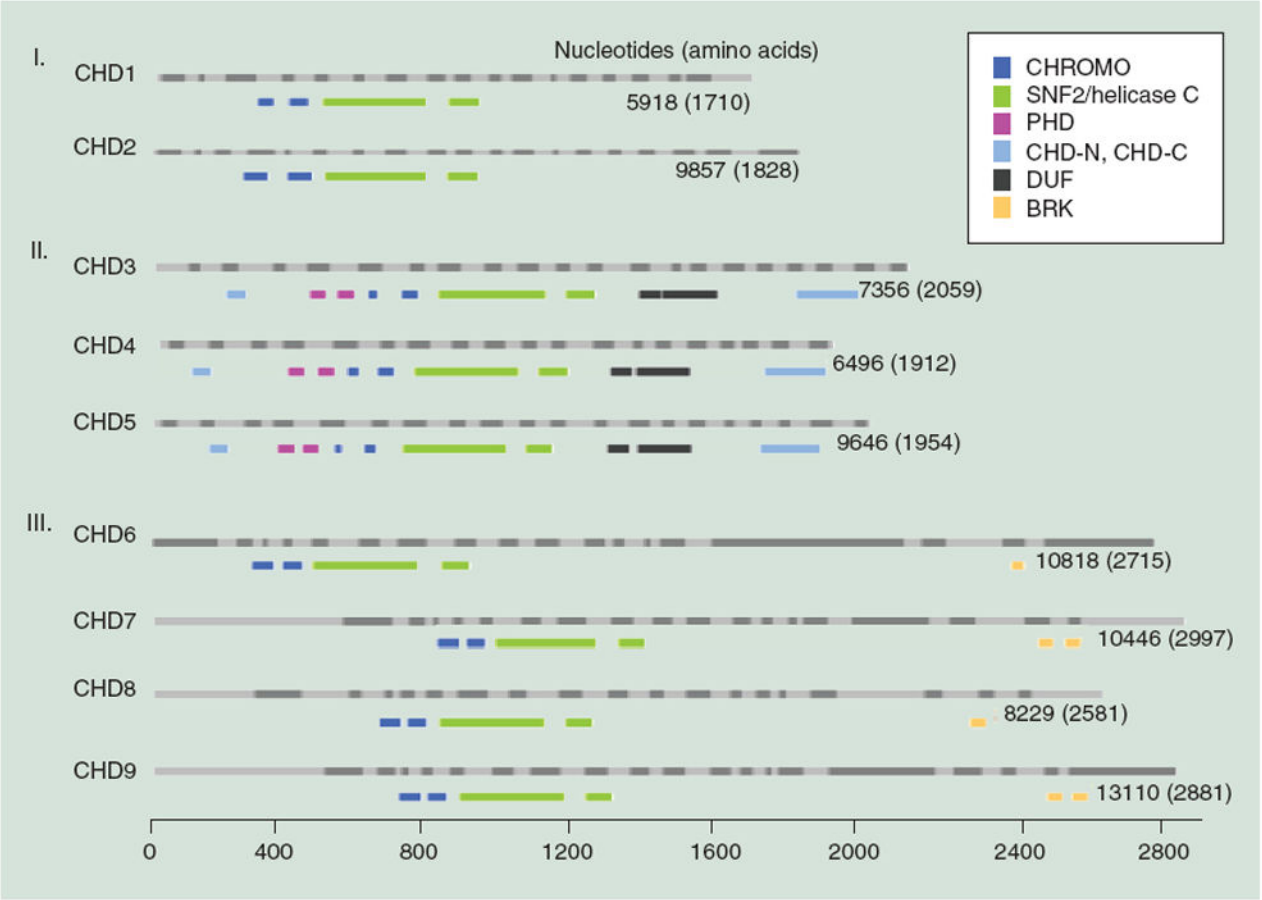

Figure 1. The chromodomain helicase DNA binding family of chromatin remodelers

CHD proteins are classified into three subfamilies (Roman numerals) based on their functional motifs (see legend). The human CHD family based on ensemble is drawn to scale, with light and dark gray bars depicting alternating exons (above) and the functional motifs from PFAM (a database of protein families of multiple sequence alignments generated using hidden Markov models) shown in color (below) for each CHD member. The number of nucleotides and amino acid residues for the CHD transcript and protein, respectively, are shown.

BRK: Brahma and Kismet domains; CHD: chromodomain helicase DNA binding; CHROMO: Chromodomain; CHD-N, CHD-C: CHD_N and CHD_C are shown in upstream and downstream region, respectively; DUF: Domain of unknown function; PHD: Plant homeodomain; SNF2/helicase C: SNF2_N and helicase_C are shown in upstream and downstream region, respectively.

Table 1

Chromo domain helicase DNA binding (CHD) proteins and human disease.

Gene	Cancer	Developmental diseases	Neurologic diseases
CHD1	Prostate cancer [74-76], gastric cancer [67], colorectal cancer [67]	Abnormal wing development, male infertility and female subfertility in *Drosophila melanogaster* [136] ovarian follicle development in the silkmoth *Bombyx mori* [137]	Autism spectrum disorder [89]
CHD2	Lymphoma [35], cystic endometrial hyperplasia [87]	Scoliosis [87], embryogenesis, growth retardation, kidney, heart, eye and fatty tissue development in mouse [87,125,126], myogenesis [148]	Autism spectrum disorder [89,104,105], epilepsy [104-109], intellectual disability [110]
CHD3	Prostate cancer [149], breast cancer [83] gastric cancer [67], colorectal cancer [67]		Autism spectrum disorder [91]
CHD4	Serous endometrial tumors [79,80], prostate cancer [149], breast cancer [83]	Astrogenic differentiation [128], Schwann cell-mediated peripheral nerve myelination [116], T-cell development [129], skin development and morphogenesis of hair follicles [131], dermatomyositis [132]	Epileptic encephalopathy [109], abnormal motor co-ordination and hind limb reflexes [116]
CHD5	Neuroblastoma [43-47], glioma [40,48,49], breast cancer [48,50], lung cancer [51], ovarian cancer [52], gastric cancer [53], gallbladder carcinoma [54], colorectal cancer [48,55,56], hepatocellular carcinoma [57], melanoma [58], leukemia [59], squamous cell carcinoma [60]	Sperm development [64,65], neurogenesis [16,63]	Intellectual disability [117,118], hyperactivity and repetitive behaviors (Mills, unpublished)
CHD6	Colorectal cancer [84,85], bladder carcinoma [86]		Mental retardation [111], ataxia syndromes [112-115],
CHD7	Colorectal cancer [67,68], pancreatic ductal adenocarcinoma [71], small-cell lung cancer [72,73]	CHARGE syndrome [93-98] scoliosis [124] neurogenesis, ear morphogenesis, osteoblast formation and somitogenesis [119,121-123]	Autism spectrum disorder [91,103,99-102]
CHD8	Colorectal cancer [67,68], gastric cancer [69]	Embryogenesis [133] head development [135]	Autism spectrum disorders [88-91], schizophrenia [92]