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Nervous System Development and Disease: A Focus on Trithorax Related Proteins and Chromatin Remodelers

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Abstract

The nervous system comprises many different cell types including neurons, glia, macrophages, and immune cells, each of which is defined by specific patterns of gene expression, morphology, function, and anatomical location. Establishment of these complex and highly regulated cell fates requires spatial and temporal coordination of gene transcription. Open chromatin (euchromatin) allows transcription factors to interact with gene promoters and activate lineage specific genes, whereas closed chromatin (heterochromatin) remains inaccessible to transcriptional activation. Changes in the genome-wide distribution of euchromatin accompanies transcriptional plasticity that allows the diversity of mature cell fates to be generated during development. In the past 20 years, many new genes and gene families have been identified to participate in regulation of chromatin accessibility. These genes include chromatin remodelers that interact with Trithorax group (TrxG) and Polycomb group (PcG) proteins to activate or repress transcription, respectively. Here we review the role of TrxG proteins in neurodevelopment and disease.

Keywords

Trithorax; Chromatin; Neurodevelopment; Disease

1. Introduction

Embryonic development proceeds from a single multipotent cell to a multicellular complex organism with distinct organs, tissues, and cell types that retain their identities over developmental space and time. While some mature cells and tissues exhibit high levels of proliferative and regenerative potential (i.e, skin and gut epithelial cells), others (i.e, neurons) are quiescent and unable to self-renew upon injury. The mechanisms by which specific cell types maintain their fate or “memory” that instructs profiles of gene expression

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despite active DNA replication and mitosis remain a mystery; however, much work has been done to identify the genes, molecules, and chromatin-associated factors involved in this process. Chromatin structure has a regulatory role on the transcriptional profile on processes that underlie cellular proliferation and maintenance of cell fate. Identifying the molecular pathways that direct chromatin structure and gene expression is a central goal in developmental biology, and has important relevance for understanding basic mechanisms of developmental disorders.

This review explores mechanisms of human developmental disorders caused by pathogenic variants in human homologs of *trithorax* group (TrxG) genes encoding histone methyltransferases, demethylases, and chromatin remodelers (Table 1). TrxG is a family of proteins that form large multi-protein complexes exhibiting histone methyltransferase and/or chromatin remodeling functions (Schuettengruber et al., 2011). Drosophila *trithorax (trx*) was first identified as a spontaneous pathogenic variant in flies with abnormalities of head, thoracic, and abdominal structures, consistent with transformations of body segment identity (Ingham, 1983). In the fly, *trx* encodes for a histone methyltransferase and acts to suppress the functions of Polycomb group (PcG) genes. TrxG and PcG genes are highly conserved across evolution, and act antagonistically at genetic targets such as the *Hox* gene cluster to regulate gene expression (Steffen and Ringrose, 2014). In general, PcG genes encode proteins that function as transcriptional repressors, whereas TrxG genes encode proteins that act as transcriptional activators (Fig. 1). This mutual antagonism has led to a model whereby PcG and TrxG proteins switch between stably repressed or activated patterns of gene expression during development.

TrxG proteins generally function as large multi-protein complexes, where they localize to transcription start sites, enhancers, and gene bodies, with variable roles that are influenced largely by their interacting partners and target sites in the genome. Based on their molecular functions, TrxG proteins are categorized into three general classes. The first class of TrxG proteins comprises SET-domain histone methyltransferases. This class includes the COMPASS (complex of proteins associated with Set1) members SET1A, SET1B, and mixed lineage leukemia-1-4 (MLL1, MLL2, MLL3 and MLL4), among others (Piunti and Shilatifard, 2016). The second class of TrxG proteins contains ATP-dependent chromatin remodelers that “read” the histone modifications established by SET domain-containing enzymes. This class includes switch/sucrose non-fermenting (SWI/SNF) proteins, imitation switch (ISWI), inositol auxotroph 80 (INO80), and chromodomain-helicase-DNA binding (CHD) proteins. Chromatin remodelers harness the energy of ATP to slide nucleosomes along DNA, evict nucleosomes from DNA, or exchange histone dimers, thereby altering the chromatin architecture and making it more or less accessible to transcription factors and other regulatory proteins or RNA. The third class of TrxG proteins bind specific DNA sequences called TrxG response elements (TREs), which often coincide with PcG response elements (PREs) that switch status between activation and silencing by mechanisms that involve noncoding RNA transcription (Herzog et al., 2014). This general classification of TrxG proteins is still evolving, as new information is obtained about the functions of this large group of proteins and associated factors.

2. Histone modifications and developmental disorders

2.1 Epigenetic mechanisms

Abundant post-translational modifications of histone tails (phosphorylation, methylation, acetylation, ubiquitination, sumoylation), which regulate accessibility of genetic information, are a distinguishing feature of eukaryotic organisms. Epigenetic regulation of gene expression requires involvement of many different histone modifying enzymes, including “writers” that attach modifications to histone tails, and “erasers” that remove modifications, whereas “readers” recognize modifications distributed in a cell-specific manner across the genome. A function of histone modifications is to coordinate chromatin remodelers and transcriptional machinery for transcriptional regulation. Histone modifications function together with histone variants, chromatin-remodeling activities, DNA methylation, and histone chaperones to contribute to the faithful establishment and maintenance of the chromatin environment.

Among various post-translational modifications, histone H3 Lysine 4 (H3K4) methylation (H3K4me) is evolutionarily conserved and closely associated with transcriptionally active chromatin (Bannister and Kouzarides, 2011; Shilatifard, 2006). Data supports H3K4 methylation in pivotal early steps of the signaling cascade leading to transcriptional activation (Campos and Reinberg, 2009; Ruthenburg et al., 2007). Also, H3K4me recruits basic transcriptional machinery (Tang et al., 2013; Vermeulen et al., 2007), including histone acetyltransferases and ATP-dependent chromatin remodeling proteins of the CHD family such as CHD7 and CHD8 (Ruthenburg et al., 2007; Schnetz et al., 2009; Schnetz et al., 2010; Taverna et al., 2007; Wysocka et al., 2006). Genome-wide analyses show that H3K4me, which is highly enriched at gene promoters and enhancers, positively correlates with transcription rates, occupancy of RNA Pol II, and histone acetylation at 5′ regions of active genes (Barski et al., 2007; Heintzman et al., 2007). H3K4me is also enriched at chromatin regions ‘poised’ for differentiation and lineage specification in embryonic stem cells (ESCs), juxtaposed with the antagonistic H3K27me3 mark (Azuara et al., 2006; Bernstein et al., 2006; Pan et al., 2007). Thus, specific histone marks or combinations of histone marks serve as tags for unique functional regions of the genome.

2.2 Disorders of epigenetic factors

Disruptions of histone modifications and chromatin accessibility comprise an important class of human developmental disorders (Fahrner and Bjornsson, 2014; Lopez and Wood, 2015). Human genetic disorders caused by pathogenic variants in epigenetic modulators include CHARGE, Kabuki, Coffin-Siris, Kleefstra, Wiedemann-Steiner, and Nicolaides-Baraitser syndromes (Table 1)(Jones et al., 2012; Mendelsohn et al., 2014; Strom et al., 2014). Neurodevelopmental disorders have also been associated with pathogenic variants in TrxG genes, COMPASS members, and other ATP-dependent chromatin remodelers. Perhaps not surprisingly, altered dosage and function of TrxG-related proteins leads to a variety of cancers such as leukemia, rhabdoid tumors, and meningioma (Table 1) (Schuettengruber et al., 2017).

3. ATP-dependent chromatin remodelers

3.1 ISWI

Goodwin and Picketts, in this issue, provide a comprehensive review of ISWI and its role in neurodevelopmental disorders, including genes that encode ISWI components *BAZ1B* and *CECR2* in Williams-Beuren and Cat Eye syndrome, respectively (Banting et al., 2005; Bozhenok et al., 2002; Footz et al., 2001; Lu et al., 1998; Mellor, 2006; Peoples et al., 1998). Readers are encouraged to read their paper for more information on this important class of ATP-dependent chromatin remodelers.

3.2 SWI/SNF

SWI/SNF (also known as BRG1/BRM associated factor (BAF)) complexes are comprised of at least 15 different subunits that are enriched at gene promoters, enhancers, and super-enhancers (Sokpor et al., 2017). Dynamic switching among BAF subunits during neuronal development has the potential to generate hundreds of different complexes (Lessard et al., 2007). Five genes encoding subunits of the SWI/SNF family (*SMARCA4 (BRG1)*, *SMARCB1 (SNF5)*, *SMARCE1 (BAF57)*, *ARID1A (BAF250A)*, and *ARID1B (BAF250B)*) have been implicated in Coffin-Siris syndrome (Santen et al., 2012; Tsurusaki et al., 2012), and pathogenic variants in *SMARCA2* (*BRM*) cause Nicolaides-Baraitser syndrome (Sousa et al., 2014; Van Houdt et al., 2012). Pathogenic variants in *SMARCA4* (Coffin-Siris syndrome) and *SMARCA2* (Nicolaides-Baraitser syndrome) are predicted to result in functionally inert proteins that retain their abilities to interact with and target specific regions of the genome with other subunits of SWI/SNF. Pathogenic variants in *SMARCA1* (*SNF2L1*) have been reported in individuals with schizophrenia, microcephaly, intellectual disability, and Rett-like phenotypes (Homann et al., 2016; Karaca et al., 2015; Lopes et al., 2016). Mechanistically, SWI/SNF and CHD proteins share the common property of flanking nucleosome-free regions (NFRs) in embryonic stem cells, suggesting that complex interactions between these protein classes are necessary for regulating distinct patterns of chromatin and gene expression (de Dieuleveult et al., 2016).

3.3 INO80

INO80 proteins, unlike other chromatin remodelers, have unique structural features and functions that include regulation of DNA replication and repair. INO80 promotes progression of the DNA replication fork, evicts RNA polymerase II at transcribed genes upon interaction with the replication fork, and releases nucleosomes after oxidative DNA damage (Poli et al., 2017). Recently, *INO80* was described as a candidate disease gene for an individual who presented with primary microcephaly and global developmental delay in a cohort of consanguineous families (Alazami et al., 2015). In addition, variants in *YY1AP1*, a component of the INO80 complex, were identified as a cause of Grange syndrome (Guo et al., 2017). Pathogenic variants in the INO80 homolog *SRCAP* cause Floating-Harbor syndrome, a neurodevelopmental disorder with expressive language delay, short stature, and abnormal skeletal/craniofacial development (Hood et al., 2012; Hood et al., 2016; Nikkel et al., 2013). Ultimately, evidence from these human genetic studies points to the importance of chromatin remodeling in DNA replication, damage, and transcription as critical during

development, and perturbation of these processes leads to overlapping phenotypes that affect neurodevelopment.

3.4 CHD

The CHD family comprises nine chromatin remodeling members characterized by the presence of two chromodomains (chromatin organization modifier), a structural domain of about 40–50 amino acid residues, centrally located DNA helicase domains, and less well-defined carboxyl terminal domains (Shur and Benayahu, 2005; Woodage et al., 1997). Chromodomains are not unique to the CHD family; they are also present in repressive Polycomb protein Pc and heterochromatin associated protein HP1 of *D. melanogaster*, where they were first described (Paro and Hogness, 1991). CHD proteins, similar to SWI/SNF proteins, regulate access to DNA by using the energy of ATP hydrolysis to alter chromatin structure, slide nucleosomes along DNA, or evict nucleosomes from the DNA strand during transcription or replication (Becker and Hörz, 2002; Eberharter and Becker, 2004; Lusser and Kadonaga, 2003; Manning and Yusufzai, 2017; Narlikar et al., 2002; Smith and Peterson, 2005). Moreover, CHD proteins "read" H3K4 methylation at transcription start sites and enhancers and exhibit pleiotropic functions during development, including regulation of pluripotency, stem cell proliferation, and lineage determination (Dowen et al., 2014; Hnisz et al., 2013; Niederreiter et al., 2015). The CHD family exhibits high evolutionary conservation back to *S. cerevisiae* and *D. melanogaster* with one and four members, respectively. In vertebrates, the nine CHD proteins are divided into three distinct subfamilies on the basis of similarities in amino acid sequence and functional protein domains (Liu et al., 2015; Woodage et al., 1997). CHD proteins were also recently shown to target specific nucleosomes near MNase-defined NFRs (de Dieuleveult et al., 2016).

3.4.1 The CHD Family Subclass I—Subclass I of human CHD proteins is comprised of CHD1 and CHD2, both of which are associated with human disease. Notably, subclass I proteins display the ability to interact with histone modifications (methylation of H3K4), through a chromodomain aromatic cage (Flanagan et al., 2007), and the ability to bind DNA through a C-terminal domain structure that resembles a SWI3, ADA2, N-CoR, and TFIIIB (SANT) domain and a SANT-like ISWI domain (SLIDE domain) (Aasland et al., 1996; Delmas et al., 1993; Grune et al., 2003; Ryan et al., 2011; Stokes and Perry, 1995; Woodage et al., 1997). Heterozygous pathogenic variants in *CHD1* were recently identified in six individuals with autism, developmental delay, speech apraxia, and craniofacial dysmorphisms (Pilarowski et al., 2017). *CHD2* was first implicated in neurodevelopment disease through case reports describing *de novo* deletions of 15q26 in individuals with epilepsy, developmental delay and craniofacial dysmorphisms (Capelli et al., 2012; Veredice et al., 2009). However, the definitive involvement of this chromatin remodeler in neurodevelopment, independent of other 15q26 genes, was not discovered until cohort studies applied targeted and whole exome sequencing approaches. *De novo* pathogenic variants and copy number variants (CNVs) in *CHD2* were later discovered in epileptic encephalopathy, non-syndromic intellectual disability, and autism spectrum disorder cohorts, suggesting that pathogenic variants in *CHD2* cause a spectrum of neurological phenotypes including seizures (Carvill et al., 2013; Chenier et al., 2014; Epi et al., 2013; Lund et al., 2014; O'Roak et al., 2014; Pinto et al., 2014; Rauch et al., 2012; Suls et al., 2013).

The underlying mechanism of *CHD2* pathogenic variants has not been precisely defined. Suls et al. utilized morpholino knockdown of *chd2* in zebrafish, and reported that larvae with *chd2* partial knockdown exhibited epileptiform discharges and abnormal twitching behavior (Suls et al., 2013). Several other phenotypes were also observed in *chd2* partial knockdown zebrafish, including microcephaly, growth retardation, curved body appearance, absence of the swim bladder, and pericardial edema. Consistent with multiple abnormalities observed in *chd2* mutant zebrafish, *Chd2* mutant mice that lack the C-terminal DNA binding domain also exhibit small size, a hunched appearance, and multiple organ abnormalities in the heart, spleen, liver, kidney and lymph nodes (Marfella et al., 2006). *Chd2* is expressed in adult mouse brain tissue; however, no brain abnormalities were reported upon necropsy or histopathology examination, nor was epileptic behavior observed (Marfella et al., 2006). It is possible that the lifespan of *Chd2* mutant mice (32 to 64 weeks) is too short to observe neurological phenotypes, or neurological abnormities are too subtle to be detected by the macroscopic and histopathology methods used for evaluation. Alternatively, expression of the mutant CHD2 protein (which retains the chromodomains and ATPase domain) may be sufficient to prevent neurological disease. Alternatively, there may be species-specific differences in CHD2 function between humans, zebrafish, and mice.

The chromatin remodeling role of CHD2 appears to influence the deposition of histone variant H3.3 at genes important for development. H3.3 is generally observed at chromatin associated with active transcription, but also contributes to the chromatin environment at bivalent gene promoters (Goldberg et al., 2010). Interestingly, depletion of H3.3 or Hira, the histone chaperone that deposits H3.3 at genic regions, leads to reduced H3K27me3 at bivalent gene promoters in mouse embryonic stem cells (ESCs), whereas *Chd2* depletion results in a greater enrichment of both H3.3 and H3K27me3 (Banaszynski et al., 2013; Semba et al., 2017). These studies highlight the importance of histone chaperones and CHD proteins in balancing repressive and active histone modifications at developmentally critical genes.

3.4.2 The CHD Family Subclass II—The CHD subclass II proteins CHD3, CHD4 and CHD5 are distinguished from the other two subclasses in that they display two plant homeodomain (PHD) zinc finger domains capable of reading lysine 4 methylated H3 (Bienz, 2006; Sanchez and Zhou, 2011). Interestingly, members of the CHD subclass II are components of the nucleosome remodeling and histone deacetylation (NuRD) complex (Tong et al., 1998; Xue et al., 1998; Zhang et al., 1998). The NuRD complex contains at least six subunits histone deacetylase-1 (HDAC1) and -2 (HDAC2), and chromatin remodeling functions from CHD3-5 (Basta and Rauchman, 2015; Bowen et al., 2004; Lai and Wade, 2011). The composition of NuRD during mouse cortical development implicates each of the three-chromatin remodelers (CHD3, CHD4 and CHD5) in a different stage of corticogenesis with generally non-redundant roles (Nitarska et al., 2016). Studies of NuRD in rat postnatal cerebella demonstrate that CHD4 regulates gene repression and drives synaptogenesis of granule neuron parallel fibers and Purkinje cells (Yamada et al., 2014). CHD4 also complexes with Polycomb Repressive Complex 2 (PRC2) catalytic component EZH2 in mouse neural progenitor cells to maintain the sequential order of transcriptional programs, specifically to suppress glial gene expression (Sparmann et al., 2013).

All CHD subclass II members are associated with human disease. Levels of CHD3 (formerly autoantigen Mi-2) and CHD4 were reported to be elevated in sera of patients with arthritis and dermatomyositis (Ge et al., 1995; Seelig et al., 1996). Phenotypes associated with pathogenic *CHD4* variants are clinically heterogeneous; however, all individuals are reported to have abnormal neurodevelopment. *De novo CHD4* variants, including missense and an in-frame deletion, have been identified in individuals with non-specific neurodevelopmental disorders and in a cohort of individuals with congenital heart defects (Sifrim et al., 2016; Weiss et al., 2016), and some of these individuals have structural brain anomalies such as macrocephaly and ventriculomegaly. The underlying molecular pathologies of the *CHD4* pathogenic variants observed in humans are under intense study. Functional studies in HEK293 cells showed that pathogenic *CHD4* variants in the C-terminal helicase domain (p.Arg1127Gln and p.Arg1173Leu) do not alter the ability of the mutant CHD4 protein to localize to the nucleus and interact with Histone Deacetylase 1 (HDAC1) (Weiss et al., 2016). Conditional deletion of *Chd4* in mice results in mild microcephaly, contrasting the macrocephaly noted in some individuals with *CHD4* pathogenic variants (Nitarska et al., 2016). The discordance between human and mouse CHD4 deficiency phenotypes suggests either that this model system does not fully recapitulate human brain development or that the molecular pathology of human *CHD4* pathogenic variants deviates from loss-of-function.

CHD5 is highly expressed in the nervous system and is regulated by retinoic acid in neuroblastoma cells (Egan et al., 2013; Higashi et al., 2015). CHD5 is a tumor suppressor in the p19(Arf)/p53 pathway controlling cell proliferation, apoptosis, and senescence (Bagchi et al., 2007).

3.4.3 The CHD Family Subclass III—CHD subfamily III contains CHD6, CHD7, CHD8, and CHD9. Subclass III CHD proteins are unique from the other chromodomain proteins in having a SANT domain and two BRK domains C-terminal to the helicase domain. The SANT domain is conserved among many regulators of transcription and chromatin structure, and is believed to function as a histone tail binding module (Boyer et al., 2004). The BRK domain is found only in CHD subclass III proteins, in the catalytic subunit of the SWI/SNF complex, and in *Drosophila brahma* and *kismet* (Daubresse et al., 1999; Dorighi and Tamkun, 2013). BRK domains are proposed to reorganize chromatin structure via formation of a chromodomain aromatic cage similar to CHD subfamily I, suggesting BRK may also participate in binding methylated lysine residues (Daubresse et al., 1999; Doerks et al., 2002).

The *Drosophila kismet* (*kis*) gene is highly related to mammalian CHD class III members. The *kismet* gene was identified in a genetic screen for dominant suppressors of *polycomb*, a group of genes that act as transcriptional repressors of homeotic genes (Daubresse et al., 1999). Loss of *kismet* results in homeotic transformations, suggesting that *kismet* is a member of the TrxG of gene activators. *Brahma*, the catalytic subunit of the *Drosophila* SWI/SNF complex, may also function by a similar mechanism (Boyer et al., 2004; Daubresse et al., 1999; Kennison and Tamkun, 1988; Tamkun et al., 1992). Loss of maternal *kismet* leads to significant defects in larval body segmentation, and expression of the segment polarity gene *engrailed* is significantly altered in *kismet* mutant flies, indicating that

engrailed and other genes important for proper segmentation require normal *kismet* function (Daubresse et al., 1999).

Of the four CHD subfamily III members, only *CHD7* and *CHD8* have been shown to be associated with human genetic disease. In humans, heterozygous *CHD7* pathogenic variants cause CHARGE syndrome, a clinically variable, multiple congenital anomaly condition affecting development of the inner ear, eyes, heart, choanae (the region between the oropharynx and nasal passages), genitalia, nervous system, and craniofacial structures including the hard and soft palates, lip, external ear, midface, and olfactory system (Hall, 1979; Vissers et al., 2004). CHARGE is a common cause of deaf-blindness, balance disorders, and congenital heart malformations, with an estimated incidence of 1:8500–1:12,000 in newborns (Harris et al., 1997; Issekutz et al., 2005; Kallen et al., 1999). Heterozygous nonsense, deletion, or missense *CHD7* pathogenic variants are estimated to occur up to 90% of patients with CHARGE (Aramaki et al., 2006; Jongmans et al., 2006; Lalani et al., 2006; Sanlaville et al., 2005; Vissers et al., 2004). *CHD7* pathogenic variants are distributed throughout the coding sequence and do not correlate with specific aspects of the clinical phenotype. In addition, most human *CHD7* pathogenic variants identified thus far are *de novo*; however, evidence for germline mosaicism has been reported in a family with affected siblings (Jongmans et al., 2006) and in a father of two children with CHARGE syndrome (Pauli et al., 2009).

CHD7 preferentially binds to enhancers and transcription start sites, some of which are marked by methylation of H3K4 (Scacheri et al., 2006). In addition, CHD7 regulates rRNA transcription along with key transcription factors and signaling molecules that control neurogenesis (Basson and van Ravenswaaij-Arts, 2015; Feng et al., 2013; Jones et al., 2015; Layman et al., 2011; Layman et al., 2009; Micucci et al., 2014; Whittaker et al., 2017; Zentner et al., 2010). Ethylnitrosourea (ENU) mutagenesis projects have led to characterization of nine different lines of *Chd7* mutant mice, each with an identifiable single base pair *Chd7* pathogenic variant (Bosman et al., 2005; Nolan et al., 1995). These *Chd7* mutant mice are viable and exhibit hyperactivity, head bobbing, circling behaviors, disrupted lateral semicircular canals, reduced postnatal growth, variable cleft palate, choanal atresia, cardiac septal defects, hemorrhage, prenatal death, genital abnormalities, and keratoconjunctivitis sicca (dry eye) (Bosman et al., 2005; Hawker et al., 2005; Kiernan et al., 2002; Nolan et al., 1995; Pickard et al., 1995). Another mutant mouse (*Wheels*) has a similar phenotype and maps to the same region of mouse chromosome 4 but is not known to harbor a *Chd7* pathogenic variant (Alavizadeh et al., 2001; Bosman et al., 2005; Nolan et al., 1995; Pickard et al., 1995). Our laboratory generated and characterized a *lacZ*-expressing, *Chd7* gene trap null allele (*Chd7*^{Gt}) that results in homozygous intrauterine lethality by E11.5 and heterozygous phenotypes similar to other *Chd7* mutant mice (Hurd et al., 2007). *Chd7*$^{Gt/+}$ mice also have the advantage of expressing β-galactosidase (β-gal) from a null *Chd7* allele and can be used to track *Chd7* mutant cells. Together, these observations demonstrate that CHD7 is involved in epigenetic regulation of gene transcription during development and CHD7 deficiency causes similar phenotypes in mice and humans.

CHD8 was recently identified as a novel candidate gene for Autism Spectrum Disorder (ASD) (Bernier et al., 2014; O'Roak et al., 2012a; O'Roak et al., 2012b; Zahir et al., 2007).

Although ASD is genetically heterogeneous, many studies utilizing whole exome sequencing and molecular inversion probe sequencing methods have demonstrated that individuals with ASD show enrichment for both truncating and non-truncating *CHD8* variants (Bernier et al., 2014; De Rubeis et al., 2014; Neale et al., 2012; O'Roak et al., 2014; O'Roak et al., 2012a). Interestingly, individuals with *CHD8* pathogenic variants often have macrocephaly, facial dysmorphisms and gastrointestinal dysfunction, suggesting important roles for CHD8 related chromatin remodeling in brain and craniofacial development.

The combination of both ASD and macrocephaly phenotypes has sparked many studies utilizing animal model systems to determine the biological function of CHD8 during neurodevelopment. Knockout of *Chd8* is embryonic lethal, and both knockdown and heterozygous germline editing approaches have been utilized to study morphological features attributed to CHD8 depletion (Nishiyama et al., 2004; Nishiyama et al., 2009). Studies utilizing zebrafish with morpholino knockdown of *chd8* and generation of *chd8* microdeletions by CRISPR-Cas9 were shown to recapitulate macrocephaly, the distinct facial feature of increased distance between the eyes, and a gastrointestinal phenotype observed in humans with *CHD8* pathogenic variants (Bernier et al., 2014). Similarly, reports of germline edited heterozygous *Chd8* mutant mice have noted increases in brain volume, ASD-related behaviors, increased distance between eyes, and gastrointestinal defects (Katayama et al., 2016; Platt et al., 2017). Taken together, the highly consistent morphological features between individuals with *CHD8* pathogenic variants and animal models highlight the importance of *CHD8* for building a normal brain.

4. Common Targets and Potential Therapies for Epigenetic Diseases

Collectively, disruptions of histone methyltransferases and chromatin remodelers impact epigenetic regulation of gene transcription, suggesting there may be common genetic targets and potential therapies with broad application for these conditions. One promising example of such a therapy is the use of topoisomerase inhibitors to de-repress the silenced allele in Angelman syndrome (Huang et al., 2012). In CHARGE syndrome, the majority of pathogenic variants result from disruption of a single copy of *CHD7* (Janssen et al., 2012). Thus, therapies that (a) alter histone modifying activities, (b) increase CHD7 expression, or (c) counteract changes in downstream gene expression may be relevant for CHARGE and other TrxG protein-related disorders. A recent study showed that CHD7 interacts with Topoisomerase 2b (Feng et al., 2013), suggesting that regulation of Topoisomerase may also be an effective approach for conditions where CHD7 is dysfunctional or absent. For those epigenetic disorders caused by haploinsufficiency, enhancement of expression or functionality of the remaining wild type allele could improve chromatin recruitment and remodeling activities. Pharmacologic agents that target epigenetic regulators may prove to be particularly effective for neurodevelopmental disorders. Additional research is needed to identify novel epigenetic mechanisms underlying brain, craniofacial, neural, and embryonic development. Such studies could provide critical information about chromatin remodeler and histone methyltransferase target genes and regulatory complexes, and will help lay the foundation for further mechanistic studies of histone modifications, nucleosome positioning and basic chromatin biology of cellular proliferation and differentiation.

5. Conclusions

Human homologs of TrxG genes encoding methyltransferases, demethylases, and chromatin remodelers contribute vital regulation of the epigenetic landscape in the cell nucleus. In turn, the corresponding chromatin configurations influence the dynamic states of gene expression, which ultimately dictate proliferative outcomes and cell fates. Pathogenic variants impacting TrxG-related genes occur in a variety of human disorders in which the brain is commonly affected. These genetic disorders display a high degree of phenotypic overlap, suggesting that similar biological pathways or stages of development are impacted. In this review, we have highlighted human studies and animal models which have established the molecular pathologies of disease from altered TrxG, COMPASS, and ATP-dependent chromatin remodelers. Results from these studies have set a foundation for future explorations of the mechanisms controlling the histone code, accessibility of DNA to trans-acting factors, and gene expression.

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Highlights

- Epigenetic regulators and chromatin remodelers influence chromatin accessibility.
- Human homologs of Trithorax related genes are associated with neurodevelopmental disorders.
- Animal models and biochemical studies highlight roles for ATP-dependent chromatin remodeling in brain development.

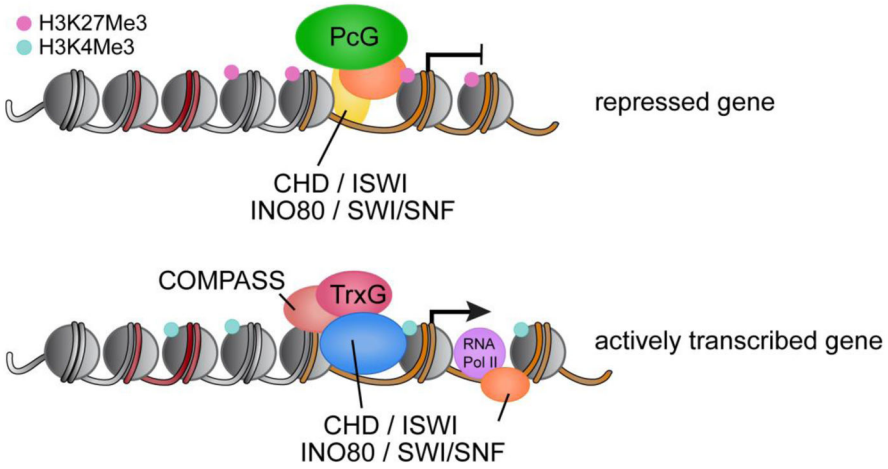

Figure 1. Schematic of Polycomb and Trithorax Related Proteins at Promoters of Repressed and Active Genes

Repressed genes are bound by Polycomb group proteins (PcG) whereas Trithorax-related proteins (TrxG) localize to actively transcribed genes. COMPASS (complex of proteins associated with Set1) opposes PcG activity to activate transcription. ATP-dependent chromatin remodelers (CHD, ISWI, INO80, and SWI/SNF) regulate DNA accessibility, which influences gene repression and activation during embryonic development.

Table 1
Human genetic diseases associated with Trithorax group related genes

Human disease associations, and Autism susceptibility according to SFARI gene classification for Trithorax group related genes. Scoring for SFARI gene is as follows: syndromic (S), high confidence (1), and strong candidate (2).

Trithorax Group Class	Gene Name	Human Disease Association	SFARI Gene Score	SFARI Syndromic
Histone Methyltransferases	*KMT2F* (*SET1A*)	Association with Schizophrenia and neurodevelopmental disorders		
	KMT2A (*MLL1*)	Wiedemann-Steiner syndrome and Leukemia Myeloid	2	S
	KMT2D (*MLL2*)	Kabuki syndrome 1		
	KMT2C (*MLL3*)	Kleefstra syndrome	2	
	KMT2B (*MLL4*)	Dystonia		
Histone Demethylase	*KDM6A* (*UTX*)	Kabuki syndrome 2		
ATP-Dependent Chromatin Remodelers - SWI/SNF	*SMARCA1* (*SNF2L1*)	Schizophrenia, Microcephaly with intellectual disability, Rett-like phenotypes		
	SMARCA2 (*BRM*)	Nicolaides-Baraitser syndrome and Schizophrenia	S	S
	SMARCA4 (*BRG1*)	Coffin-Siris syndrome 4 and Rhabdoid Tumor Predisposition syndrome 2		
	SMARCB1 (SNF5)	Coffin-Siris syndrome 3, somatic Rhabdoid tumors, Rhabdoid Predisposition syndrome 1, and susceptibility to Schwannomatosis-1		
	SMARCE1 (BAF57)	Coffin-Siris syndrome 5, susceptibility to familial Meningioma		
	ARID1A (*BAF250A*)	Coffin-Siris syndrome 2		
	ARID1B (*BAF250B*)	Coffin-Siris syndrome 1	1	S
ATP-Dependent Chromatin Remodelers - INO80	*YY1AP1* (*YAP*)	Grange syndrome		
	SRCAP (*SWR1*)	Floating-Harbor syndrome	2	
ATP-Dependent Chromatin Remodelers - CHD	*CHD1*	Pilarowski-Bjornsson syndrome		
	CHD2	Childhood-onset Epileptic Encephalopathy	2	S
	CHD4	Sifram-Hitz-Weiss syndrome		
	CHD7	CHARGE syndrome	S	S
	CHD8	Autism Spectrum Disorder	1	S