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Reprogramming of the epigenome in neurodevelopmental disorders

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Abstract

The etiology of neurodevelopmental disorders (NDDs) remains a challenge for researchers. However, in recent years, with the surge of clinical sequencing studies, many of these disorders have been determined to be monogenic and monoallelic in nature. Human brain development is tightly regulated, and it is sensitive to cellular alterations caused by endogenous or exogenous factors. Chromatin dysfunction was described as a molecular pathway highly dysregulated in NDDs, with many of these syndromes demonstrate phenotypic overlap with one another. Among these patients, intellectual disability appears to be a typical phenotype across disorders. Here we discuss mutations on the epigenetic machinery; writers, erasers, readers, remodelers, and even histones, that are predicted to affect gene regulation. First, we discuss disorders associated with mutations in histone acetylation enzymes. Second, we highlight syndromes involving histone methylation enzymes followed by chromatin remodeling enzymes. Lastly, we touch on recently discovered germline histone mutations and their pathogenic outcome on neurological function. Throughout this review, we discuss various animal and iPSC models of these disorders and their usefulness in determining pathomechanism and potential therapeutics. Ultimately, classifying these disorders based on their effects on the epigenome will not only aid in prognosis in patients but to elucidate the role of epigenetic machinery throughout neurodevelopment.

INTRODUCTION

Neurodevelopmental disorders (NDD) ranging from attention-deficit hyperactivity disorder (ADHD), Fragile X syndrome, autism spectrum disorder (ASD) and intellectual disability (ID) disorders, occur when the central nervous system (CNS) develops abnormally. ID, which involves defects in general cognition and adaptive behavior, has a prevalence of 3% world-wide, affecting 1 in 6 children in the US alone. NDD patients often exhibit ID as well as other comorbidities such as developmental delay (DD), epilepsy, autism spectrum disorder (ASD) and psychomotor impairments. The etiology of ID is heterogeneous as it has been linked to environmental factors during pregnancy, infections, chromosome deletions and recently *de novo* point mutations. Next-generation sequencing has propelled the study of these disorders through identification of 750 genes, all proposed to be causative of ID (Kochinke et al. 2016). Importantly, many of these are considered monogenic disorders, however, the pathological mechanism driving ID disorders are largely unknown. Interestingly, epigenetic determinants account for 8% of ID disorders and are starting to be recognized as major players in neurological disorders (Tjitske Kleefstra et al. 2014).

Epigenetics refers to processes that influence gene expression patterns and cellular phenotypes, but do not involve changes in DNA sequence (Dupont, Armant, and Brenner 2009). At the molecular level, epigenetic mechanisms primarily involve covalent modifications on DNA and histone proteins, however, this review will not cover DNA modifications (Dupont, Armant, and Brenner 2009). Histone modifications facilitate the condensation of chromatin, ultimately regulating DNA accessibility by transcriptional machinery. Histone post-translational modifications (PTMs), including acetylation, methylation and phosphorylation occur on the flexible N-terminus tails. These PTMs are regulated by epigenetic machinery, often protein complexes, that are responsible for the deposition (writers), removal (erasers) and recognition (readers) of the histone code (Figure 1) (Strahl and Allis 2000). Generally, histone “writers” deposits PTMs at specific genomic loci which may result in the promotion or inhibition of transcription due to chromatin accessibility. More often than not, histone acetylation defines active transcription whereas histone methylation is more complex and will be discussed in the review (Figure 2). “Eraser” proteins remove histone PTMs allowing for tight regulation of gene expression as PTM removal often results in the opposite chromatin state. “Reader” domains are often found on or in conjunction with writer proteins and chromatin remodelers, who move nucleosomes in an ATP-dependent manner. These proteins are highly regulated, resulting in a cell-type-specific steady state of histone PTMs which is malleable and allows for rapid response to cellular signals. Therefore, our understanding of the fine-tuned mechanisms that regulate the epigenetic machinery under normal conditions is critical to elucidate the mechanisms of pathogenic variants in disease.

Thanks to techniques such as tandem mass spectrometry (MS) and chromatin-immunoprecipitation sequencing (ChIP-seq), histone PTM co-occurrences, their differential abundance in a variety of *in vitro* and *in vivo* models, and their genomic localization has gained appreciation in the last decade(Vermeulen et al. 2010). Particularly, the co-occurrence of H3K4me3 (activating mark) and H3K27me3 (repressive mark) at developmental genes has been shown to “poise” these loci for rapid transcriptional activation; this specific co-ocurrance has been defined as bivalency (Voigt, Tee, and Reinberg 2013). Collectively, extensive studies have displayed the importance of establishing and maintaining histone PTMs during development and disease progression. Bivalency has been demonstrated to be necessary for proper differentiation of both neuronal and neural crest stem cells (Burney et al. 2013). Interestingly, dynamic H3K27me3 changes on transcription factor promoters mediates neocortex development, again highlighting the importance of histone PTMs in the developing brain (Albert et al. 2017). Furthermore, profiling of histone marks in neural progenitor cells reinforces this notion as PTMs were shown to influence cellular identity (Mikkelsen et al. 2007). In mature neurons, histone acetylation and methylation has been shown to drive activity-dependent modulation of neuronal networks (Bonnaud, Suberbielle, and Malnou 2016). Mice with heterozygous mutations in histone modifying enzymes exhibit altered synaptic plasticity resulting in decreased learning, short and long-term memory, and behavioral anomalies (Levenson and Sweatt 2005). Moreover, chromatin factors are ubiquitously expressed in the brain in key regions for learning, memory and movement (Figure 3).

Intriguingly, individuals carrying germline mutations in epigenetic machinery often demonstrate severe neurological dysfunction often manifesting as developmental and psychomotor delay. This suggests that the consequences of improper epigenetic regulation result in neuronal dyshomeostasis and ultimately severe impairment to the CNS. Although these germline mutations are ubiquitously expressed, it is interesting that the brain is the most affected organ in these individuals. Thus, there is sufficient evidence depicting the importance of epigenetic machinery in not only neurodevelopment but also neuronal function. However, it is imperative to illustrate how alterations to the epigenetic landscape and gene expression profiles result in observed phenotypes in these individual disorders. In this review, we focus on driver mutations of chromatin modifying enzymes in ID disorders (Table 1). Specifically, writers and erasers of histone acetylation and methylation, chromatin remodeling enzymes, and even mutations in histones themselves.

ACETYLATION

Lysine acetylation, a ubiquitous modification found on histone proteins, is a key modulator of chromatin structure and gene expression (Allfrey, Faulkner, and Mirsky 1964). All histones, including variants and linker histones, can undergo acetylation. The negative charge of the acetyl group neutralizes the positive charge of the lysine residue, reducing the interaction with negatively charged DNA. This impedes the generation of higher order chromatin structure, ultimately resulting in an open chromatin state. Histone acetylation, commonly found in active promoters and enhancers, plays a critical role in gene activation (Kuo et al. 1998; Imhof and Wolffe 1998; Lawrence, Daujat, and Schneider 2016; Z. Wang et al. 2008). Histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Michael Haberland, Montgomery, and Olson 2009; Gong and Miller 2013). Human HATs are classified into two groups based on their subcellular localization: type A and type B. Type A HATs reside in the nucleus and contain bromodomains that recognize acetylated lysines, and often interact with other chromatin remodeling complexes and transcription factors (Dhalluin et al. 1999; Marmorstein and Zhou 2014; Sanchez and Zhou 2009). Type A HATs are further subdivided into five homology superfamilies: (1) the Gcn5-related acetyltransferase (GNAT) family, (2) the p300/CBP family, (3) the MYST family, the basal transcription factors, and the nuclear receptor cofactors (Steunou, Rossetto, and Côté 2013). On the other hand, type B HATs, which often lack bromodomains, are located in the cytoplasm and regulate the acetylation of newly synthesized histones (Richman et al. 1988; Bannister and Kouzarides 2011). In this section, we will discuss Type A HATs, specifically within the p300/CBP and MYST family, that have been identified as causative mutations in NDD and discuss their roles in CNS development and function.

p300/CBP Family

The cyclin AMP response element-binding protein (CREB) binding protein, CBP (also known as CREBBP or KAT3A) and p300 (EP300 or KAT3B) are two members of the p300/CMB subfamily of HATs. CBP mutations are the major cause of 55–60% Rubinstein-Taybi syndrome (RSTS) 1 (MIM: 180849) cases, while p300 mutations are causative in 8% of RSTS2 (MIM: 613684) cases (Roelfsema et al. 2005; Menke et al. 2016).

RSTS1 is a rare congenital disorder characterized by mild to severe intellectual disability, microencephaly, growth retardation and distinct facial features (RUBINSTEIN and TAYBI 1963). RSTS2, although similar to RSTS1, results in less severe facial dysmorphism and overall better cognitive function compared to RSTS1; however, they tend to have more severe microencephaly and malformation of facial bone structures(Bartsch et al. 2010). In the vast majority of RSTS2 cases other comorbidities exist such as psychomotor deficits, language and gastrointestinal problems (Pérez-Grijalba et al. 2019). The CBP/p300 complex primarily regulates gene expression through their combined HAT activity in acetylating H2B at residue K85, H3 on residues K9, K14, K36, K56 and H4 on residues K12, K20 and K44 (Bannister and Kouzarides 1996; Das et al. 2009; Carré et al. 2018). In addition to their collective HAT activity, they regulate gene expression through recruitment of transcription factors or basal transcription machinery. Considerably, CBP and p300 are implicated in cell differentiation, proliferation and apoptosis. CBP or p300-deficient embryos exhibit heart and neural tube defects, often resulting in gestational death (T.-P. Yao et al. 1998; Tanaka et al. 2000). Therefore, CBP/p300 are required for proper brain development, and mutations in either of these HATs can result in a neurological disorders (T.-P. Yao et al. 1998; Tsui et al. 2013; Viosca et al. 2009).

The pathogenic variants of both CBP and p300 in RSTS1/2 resulting from frameshift, nonsense, or splice-site mutations are predicted to have a loss-of-function mechanism resulting in haploinsufficiency (Alari et al. 2018). CBP haploinsufficiency leads to a decrease in the number of neurons generated and is seen to regulate neurogenesis and cortical precursor differentiation in mice (Jing Wang et al. 2010; Valor et al. 2011). Loss-of-function CBP in mice resulted in the defects in hippocampal memory which was rescued by two different HDAC inhibitions (Korzus, Rosenfeld, and Mayford 2004). Moreover, an in vitro neuronal model of RSTS1 and RSTS2 was developed using patient-derived induced pluripotent stem cells (IPSCs). In this study, they observed morphological changes and decreased neuronal excitability (Alari et al. 2018). Furthermore, these patient-derived neurons had increased number of branches; however, the length of the branches was reduced (Alari et al. 2018). Interestingly, heterozygous mutations in exons 30–31 of CBP or p300 have recently been discovered to have a substantially distinct phenotype from RSTS. Patients harboring these mutations display developmental delay, autistic behavior, short stature, microcephaly and distinct facial anomalies (Menke et al. 2016; 2018; Siddharth Banka et al. 2019). Depending on the causative gene, it is known as Menke-Hennekam syndrome (MKHK) 1 for CBP mutations and MKHK2 for p300 mutations. It is hypothesized that CBP mutations confer a gain of function mechanism and p300 mutations are specifically affecting the conformation of the zinc finger domains. It is important to note that despite similarity in causative genes and overall symptoms, RSTS and MKHK are very phenotypically distinct. Ultimately, mutations in either CBP or p300 lead to aberrant neurodevelopment through either dysregulation of its HAT activity or improper recruitment of transcription factors.

MYST Family

The MYST subfamily is comprised of five human HATs that all share a highly conserved MYST domain: Tip60, HBO1, KAT6A, KAT6B and KAT8. These HATs are involved

in many cellular processes such as proliferation and differentiation, therefore it is not surprising that dysfunction of these proteins have been linked to neurological diseases. KAT6A (also known as MYST3/MOZ) or its paralog KAT6B (or MYST4/MORF) form a stable complex with ING5, EAF6 and BRPF proteins (Ullah et al. 2009). In recent years, heterozygous KAT6A mutations were identified in Arboleda-Tham syndrome (ARTHS) (MIM: 616268), formerly known as autosomal dominant mental retardation 32 (Arboleda et al. 2015; Tham et al. 2015). ARTHS patients share common features such as impaired intellectual development, dysmorphic facial features, speech delay, congenital heart disease and microecephaly (Kennedy et al. 2018). KAT6A and KAT6B both acetylate H3K9 and K18, while KAT6B also acetylates H3K23 (Lv et al. 2017; K. Yan et al. 2020). KAT6A-deficient mouse embryos lead to H3K9 hypoacetylation, which is linked to reduced transcription of *Hox* genes and abnormal craniofacial development (Kong et al. 2014; Voss et al. 2009). Functional studies in ARTHS patient-derived fibroblasts revealed substantial reduction in H3K9 acetylation with increased K18 acetylation as well as dysregulation in signaling pathways of p53, which is a non-histone KAT6A substrate (Arboleda et al. 2015).

Interestingly, KAT6B, the paralog of KAT6A, is known to be mutated in multiple neurodevelopmental disorders; however, it is the causative gene in Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome (SBBYSS) (MIM:603736) and Genitopatellar syndrome (GTPTS) (MIM: 606170) (Simpson et al. 2012; Clayton-Smith et al. 2011). SBBYSS is clinically characterized by craniofacial abnormalities involving blepharophimosis (underdeveloped eyelids) and cleft palates, severe ID, hypotonia, and cardiac defects (Clayton-Smith et al. 2011). These *de novo* truncating KAT6B mutations mainly affect exons 16–18 of the gene and are predicted to cause haploinsufficiency (Clayton-Smith et al. 2011; Marangi et al. 2018). KAT6B is critical for mammalian CNS development as homozygous mutations of KAT6B in mice resulted in a smaller cerebral cortex and cortical plate when compared to wildtype animals (You, Yan, et al. 2015). Furthermore, these mice exhibited craniofacial abnormalities similar to the SBBYSS patients (You, Yan, et al. 2015). Although the causative gene in GTPTS is KAT6B, these patients do not exhibit distinct craniofacial abnormalities (Simpson et al. 2012; Cormier-Daire et al. 2000). However, they do exhibit severe ID, thin corpus callosum, psychomotor retardation, cardiac defects and genital anomalies. As with SBBYSS, GTPTS is delineated by truncation mutations that occur at the proximal end of exon 18; this creates KAT6B variants lacking methionine-rich domains which is known to bind to the transcription factors *RUNX1* and *RUNX2*. The role of RUNX genes in mammalian CNS involves formation of neural circuits, specifically mediating somatosensory sensation, olfaction and motor control.

It is important to note that the border between SBBYSS and GTPTS syndromes is almost non-existent as they both have significant overlap with regards to exon 18. With this in mind, four distinct groups of KAT6B mutations have been recently suggested (Radvanszky et al. 2017; M et al. 2015). Group 1 mutations are proximal mutations, predominantly in the MYST domain and have been mainly associated with SBBYSS. Group 2 mutations, mainly seen in GTPTS, affect the acidic patch and transcription activation domain. However, the majority of these transcripts escape nonsense mediated decay. Group 3 mutations are associated with SBBYSS and GTPTS and they lack transcription activation domain with either a truncated or intact acidic patch. Lastly, group 4 mutations, exclusive to SBBYSS,

contain truncations in the transcription activator domain. The majority of mutations (groups 2–4) reside after the MYST domain, suggesting that these truncated mutants retain HAT activity(M et al. 2015). However, without the remaining regulatory portions of the protein, these truncations may cause loss/gain-of-functions, altering cellular processes through dysregulation of histone acetylation or transcriptional activation.

MYST Family Co-Writer

BRPF1—Bromodomain and PHD finger containing protein 1 (BRPF1) serves as a scaffold mediating the interaction between KAT6A, KAT6B, ING5 and EAF6. BRPF1 is considered a “co-writer” as it is critical for HAT activity and transcriptional activation. It consists of multiple domains which are responsible for many of its protein-protein interactions, it also contains a PWWP domain which recognizes H3K36me3 (K. Yan et al. 2016, 1). In 2017, a cohort of 10 patients containing heterozygous BRPF1 mutations was identified, all exhibited mild to severe intellectual disability, dysmorphic facial features, ptosis, hypotonia, brain and behavioral anomalies (K. Yan et al. 2016). These mutations generated a truncated form of BRPF1, resulting in impaired H3K23 acetylation. Concurrently in 2017, another group identified 6 individuals who had what they referred to as an Intellectual Developmental Disorder with Dysmorphic Facies and Ptosis (IDDDFP) (Mattioli et al. 2017). Similar to the previous group, these patients all exhibited mild to moderate intellectual disability, growth retardation, ptosis and microencephaly (Mattioli et al. 2017). BRPF1, in this second cohort, retained the ability to bind KAT6A/B; however, these mutations prevented the formation of tetrameric complexes and had reduced HAT activity (Mattioli et al. 2017). Interestingly, aside from disrupting complex formation, a few of the pathogenic variants bearing mutations predominantly in the PWWP domain, maintain normal HAT activity. Therefore, a potential mechanism for this epigenetic dysregulation theoretically could be due to mislocalization of this HAT complex.

Functional studies of BRPF1 and its pathogenic variants elaborate on its role in brain development and function. BRPF1 is critical for forebrain development, as conditional knock-out in the forebrain results in small litter size with all mice exhibiting neurological and behavioral defects (You, Zou, et al. 2015, 1). Additionally, forebrain-specific inactivation of mouse Brpf1 lead to abnormal cerebral and hippocampal development (K. Yan et al. 2016). These anomalies were attributed to BRPF1 loss as it results in downregulation of neuronal migration, cell cycle progression and transcriptional control through the compromised status of neural stem and progenitor cells (You, Yan, et al. 2015). Moreover, despite the lack of intrinsic HAT activity in BRPF1 there is sufficient evidence demonstrating its interaction with KAT6A and KAT6B is critical for regulating histone acetylation both *in vitro* and *in vivo* (K. Yan et al. 2016). Heterozygous Brpf1 mice displayed a decrease in H3K23 acetylation, similar to the reduction seen in patient-derived fibroblasts (K. Yan et al. 2016). These findings illustrate the importance of co-writers, and accessory proteins in HAT complexes.

KANSL1—KAT8 regulatory NSL complex subunit 1 (KANSL1) is a part of the non-specific lethal (NSL) complex, which is a highly conserved protein complex that also includes KAT8/MOF, KANSL2 and WDR5. The NSL complex influences gene activation

through acetylation of H4K16 and the transcription factor, p53 (Mendjan et al. 2006; X. Li et al. 2009; Dou et al. 2005). The stability and activity of the NSL complex is dependent on KANSL1(Raja et al. 2010). In 2012, two unrelated patients exhibiting characteristic symptoms of chromosome 17q21.31 deletion syndrome were discovered to have the first *de novo* mutations in KANSL1 (Zollino et al. 2012). Concurrently, another group performed sanger sequencing on 16 unrelated patients, identifying 16 different *de novo* heterozygous truncating mutations in KANSL1 in two unrelated patients. All four of the aforementioned patients were all diagnosed with Koolen-de Vries syndrome (KdVS) (MIM: 610443) which is characterized by moderate to severe intellectual disability, hypotonia, and dysmorphic facial features (Zollino et al. 2012; Koolen et al. 2012; 2016). The KANSL1 haploinsufficiency seen in KdVs is sufficient to generate a full manifestation of the chromosome 17q21.31 deletion syndrome and there were no clinically important differences between the two syndromes (Zollino et al. 2012; Koolen et al. 2016).

Whole transcriptomic sequencing on EBV-transformed patient cells bearing either a KANSL1 point mutation or deletion showed that there was a high correlation between the differential expression of similar genes between both syndromes(Koolen et al. 2012). Moreover, gene ontology (GO) analysis revealed enrichment in genes associated with neuronal and synaptic processes (Koolen et al. 2012). These results were supported using chromatin immunoprecipitation as the KANSL1 Drosophila homolog, *wah*, was bound to the promoter of many genes enriched for the same GO terms (Raja et al. 2010). Global knockdown of *wah* lead to altered synapse morphology at the neuromuscular junction and endosomal maturation, which is crucial for synaptic trafficking (Lone et al. 2010). Additionally, conditional knockdown of *wah* in mushroom bodies, the learning and memory center of the Drosophila brain, resulted in a 25% reduction in learning ability (Koolen et al. 2012). Functional analysis of the KANSL1 Drosophila homolog revealed the importance of this protein in complex brain functions such as learning and memory.

DEACETYLATION

HDACs are erasers of histone acetylation, in humans there are 18 identified HDACs. These enzymes are classified into two categories, “zinc-dependent” and “nicotinamide-adeneine-dinucleotide (NAD)-dependent”, based on whether they require zinc or NAD for catalysis. There are four classes of HDACs within the zinc-dependent class: class I (HDACs 1, 2, 3, 8), class IIa (HDACs 4, 5, 7, 9), class IIb (HDACs 6, 10) and class IV (HDAC 11). All of the zinc dependent HDACs are expressed in the brain; however, they have distinct cellular and subcellular localizations. Class I HDACs are primarily found in the nucleus, while class II HDACs shuttle between the cytoplasm and the nucleus. NAD-dependent deacetylases, also known as Sirtuins, are expressed throughout the brain and are highly regulated in a spatiotemporal pattern, which has been speculated to play a role in aging (Deardorff et al. 2012). To date mutations in three HDACs (HDAC4, HDAC6 and HDAC8) (4,6,8) have been determined as causative in neurodevelopmental disorders.

HDAC4

HDAC4, a class IIa HDAC, is highly expressed in the postnatal brain and regulates neuronal cell death; however, the substrates of HDAC4, and therefore the mechanism of action, remain elusive (Bolger and Yao 2005). Homozygous HDAC4 mice exhibit impaired learning, memory and long-term synaptic plasticity (M.-S. Kim et al. 2012). Haploinsufficiency due to mutations or deletions of HDAC4 were determined to cause brachydactyly mental retardation (BDMR) syndrome (MIM: 600430) characterized by developmental delay, intellectual disability, behavioral abnormalities and dysmorphic features (Williams et al., n.d.; Villavicencio-Lorini et al. 2013). Currently, there is some debate on whether or not HDAC4 is the driver for BDMR or if mutations in the TWIST2 or FLJ43879 genes are driving the phenotype (Wheeler, Huang, and Dai 2014). HDAC4 has been shown to regulate myocyte enhancer factor-2 (MEF2) proteins during development, therefore altered HDAC4 activity potentially results in BDMR through dysregulation of MEF2 (Bolger and Yao 2005). However, it remains speculative.

HDAC6

HDAC6, a class IIb HDAC, is also highly expressed in the brain and it primarily resides in the cytoplasm; however, deacetylation of its target substrates often leads to nuclear translocation (LoPresti 2020; Nagase et al. 1998; d'Ydewalle, Bogaert, and Van Den Bosch 2012). HDAC6 is a key regulation of synaptic function during acute stress in the prefrontal cortex, a region responsible for higher-order cognition(J. B. Lee et al. 2012). X-linked dominant Chondrodysplasia with platyspondyly, distinctive brachydactyly, hydrocephaly, and microphthalmia (CPDBHM) (MIM: 300863) is caused by heterozygous mutations in HDAC6 (Chassaing et al. 2005; Simon et al. 2010). CPDBHM is characterized by macrocephaly, growth retardation, skeletal and craniofacial abnormalities and mild intellectual disabilities, these phenotypes are more pronounced in males (Chassaing et al. 2005; Simon et al. 2010). In pathological conditions, HDAC6 translocate to the nucleus, dysregulating synaptic function due to decreased expression of brain-derived neurotrophic factor (BDNF) (J. B. Lee et al. 2012). Furthermore, HDAC6 has been implicated in many neurological conditions such as Alzheimer's' disease, Charcot-Marie-Tooth disease and mood disorders. However, whether this regulation is mediated through deacetylation of its known substrates (β-catenin, α-tubulin) or another target of HDAC6 remains unclear.

HDAC8

HDAC8 is known to deacetylate H3 and H4 *in vitro*, and structural maintenance of chromosomes 3 (SMC3) in the cohesin complex (Deardorff et al. 2012; Hans Tomas Bjornsson 2015). Loss of HDAC8 activity results in increased SMC3 localization to chromatin, leading to amplified cohesin localization which results in altered transcriptional activity (Deardorff et al. 2012). Mutations in HDAC8 are responsible for Cornelia De Lange Syndrome (CdLS) 5 (MIM: 300882) (Boyle et al. 2014; Mordaunt and McLauchlan 2015; Kaiser et al. 2014). CdLS5 is defined by intellectual disability, facial dysmorphism, pre- and post-natal delay, microcephaly, heart defects, upper limb abnormalities, and genitourinary anomalies (Yuan et al. 2015). Notably, mutations in HDAC2 have been recently discovered in another form of CdLS; however, further studies are needed to compare the similarities

between these class I HDAC mutations (V. F. Wagner et al. 2019). A characteristic feature of CdLS5 is abnormal skull formation. Interestingly, HDAC8 represses homeobox transcription factors, Otx2 and Lhx1, in cranial neural crest cells; thus, HDAC8 mediates patterning of the skull and deletion in mice leads to perinatal lethality due to skull instability (M Haberland et al. 2009). To this date, no *in vivo* studies have elucidated the role of HDAC8 in cognition or behavior despite the accumulating number of mutations in HDAC8 related to intellectual disability syndromes.

METHYLATION

Histone methylation occurs on both arginine and lysine residues and plays a critical role in transcriptional regulation (Allfrey and Mirsky 1964; Allfrey, Faulkner, and Mirsky 1964). Unlike acetylation, a binary system (acetylation or no acetylation), methylation is more complicated. Histone lysine methylation is a quaternary system as lysine residues can be mono-, di-, and trimethylated, while arginine residues can be mono- and di-methylated. Importantly, none of these modifications alter the lysine's positive charge. Histone methylation is ambiguous as it is associated with both activation and repression of gene expression depending on the residue modified and the number of methyl groups added (Y. Zhang 2001; Black, Van Rechem, and Whetstine 2012). To this date, only methylation on histone H3 and H4 have been identified. Methylation on H3K4, H3K36, and H3K79 has been shown to mark active regions, whereas H3K9, H3K27, and H4K20 methylations are associated with repressed chromatin (Black, Van Rechem, and Whetstine 2012). There are two classes of lysine methyltransferases (KMT) in humans, and this classification depends on the presence or absence of the catalytic Su(var)3–9, E(z) (enhancer of zeste), and trithorax (SET) domain (Jenuwein 2006; Dillon et al. 2005; Nguyen and Zhang 2011). Despite having distinct catalytic domains, all KMTs utilize S-adenosyl-L-methionine (SAM) as the methyl group donor, and have high specificity to certain residues as well as the degree of methylation (Dillon et al. 2005; Nguyen and Zhang 2011). This section will discuss the role of KMTs in neurodevelopment and the implications of their dysregulation.

KMT2A

Lysine methyltransferase 2A (KMT2A), also known as mixed lineage leukemia 1 (MLL1), catalyzes the trimethylation of histone H3K4 (Dou et al. 2006; Schneider et al. 2005). KMT2A, like other SET domain-containing KMTs, is often found in a complex with four other subunits: ASH2L (absent, small, or homeotic-2 like), WDR5 (WD repeat domain 5), DPY30, and RbBP5 (retinoblastoma binding protein 5). KMT2A also interacts with Menin and HCF1, forming COMPASS-like complex (Shilatifard 2012). Importantly, H3K4 mono-, di- and trimethylation distinctly mark active genomic regions where K4me1 is enriched at enhancers, K4me2 at 5' end of actively transcribed genes, and K4me3 at actively transcribed promoters (Heintzman et al. 2007; T. Kim and Buratowski 2009; Santos-Rosa et al. 2002). In 1989, three groups reported clinical findings from unrelated patients, all detailing hypertrichosis cubiti (abnormal amount of body hair), short stature, craniofacial abnormalities, and developmental delays(Hans-Rudolf Wiedemann et al. 1989; Flannery et al. 1989; MacDermot et al. 1989). From 1989 to 2010, seven other groups reported approximately 40 patients all exhibiting distinct facial features, developmental delays,

and short stature (Edwards et al. 1994; W. D. Jones et al. 2012; Steiner and Marques 2000; Polizzi et al. 2005; Koç et al. 2007; Koenig et al. 2010). This disorder was named Weidemann-Steiner (WDSTS) (MIM 605130) and Jones et al. identified heterozygous *de novo* truncating mutations in the KMT2A gene in four of these WDSTS patients (W. D. Jones et al. 2012).

By employing whole-exome sequencing and confirmatory Sanger sequencing, a variety of mutations were observed: missense, nonsense, and frameshift truncating mutations. These mutations result in a loss-of-function or haploinsufficient KMT2A in patients presenting clinically similar phenotypes (Koenig et al. 2010; Y. Sun et al. 2017; Nardello et al. 2020; Stellacci et al. 2016; Jinxiu et al. 2020; N. Li et al. 2018; N. Miyake et al. 2016). Based on these findings, KMT2A was concluded to be the causative gene in WDSTS. Experimental studies revealed the critical role of KMT2A in neurogenesis in the mouse postnatal-brain, specifically with neuronal differentiation(Lim et al. 2009). In KMT2A-deficient brains, neuronal differentiation is severely impaired through reduced size and number of neurons, potentially due to the decrease in bivalent promoters in neural precursor cells (Lim et al. 2009). It also has been demonstrated that KMT2A-mediated H3K4 trimethylation is critical in prefrontal neurons as it regulates a subset of genes involved in cognition and behavior (Jakovcevski et al. 2015). Lastly, mice deficient for KMT2A had reduced dendritic spines and increased aggression (Vallianatos et al. 2020). These studies taken together reveal the role of KMT2A in neurogenesis and CNS function, and it is suspected that these functions are impaired in WDSTS patients (W. D. Jones et al. 2012). The phenotype of this syndrome continues to expand; however, the molecular mechanism remains poorly understood. To further understand this disorder, more functional assessments in model organisms must be conducted to elucidate the role of KMT2A in cognition.

KMT2B

Lysine methyltransferase 2B (KMT2B), also known as MLL4, is a paralog of KMT2A and is responsible for the trimethylation of H3K4 (FitzGerald and Diaz 1999, 2). KMT2B has been linked with gene-specific activation and functions in preimplantation development as well as embryonic genome activation(Shao et al. 2014). In 2016, an autosomal dominant neurological disorder was discovered where patients exhibited microencephaly, mild intellectual disability, and developmental delay; this disorder was classified as childhood-onset dystonia-28 (DYT28) (Zech et al. 2016). Several groups provided evidence that *de novo* mutations in the KMT2B gene result in haploinsufficiency, causing DYT28 (MIM 617284) (Zech et al. 2016; 2017; Kawarai et al. 2018). Mutations have been observed in over 75 patients to date. They encompass frameshift, missense, nonsense, and splice-site mutations, and all affect KMT2B function (Zech, Lam, and Winkelmann 2019). KMT2B is highly expressed in human tissue and ubiquitously expressed in the brain, with the highest expression in the cerebellum (Meyer et al. 2017). This expression is reduced in DTY28 patients; however, the levels on H3K4 methylation were not significantly altered, suggesting a potential role of KMT2B beyond K4 methylation (Meyer et al. 2017). *In vitro*, KMT2B knockdown results in decreased neuronal differentiation from embryonic stem cells (Lubitz et al. 2007). Moreover, KMT2B is critical in neuronal programming as ablation impairs transdifferentiation of fibroblasts to induced neuronal cells (iNs) conversion (Barbagiovanni

et al. 2018). The loss of KMT2B leads to redistribution of H3K4me3 rather than reduction, explaining why previous studies found similar levels of methylation between patients and controls (Meyer et al. 2017; Barbagiovanni et al. 2018). The mechanism driving the dystonia caused by KMT2B remains elusive. However, promising studies are working to elucidate the dysregulated pathways involved in DYT28.

KMT2C

Lysine methyltransferase 2C (KMT2C), also known as MLL3, mediates H3K4 mono- and dimethylation (Ruault et al. 2002; Sedkov et al. 2003; Herz et al. 2012). KMT2C is functionally active in the COMPASS complex and is often recruited to enhancers and active gene promoters (D. Hu et al. 2013). Additionally, KMT2C is a central component of the activating signal cointegrator-2 (ASC-2) complex, which acts as a co-activator for hormone receptors (S. Lee et al. 2009; Goo et al. 2003). Knockdown of the Drosophila KMT2C, thrithorax related (trr), in the brain impaired short-term memory highlighting its role in synaptic plasticity and cognition (Koemans et al. 2017). Kleefstra et al. performed whole-exome sequencing on five individuals with the same clinical phenotype, including psychomotor delay, severe intellectual disability, dysmorphic facial features, and behavioral problems (Tjitske Kleefstra et al. 2012). They discovered a heterozygous *de novo* nonsense mutation in the KMT2C gene in a female patient, resulting in truncation of KMT2C(Tjitske Kleefstra et al. 2012). This truncation is predicted to reduce methyltransferase activity as it lacks the enzymatic SET domain. Another group identified five unrelated patients with *de novo* mutations in the KMT2C gene, all which are predicted to cause loss-of-function variants(Koemans et al. 2017). These patients, previously diagnosed with an undefined developmental disorder, were classified as all suffering from Kleefstra Syndrome-2 (KLEFS2) (MIM: 617768)(Koemans et al. 2017). It is evident that dysregulation of KMT2C's function potentially underlies the broad spectrum of neurodevelopmental abnormalities observed. To investigate the role of KMT2C in neurons, researchers made a knockdown of its Drosophila paralog, trr, in the mushroom body of the fly brain revealing impaired short-term memory(Koemans et al. 2017). Unfortunately, specific gene targets of KMT2C remain unknown, but future research will likely reveal molecular targets of KMT2C haploinsufficiency. Furthermore, it has been recently shown that when KMT2C is promoter-bound, this represses gene transcription through recruitment of specific factors(Cheng et al. 2014). Based on these studies, KMT2C can potentially both activate and repress genes. Understanding its role in chromatin regulation will clarify its effect in transcriptional regulation during brain development, ultimately aiding in the development of therapeutics.

KMT2D

Lysine methyltransferase 2D (KMT2D), also known as MLL2, is a paralog of KMT2C and, as such, mediates mono- and dimethylation of H3K4 in mammalian cells as well(D. Hu et al. 2013; J.-E. Lee et al. 2013). Exome sequence uncovered KMT2D variants as the causative gene in Kabuki syndrome (KS1) (MIM 147920) (Ng et al. 2010). KS1 is an autosomal-dominant disorder phenotypically similar to aforementioned neurodevelopmental disorders; it is characterized by infantile hypotonia, craniofacial abnormalities, mild-moderate intellectual disability, and developmental delay (Ng et al. 2010, 2). There are

dozens of clinical reports detailing over 100 unique *de novo* mutations of KM2D identified in individuals with KS1 (Tsukahara et al. 1997; Kobayashi and Sakuragawa 1996; Ilyina et al. 1995; Lerone et al. 1997; Kawame et al. 1999; Ewart-Toland et al. 1998; McGaughran, Donnai, and Clayton-Smith 2000; S. Banka et al. 2013; Siddharth Banka et al. 2012; Hannibal et al. 2011; Micale et al. 2011; Paulussen et al. 2011). These mutations all result in loss-of-function variants by disrupting its reader domains (PHD fingers), loss of its catalytic SET domain, or disruption of the 3D structure (S. Banka et al. 2013, 2; Dhar et al. 2012; Bögershausen and Wollnik 2013). *In vitro* studies determined that KMT2D mediates neural differentiation by activating neuronal differentiation genes, *HOXA1–3* and *NESTIN*, via H3K4me3 deposition(Dhar et al. 2012). These studies suggest that the loss-of-function mutations affecting the tandem PHD domains or SET domain will likely lead to loss of H3K4me3, which is necessary for neuronal differentiation gene expression. Van Laarhoven et al. performed morpholino-mediated knockdown of KMT2D in zebrafish and observed significant craniofacial and cardiac defects (Van Laarhoven et al. 2015). Additionally, this knockdown resulted in the reduction of mature neurons and brain size despite the accumulation of neural precursor cells, suggesting the defects were due to cellular dysfunction rather than perturbed development. Further functional studies on this writer will prove beneficial for understanding its role in neuronal maturation and function.

KMT2E

Lysine methyltransferase 2E (KMT2E), also known as MLL5, diverges from the KMT2 family of methyltransferases since it lacks histone methyltransferase activity(Sebastian et al. 2009). Nonetheless, it has been reported to play critical roles in cell cycle progression, genomic stability maintenance, and differentiation (Sebastian et al. 2009, 5). Despite the lack of KMT activity, the KMT2E homolog in Drosophila, UpSET, regulates promoter-associated histone acetylation and H3K4 di- and trimethylation when in complex with Rpd/Sin3-repressor proteins (Rincon-Arano et al. 2012). O'Donnell-Luria-Rodan syndrome (ODLURO) (MIM: 618512) is a neurodevelopmental disorder characterized by developmental delay, intellectual disabilities, and subtle craniofacial abnormalities with heterozygous mutations in KMT2E being the causative gene (O'Donnell-Luria et al. 2019). Individuals with ODLURO either have protein-truncating variants or missense mutations in the KMT2E gene, with the latter resulting in increased severity (O'Donnell-Luria et al. 2019). Moreover, the individuals with missense mutation often develop drug-resistant infantile epileptic encephalopathy(O'Donnell-Luria et al. 2019). To this date, no functional analyses have been conducted; however, it has been hypothesized that haploinsufficiency is potentially the pathogenic mechanism for the truncation and missense mutations. Collectively, these mutations are hypothesized to produce loss-of-function variants.

SETD1A

SET domain-containing protein 1A (SETD1A), also known as KMT2F, mediates the trimethylation of H3K4 at promoters of active genes (J.-H. Lee and Skalnik 2008, 1). SETD1 associates with the canonical COMPASS complex, in addition to CpG-binding protein (CXXC1) and WD repeat domain 82 (WDR82) (J.-H. Lee and Skalnik 2008, 82; 2005; Deng et al. 2013). Loss-of-function variants in SETD1A have been implicated as causative in two neurodevelopmental disorders and schizophrenia(Swedish Schizophrenia

Study et al. 2016). In 2019, *de novo* heterozygous mutations in SETD1A were discovered in individuals with early-onset epilepsy with or without developmental delay (EPEDD) (MIM: 618832) (X. Yu et al. 2019). Mutant SETD1A expression decreased the number of excitatory synapses on mouse cortical primary neurons (X. Yu et al. 2019). Significantly, these mutations did not affect general neuronal morphology which suggests a role of SETD1A in synapse formation (X. Yu et al. 2019). Kummeling et al. discovered *de novo* heterozygous mutations in the SETD1A gene in 15 unrelated patients with a neurodevelopmental disorder with speech impairment and dysmorphic facies (NEDSID) (MIM: 619056) (Kummeling et al. 2020). These were missense, nonsense, frameshift, and splice-site mutations, all expected to disrupt the catalytic SET domain. Patient-derived fibroblasts displayed increased activation of DNA damage response, and increased DNA degradation under stress (Kummeling et al. 2020). Additionally, when SETD1A was knocked down in Drosophila mushroom bodies to assess neural programming, results determined that SETD1A is required for proper neuronal function during the formation of memory. Given that both disorders are clinically distinct despite both deriving from pathogenic SETD1A, it will be essential to elucidate this protein's role in neural development and neuronal function.

SETD1B

SET domain-containing protein 1B (SETD1B), also known as KMT2G, is a paralog of SETD1A and, as such, also mediates the trimethylation of H3K4(J.-H. Lee et al. 2007). Despite their homology, SETD1A and SETD1B localize to a nonoverlapping set of target genes suggesting that these methyltransferases have nonredundant contributions to the epigenetic control of gene expression (J.-H. Lee et al. 2007). Recent studies provided evidence that intellectual developmental disorder with seizures and language delay (IDDSELD) (MIM: 619000) is caused by *de novo* heterozygous mutations in SETD1B (Roston et al. 2020). As its name suggests, IDDSELD is characterized by global developmental delay with speech and language impairment, and the onset of myoclonic seizures early in life (Roston et al. 2020; Hiraide et al. 2019; Den et al. 2019; Hiraide et al. 2018; Palumbo et al. 2015). Additionally, individuals often exhibit behavioral abnormalities such as autism spectrum disorder and facial dysmorphism. Interestingly, the mutations discovered have been predicted to confer loss-of-function or gain-of-function effect on SETD1B. Additional functional studies on these pathogenic variants and patient cells are required to determine the pathological mechanism. Krzyzewska et al. identified a shift in the DNA methylation landscape in IDDSELD patient cells (Krzyzewska et al. 2019). Notably, SETD1B variants imposed a hypomethylated epigenetic signature which lead the authors to speculate SETD1B is enduring a loss-of-function effect (Krzyzewska et al. 2019).

EHMT1

Euchromatic histone methyltransferase (EHMT1), or G9a-like protein (GLP), catalyzes mono- and dimethylation of H3K9 and is known to recruit Polycomb Repressive Complex-2 (PRC2) (Mozzetta et al. 2014). EHMT1 predominantly deposits H3K9me2 in the genome, which promotes transcriptional repression (Peters et al. 2003; Rice et al. 2003). Heterozygous mutations on EHMT1 cause chromosome 9q34.3 deletion syndrome, better known as Kleefstra syndrome-1 (KLEFS1) (MIM: 610253) (Neas et al. 2005; Stewart et al. 2004; Harada et al. 2004; Tjitske Kleefstra et al. 2006; Iwakoshi et al. 2004,

34). Standard features in patients with KLEFS1 are severe intellectual disability, distinct facial gestalt, hypotonia, microencephaly, seizures, and cardiac defects (Tjitske Kleefstra et al. 2012; 2006). Individuals contain missense, nonsense, frameshift, and splice-site mutations (Tjitske Kleefstra et al. 2012; 2006; T Kleefstra et al. 2009). Biochemical characterization of missense mutations of EHMT1 reveals these mutations decrease its methyltransferase activity, potentially reducing H3K9me2 at specific loci, causing KLEFS1 (A. Yamada, Shimura, and Shinkai 2018). Heterozygous EHMT1 ($EHMT1^{+/-}$) mice have reduced dendritic branching and a reduced number of mature spines in hippocampal neurons resulting in learning and memory deficits, specifically during stress (M. C. M. Balemans et al. 2013). Additionally, $EHMT^{+/-}$ mice exhibited overexcitability due to deficits in inhibitory neuron maturation and excitatory impairments (Negwer et al. 2020). To ascertain whether these effects are observed in human cells, excitatory cortical neurons were generated from IPSCs derived from KLEFS1 patients (Frega et al. 2019). Frega et al. observed similar overexcitability in patient-derived neurons. They demonstrated that these changes were due to upregulation of the NMDA receptor (NMDA-R) subunit, which correlated with reduced H3K9me2 at its promoter (Frega et al. 2019). Davis et al. suggested that EHMT1 haploinsufficiency results in disrupted NMDA-R expression promoting abnormal forebrain development, ultimately resulting in information processing deficits (Davis et al. 2020). Understanding the cognitive deficits and the pathways involved would provide a basis for targeted therapeutics, since Frega et al. were able to rescue KLEFS1 patient-derived neuronal phenotypes through pharmacological inhibition of NMDA-Rs (Frega et al. 2019).

EZH2

Enhancer of zeste 2 (EZH2) in complex with suppressor of zest 12 (SUZ12) and embryonic ectoderm development (EED) acts as the catalytic subunit of Polycomb repressive complex-2 (PRC2), which functions to repress gene expression through trimethylation of H3K27 (H3K27me3) (Cao et al. 2002; O'Carroll et al. 2001). PRC2 is essential for development as reducing a single subunit results in embryonic lethality and severe developmental defects (O'Carroll et al. 2001, 2; Pasini et al. 2004). H3K27me3 deposition and removal are critical in epigenetic inheritance of repressed transcriptional landscapes and neurogenesis (Coleman and Struhl 2017; Burgold et al. 2008; Fragola et al. 2013; Park et al. 2014). Mainly, EZH2 knockdown results in abnormal migration of cortical neurons due to overexpression of Reelin, a glycoprotein that regulates neuronal migration (Zhao et al. 2015). Furthermore, chicken embryos lacking EZH2 exhibit impaired neural tube organization due to dysregulated neural progenitor cell renewal and impaired Rho signaling (Akizu and Martínez-Balbás 2016). Weaver syndrome (WVS) (MIM: 277590), an overgrowth syndrome characterized by intellectual disability, macrocephaly, developmental delay, and characteristic facial features, is caused by heterozygous mutation EZH2 (Weaver et al. 1974; Gibson et al. 2011). Cohen et al. determined that WVS-causing EZH2 mutations reduce PRC2 activity *in vitro*, suggesting that WVS is caused by altered PRC2 function (A. S. A. Cohen et al. 2016). Interestingly, despite the decreased activity, PRC2 harboring WVS-causing EZH2 mutations displayed increased association with chromatin, suggesting dysregulated disengagement between the complex and chromatin (C.-H. Lee et al. 2018). Mice bearing EZH2 mutations result in perinatal lethality when homozygous,

and overgrowth when heterozygotes (Lui et al. 2018). Loss of PRC2 during differentiation severely compromised neural gene induction due to marked loss of bivalent enhancers (Cruz-Molina et al. 2017). Collectively, this evidence suggests EZH2 plays a critical role in neurodevelopment; however, understanding how these mutations impart their effects on human neurogenesis remains unclear.

ASH1L

ASH1-like histone lysine methyltransferase (ASH1L), also known as KMT2H, catalyzes mono- and dimethylation of H3K36, promoting gene expression by counteracting Polycomb silencing (Miyazaki et al. 2013). Moreover, ASH1L plays a critical role in development by activating homeobox (HOX) genes and is highly expressed in both embryonic and adult brains(Okamoto et al. 2017; Miller et al. 2014). Various groups reported ASH1L as the causative gene in Autosomal dominant mental retardation-52 (MRD52) (MIM: 617796) (Okamoto et al. 2017; de Ligt et al. 2013; T. Wang et al. 2016; Stessman et al. 2017; Krumm et al. 2015). Individuals with MRD52 have mild-severe intellectual disability, autism spectrum disorder, speech delay, facial dysmorphisms, and overall developmental delay (Okamoto et al. 2017; de Ligt et al. 2013; T. Wang et al. 2016; Stessman et al. 2017). No functional analyses have been conducted on patient cells; however, knockdown of Zebrafish homolog, ash1a, resulted in a reduction in the number of neurons in the pineal gland (Cau and Wilson, Stephen W. 2003). Furthermore, mice expressing catalytically inactive ASH1L had a wide range of skeletal anomalies and impaired fertility (Miyazaki et al. 2013; Brinkmeier et al. 2015). Interestingly, ASH1L is enriched at the promoter of neurexin1α, a presynaptic adhesion molecule essential for synapse formation, upon neuronal stimulation (Zhu et al. 2016). It will be critical to determine how the ASH1L pathogenic variants affect the synaptic formation, synaptic plasticity, and ultimately learning and memory.

NSD1

Nuclear receptor SET domain-containing 1 (NSD1; also known as KMT3B) performs methylation of H3K36 as well as H4K20 (Rayasam et al. 2003). *In vivo* analysis demonstrated NSD1 catalyzed mono and dimethylation of H3K36 and trimethylation of H4K20 (Lucio-Eterovic et al. 2010; Qiao et al. 2011; Berdasco et al. 2009; G. G. Wang et al. 2007). Haploinsufficiency of NSD1 is the primary cause of Sotos syndrome-1 (SOTOS1) (MIM: 117550), accounting for over 75% of reported cases (Türkmen et al. 2003, 1; Kurotaki et al. 2002; Sotos et al. 1964; Hook and Reynolds 1967; Bejar et al. 1970; Douglas et al. 2003; Fryssira et al. 2010; Baujat and Cormier-Daire 2007). SOTOS1 is characterized by overgrowth, distinctive facial features, mild-severe intellectual disability, macrocephaly, and seizures (Kurotaki et al. 2002; Sotos et al. 1964). Different *de novo* mutations have been reported in individuals with SOTOS1, including missense, nonsense, frameshift, or deletion mutations (Türkmen et al. 2003, 1; Kurotaki et al. 2002; Douglas et al. 2003; van Haelst et al. 2005; Visser et al. 2005; Kaminsky et al. 2011). These mutations were widely distributed across the NSD1 protein, affecting the PHD domain, SET domain, and cofactor binding regions; thus, there is no mutational hot spot (Niikawa 2004; Pasillas, Shah, and Kamps 2011). Interestingly, individuals with SOTOS1 fall into two categories those due to either NSD1 haploinsufficiency or dosage effect (Niikawa 2004). Loss of NSD1

results in reduced H3K36 methylation and gene expression *in vitro* (Lucio-Eterovic et al. 2010). This methylation recruits DNMT3A, a DNA methyltransferase, at intergenic regions. Furthermore, blood samples from individuals with SOTOS1 exhibit hypomethylation of intergenic DNA(Weinberg et al. 2019). A mouse model for SOTOS1 with a heterozygous NSD1 mutation has been generated, which could be used in future work to elucidate the molecular mechanisms of these pathogenic variants(Oishi et al. 2020).

NSD2

Nuclear receptor SET domain-containing 2 (NSD2) is also known as Wolf-Hirschhorn syndrome candidate 1 (WHSC1) or multiple myeloma SET domain (MMSET). Similar to NSD1, NSD2 mono- and di-methylates H3K36(E. J. Wagner and Carpenter 2012). Interestingly, NSD1 and NSD2 loss of function results in distinctly different phenotypes despite deposition of the same histone modification. NSD1 knockdown mice have impaired gastrulation, whereas NSD2 knockout mice showed growth retardation and developmental defects (Rayasam et al. 2003; Nimura et al. 2009). Moreover, where mutations in NSD1 result in Sotos syndrome, haploinsufficiency of NSD2 results in the majority of Wolf-Hirschhorn syndrome (WHSC) (MIM: 194190) characterized by growth abnormalities, microcephaly, intellectual disability, seizures, and severe craniofacial abnormalities (Stec et al. 1998; Paradowska-Stolarz 2014). Mutations in NSD2 attributed with WHSC result in *de novo* loss-of-function variants (Derar et al. 2019; Jiang et al. 2019; Barrie et al. 2019; Lozier et al. 2018). Studies reported reduced cellular proliferation and cell viability in WHSC patient-derived fibroblasts suggesting that the haploinsufficiency either reduces cellular proliferation or increases cell death (Nevado et al. 2020). Severe craniofacial abnormalities are characteristic phenotypes of WHSC. To explore this, NSD2 expression was reduced in Xenopus laevis which correlated with decreased expression of several NSD2 associated genes(Mills et al. 2019). This reduction significantly affected craniofacial patterning, specifically cartilage formation and neural crest motility (Mills et al. 2019). Additionally, NSD1 has been demonstrated to regulate gene expression through Runx2, and p300 (Y. F. Lee et al. 2014). Researchers observed that NSD1 regulates the expression of bone-related genes through modulation of H3K36 dimethylation (Y. F. Lee et al. 2014). Lastly, knockdown of zebrafish NSD2 homolog, DrWhsc1, affected endbrain enlargement, abnormal cartilage, bone reduction, and incomplete motor neuron formation (Yamada-Okabe et al. 2010). Despite all these functional studies, there are currently no therapeutics developed for WHSC, suggesting that the pathomechanism remains elusive. Currently, only symptomatic treatments are available.

SETD2

SET domain-containing protein 2 (SETD2) is the primary methyltransferase for trimethylation of H3K36 (H3K36me3) (M. Hu et al. 2010; X.-J. Sun et al. 2005). SETD2 mediates genomic imprinting and embryonic development, as $SETD2^{-/-}$ embryos result in embryonic lethality (Q. Xu et al. 2019). SETD2 ablation causes Luscan-Lumish syndrome (LLS) (MIM: 616831), previously known as Sotos-like syndrome. LLS, is categorized by macrocephaly, facial dysmorphism, intellectual disability, speech and language developmental delay, and behavioral problems, including autism spectrum disorder (Luscan et al. 2014; Lumish et al. 2015). Thus far, *de novo* SETD2 mutations are proposed

to be loss-of-function either due to truncation or missense mutations (Marzin et al. 2019). SETD2 conditional knockout mice mimicked phenotypes seen in patients such as defective social interaction, reduced motor learning, and spatial memory (L. Xu et al. 2021). Xu et al. concluded that SETD2 is required for cortical arealization, the process of subdividing neocortex, and for the formation of cortical circuits (L. Xu et al. 2021). Functional studies utilizing patient samples are needed to determine the pathogenicity of the SETD2 mutations in neurodevelopment.

SETD5

SET domain-containing protein 5 (SETD5) mediates trimethylation of H3K36 (Dillon et al. 2005; Xiao, Wilson, and Gamblin 2003; Sessa et al. 2019). SETD5 mutations have been associated with neurodevelopmental disorders, including Cornelia de Lange and autism spectrum disorder (Parenti et al. 2017; Fernandes et al. 2018; Pizzo et al. 2019). Furthermore, heterozygous loss-of-function mutations in SETD5 cause autosomal dominant mental retardation-23 (MRD23) (MIM: 615761) characterized by psychomotor delay, speech impairments, dysmorphic facial features, intellectual disability, and behavioral abnormalities (Kuechler et al. 2015; Grozeva et al. 2014; Rauch et al. 2012; Green et al. 2017; Fang et al. 2019; Stur, Soares, and Louro 2017; Crippa et al. 2020). Deliu et al. demonstrated that SETD5-haploinsufficient mice have impairments in cognitive tasks due to dysregulated transcription via interaction with HDAC3 and PAF1 (Deliu et al. 2018). Haploinsufficiency of SETD5 in both mice and zebrafish resulted in global alterations to H3K36me3, impaired proliferation of neural progenitor cells, and defective synapse formation, ultimately resulting in learning and behavioral abnormalities (Sessa et al. 2019). Finally, Nakagawa et al. showed that SETD5 mediates ribosomal DNA expression through recruitment of HDAC3, and this regulation is critical for neural cell proliferation (Nakagawa et al. 2020). Sufficient evidence proves that SETD5 haploinsufficiency drives abnormal neurodevelopment. Future studies are needed to continue elucidating the pathology of MRD23 and other SETD5-related syndromes.

DEMETHYLATION

Like acetylation, methylation is removed by a group of enzymes; these are known as lysine demethylases (KDMs) (Yujiang Shi et al. 2003). For decades, lysine methylation was presumed static and irreversible due to the slow turnover of methylated histones, and the fact that no demethylases were known. In 2004, the first bonafide lysine demethylase was discovered, revealing that methylation was a dynamic mark that can be altered to mediate gene expression (Yujiang Shi et al. 2004). To this date, there are two classes of KDMs those based on the catalytic domain, either flavin adenine nucleotide (FAD)-dependent oxidase domain or Jumonji C (JmjC) domain (Yujiang Shi et al. 2004; Yang Shi and Whetstine 2007). Similar to KMTs, KDMs have a high degree of specificity for its target substrates. In this section, we will discuss clinical phenotypes that manifest when KDMs are mutated.

KDM1A

Lysine-specific demethylase 1A (KDM1A or LSD1), the first demethylase discovered, catalyzes FAD-dependent oxidative demethylation of mono and dimethylated H3K4, which

results in gene repression (Shao et al. 2014). Heterozygous mutations in KDM1A are causative for a syndrome of cleft palate, psychomotor retardation, and distinctive facial features (CPRF) (MIM: 616728) (Chong et al. 2016; Tunovic et al. 2014). Individuals with pathogenic KDM1A variants present global developmental delay, intellectual disabilities, and craniofacial abnormalities (Chong et al. 2016; Tunovic et al. 2014). One such pathogenic variant contains a replacement of an evolutionarily conserved tyrosine(Y385), potentially conferring a gain-of-function mutant giving rise to decreased H3K4 methylation (Tunovic et al. 2014). Notably, KDM1A is a crucial subunit of CoREST (corepressor to the REST (RE1 silencing transcription factor/neural restrictive silencing factor) complex), which mediates repression of neuronal genes (Ballas et al. 2001; Andrés et al. 1999). Knockdown of KDM1A in mouse cortical neurons led to decreased dendritic arborizations and neurite width, suggesting it plays a critical role in neurite morphogenesis (Zibetti et al. 2010). Taken together, KDM1A regulates neuronal function and programming; however, further studies are needed to determine the factors that recruit KDM1A in specific regulatory regions in neurons and the influence of these pathogenic mutations on its function.

KDM5B

Lysine-specific demethylase 5B (KDM5B other aliases include: JARID1B, SUV420H1) is a member of the KDM5 family of JmjC domain containing demethylases and demethylates di- and trimethylated H3K4 (Xiang et al. 2007). KDM5B-mediated demethylation regulates RNA polymerase II initiation and elongation as well as alternative splicing in embryonic stem cells(He and Kidder 2017). Notably, both homozygous and heterozygous germline mutations of KDM5B have been discovered as causative in mental retardation, autosomal recessive 65 (MRT65) (MIM: 618109) (Faundes et al. 2018; Martin et al. 2018). Individuals with MRT65 display moderate-severe developmental delay, inconsistent dysmorphic facial features, and behavioral abnormalities (Faundes et al. 2018; Martin et al. 2018). KDM5B−/− embryos exhibit several neural defects due to derepression of developmental regulators in early embryogenesis(Albert et al. 2013). Moreover, a loss-of-function model mimicking MRT65 exhibited similar phenotypes as seen in patients including increased behavioral abnormalities, decreased learning and skeletal abnormalities (Martin et al. 2018, 20). Zhou et al. demonstrated that KDM5B negatively regulates neurogenesis in adult subventricular zone through regulation of Reelin expression suggesting a role of KDM5B in neuronal migration and cortical circuit organization (Zhou et al. 2016). Extensive studies have found KDM5B as a major regulator of neuronal differentiation, however the specific genes involved in this disorder and how they affect neurogenesis remains elusive.

KDM5C

KDM5C (also known as JARID1C, SMCX) catalyzes the demethylation of di- and trimethylation H3K4, recognizes H3K9me3 and negatively regulates transcription through the RE-1-silencing transcription factor (REST) complex (Lan et al. 2007; Tahiliani et al. 2007). KDM5B is highly expressed in brain and skeletal muscle, pathogenic KDM5C variants account for approximately 3% of Claes-Jensen type of X-linked syndromic mental retardation (MRXSCJ) (MIM: 300534) (Jensen et al. 2005; Peng et al. 2015). Individual present intellectual disability, microcephaly, epilepsy and abnormal facial features (Jensen et al. 2005). To date, at least 30 mutations have been identified encompassing nonsense,

missense and frameshift in individuals with MRXSCJ. Functional studies of these mutations reveal decrease in KDM5C activity, suggesting a loss-of-function pathological mechanism (Tahiliani et al. 2007; Iwase et al. 2007). Patient-derived fibroblasts revealed dysregulated KDM5C genomic localization, altered DNA methylation and loci specific alterations in histone methylation (Jensen et al. 2005; Brookes et al. 2015; Grafodatskaya et al. 2013; Schenkel et al. 2018). Additionally, KDM5C is critical for neuronal development and maturation (Iwase et al. 2007; Scandaglia et al. 2017). Iwase et. al recapitulated MRXSCJ abnormalities in a condition knockout of KDM5C in mouse brains, including behavioral anomalies and memory deficits (Iwase et al. 2016). Investigation of patient mutations in Neuro2a cells revealed dysregulation of genes involved in neuronal development due to methylation changes at their promoters; the differential expression resulted in morphological changes including abnormal neurite length (Wei et al. 2016). Another promising study demonstrated that reduced functionality of KDM5C causes a lack of repression in neurodevelopmental transcripts, and a decreased KDM5C dosage resulting in neuronal defects (Poeta et al. 2019). Moreover, they demonstrated that KDM5C is a Vorinostat-sensitive gene, treatment with this HDAC inhibitor ameliorates previously compromised neuronal differentiation (Poeta et al. 2019). The role of KDM5C has been extensively studied and characterized in neuronal differentiation, its impact has been shown to be corrected *in vitro* and *in vivo* using Vorinostat, a promising therapeutic for MRXSCJ.

KDM6A

Lysine demethylase 6A (KDM6A or UTX) contains a catalytic JmjC domain and preferentially demethylates di- or trimethylated H3K27. Also, it is a member of the KMT2C/D COMPASS-like complex (Hong et al. 2007; Lan et al. 2007; C. Wang et al. 2012; Cho et al. 2007; M. G. Lee et al. 2007). As a member of the COMPASS-like complex, KDM6A regulates enhancer activation, independent of its demethylase activity (S.-P. Wang et al. 2017). Individuals presented with KS1 characteristics, described earlier, were screened for mutations in KMT2D but instead carried *de novo* heterozygous mutations in KDM6A (Noriko Miyake et al. 2013; Lederer et al. 2012). Like KS1, Kabuki syndrome 2 (KS2) clinically presents with developmental delay, intellectual disabilities, and craniofacial abnormalities (Lederer et al. 2012). Some features of KS1 were less common in KS2 individuals; however, all KS2 patients exhibited postnatal growth retardation and short stature (Noriko Miyake et al. 2013). Conditional knockout of KDM6A in neural stem cells led to increased anxiety-like behavior and impaired learning and memory in mice (Tang et al. 2017). Moreover, hippocampal neurons in these mice displayed impaired synaptic formation and plasticity, revealing a role of KDM6A in regulating cognition (Tang et al. 2017). Another model demonstrated that KDM6A loss increases neural stem cell proliferation and decreases terminal mitosis, resulting in aberrant neuronal differentiation (Lei and Jiao 2018). Interestingly both KS1 and KS2 stem from altered KMT2C/D COMPASS-like complex functions. Although extensive studies have been conducted in the context of cancer, specific pathways involved in neurogenesis remains ambiguous.

PHF8

PHD finger protein 8 (PHF8 also known as KDM7B) is the first monomethyl H4K20 demethylase established, interestingly it can also demethylate mono- and dimethylated

H3K9 (Qi et al. 2010). PHF8 binds H3K4me3, and through this interaction, positively regulates gene expression (Feng et al. 2010; Horton et al. 2010). Reduction of PHF8 in zebrafish embryos caused cell death in the developing brain and neural tube and significant defects in craniofacial development (Qi et al. 2010). PHF8 directly controls the expression of homeodomain transcription factor MSX1/MSXB, mediating signaling and developmental pathways (Qi et al. 2010). Given its role in neurodevelopment, it's not surprising that mutations in PHF8 results in a NDD, Siderius-type X-linked syndromic mental retardation (MRXSSD) (MIM: 300263) (Siderius et al. 1999; Laumonnier et al. 2005). MRXSSD primarily affects male individuals and they often have intellectual disability, mild dysmorphic features, and bilateral/unilateral cleft lip or palate(Koivisto et al. 2007). *In vitro* analysis of MRXSSD patient mutation abolished demethylase activity and transcriptional activation (Feng et al. 2010). PHF8 potentially mediates serotonin signaling and downregulation of PHF8 results in stress-induced anxiety, depression and cognitive impairment (Walsh et al. 2017). Moreover, PHF8 knockout mice displayed reduction cognition and memory due to impaired long-term potentiation. Chen et al. demonstrated PHF8 plays a role homeostasis of mTOR signaling, and suppression of mTOR recovers the cognitive deficits observed in PHF8 knockout mice. These studies provide potential targetable pathways to treat MRXSSD.

READERS

BPTF

Bromodomain PHD finger transcription factor (BPTF) is the largest subunit of the NURF complex and mediates binding to H3K4me3 (M. H. Jones, Hamana, and Shimane 2000). BPTF has been shown to promote expression of WNT8A which is crucial for neural posteriorization, through recruitment of NURF complex(Ma et al. 2015). Eight heterozygous mutations in the BPTF gene were discovered in unrelated individuals with neurodevelopmental disorder with dysmorphic facies and distal limb anomalies; NEDDFL (MIM: 617755) (Stankiewicz et al. 2017). NEDDFL is characterized by delayed psychomotor development, intellectual disability, speech impairments, microencephaly and dysmorphic features (Glinton et al. 2021). Although functional studies of patient cells have yet to be conducted, Stankiewicz et al. suggests that haploinsufficiency is the pathogenic mechanism of this disorder (Stankiewicz et al. 2017). CRISPR/Cas9-mediated knockdown of *bptf* gene in zebrafish resulted in increased cell death which recapitulated microencephaly and craniofacial abnormalities seen in patients (Stankiewicz et al. 2017). Due to the novelty of this disorder, there is currently no potential pathological mechanism for BPTF mutations in neurodevelopment.

EED

As mentioned above, EED is a major subunit of PRC2 complex as it recognizes previously methylated histones (Margueron et al. 2009). EED is required for maintaining neurogenesis and neurosphere formation through regulation of p21 (B. Sun et al. 2018). Heterozygous mutations in EED results in the overgrowth disorder Cohen-Gibson syndrome (COGIS) (MIM: 617561) (Cooney et al. 2017). Affected COGIS individuals have intellectual disability, dysmorphic facial features, advanced bone age and skeletal abnormalities (A.

S. A. Cohen et al. 2016; Cooney et al. 2017; A. S. Cohen and Gibson 2016; Imagawa et al. 2017). EED-deficient mice exhibited postnatal lethality and diminished neuronal differentiation in the hippocampal dentate gyrus potentially explaining the pathomechanism of COGIS (Liu et al. 2019). Additionally, EED establishes a chromatin landscape that selectively represses inhibitory WNT and bone morphogenetic protein (BMP) signaling which is required for oligodendrocyte differentiation and maturation (Jiajia Wang et al. 2020). Taken together, EED plays a critical role in CNS development, through regulation of neuronal and oligodendrocytic differentiation, however, the field lacks biochemical characterization of COGIS mutations.

SUZ12

Similar to the other core PRC2 subunits, EZH2 and EED, mice with mutations in SUZ12 are embryonic lethal due to severe developmental and proliferative defects(Pasini et al. 2004). SUZ12 is essential for EZH2 activity as SUZ12 deficiency *in vivo* leads to loss of di- and trimethylated H3K27 (Pasini et al. 2004). Unfortunately, the SUZ12-related overgrowth syndrome, Imagawa-Matsumoto syndrome (IMMAS) (MIM: 618786) is the least characterized of the PRC2-related syndromes (Imagawa et al. 2017; 2018). Individuals with IMMASS exhibit pre- and postnatal overgrowth, dysmorphic features, intellectual disabilities, macrocephaly and developmental delay (Imagawa et al. 2017). SUZ12 is required for proper differentiation as SUZ12-deficient stem cells are de-repressed, increasing levels of differentiation specific genes (Pasini et al. 2004). Moreover, heterozygous SUZ12 mice exhibit neural tube defects and severely impaired differentiation (Miró et al. 2009).

CHROMATIN REMODELERS

Precise temporal gene expression is critical for differentiation during development. Histone PTM patterns recruit different effector proteins, such as chromatin remodelers with the ability to alter chromatin structure. Chromatin remodelers influence the spacing of nucleosomes allowing transcriptional machinery access to DNA. Remodelers are multiprotein complexes, centered around a catalytic ATPase helicase subunit, that slide, unwrap or evict nucleosomes, as well as exchange histone variants within a nucleosome. Beyond the helicase, remodelers contain subunits that enhance activity and facilitate targeting of the complex. Many remodeler members contain reader domains such as chromodomains and bromodomains, allowing for targeting to specific PTMs. The major ATPase remodeler families are BRG1 associating factors (BAF) (also known as switch/sucrose non-fermentable (SWI/SNF)), ISWI (imitation SWI), CHD (chromodomain helicase DNA-binding), and INO80 (SWI2/SNF2 related). Recently, mutations in members of ATPase remodelers have been identified in neurodevelopmental disorders giving light to the importance of these complexes in neurodevelopment.

BAF family

BAF (BRG1/BRM associating factors) complexes are the mammalian version of yeast Switch/Sucrose Non-Fermentable (SWI/SNF) remodeler (W. Wang et al. 1996; Breeden and Nasmyth 1987; Stern, Jensen, and Herskowitz 1984; Neigeborn and Carlson 1984). Canonical BAF is comprised of approximately 15 subunits, however, at least 29 isoforms of

the subunits exist. This allows for multiple formations of BAF complexes in a single cell. For example, there are two mutually exclusive helicases, BRG1 and BRM. Though they appear to have some redundant roles, mouse studies have demonstrated distinct roles for BRG1 and BRM in development. Homozygotic BRG1 knockout is lethal pre-implantation where BRM knockouts are viable (Bultman et al. 2000). The variety of these isoforms allow for multiple formations of BAF complexes in a single cell. Ubiquitously expressed sub-complexes include Polybromo-1-BAF (P-BAF), which incorporated Polybromo-1, ARID2, BAF45a, and BRD7(W. Wang et al. 1996)and G-BAF that is comprised of GLTSCR1 and BRD9 (Alpsoy and Dykhuizen 2018). Cell-type-specific BAF compositions such as neuron progenitor and neuron-specific BAF (npBAF and nBAF) also exist (Lessard et al. 2007). BAF subunits exchange as neuron-progenitor cells differentiate into neurons and exit mitosis and this is critical for proper proliferation and differentiation of neural progenitor cells. Interestingly, BAF mutations have been identified in ID disorders with the majority of mutations associated with Coffin-Siris syndrome (CSS), Nicolaides-Baraiter, and Autism.

Coffin-Siris, first reported in 1970, is a rare genetic disorder with only about 140 cases reported in literature (Coffin and Siris 1970; van der Sluijs et al. 2019). Although patient phenotypes highly overlap, OMIM classifies CSS into 11 different types depending on what protein is mutated. Mutations have been identified in ARID1b (BAF250b) (MIM:135900, CSS1), ARID2 (BAF200) (MIM:609539, CSS6), BRG1 (MIM:614609,CSS4), BAF57(MIM:616938, CSS5), ARID1a (BAF250a) (MIM: 614607, CSS2), DPF2 (MIM:601671, CSS7), BAF47(MIM: 614608, CSS3), BAF60a (SMARCD1) (MIM: 618779, CSS11) (van der Sluijs et al. 2019; Kosho et al. 2014; Santen et al. 2012). Patients diagnosed with CSS exhibit intellectual disorders (IQ score 50–89), delayed sitting and walking, short stature, microcephaly, muscular hypotonia, coarse facial features, hypoplasia or aplasia of the fifth finger, bushy eyebrows, and excessive hair growth (van der Sluijs et al. 2019). AT-rich interacting domain 1b (ARID1b), the most frequently mutated gene in CSS (68%), was identified in 2012. Mutations resulted in a heterozygous deletion, causing haploinsufficiency, speculated to be the driver of CSS. The ARID subunits (ARID1a, ARID1b, and ARID2) are predicted to bridge the ATPase to the complex and their incorporation determines which BAF subtype is formed (Mashtalir et al. 2018). Interestingly, ARID1b incorporation into BAF is mutually exclusive with ARID1a (which is 60% identical). Additionally, ARID1b, but not ARID1a, represses WNT/Beta-catenin signaling, involved in proliferation, differentiation, and pluripotency (Vasileiou et al. 2015). Activation of this pathway in haploinsufficient cells may be a driving mechanism of CSS. In mouse models recapitulating the ARID1b haploinsufficiency, mice exhibited growth retardation, hypotonia, and agenesis of the corpus callosum, as well as anxiety and abnormal social behaviors (Celen et al. 2017).

Other BAF subunits are less commonly mutated in CSS and unlike ARID1b, result in expression of mutated protein and are predicted to have either loss or gain-of-function mechanisms (van der Sluijs et al. 2019). BAF47 mutations occur in exon 8 and 9 with the only reoccurring mutations being pLys364 deletion. One study utilized an inversion *NesCre* system to decrease BAF47 expression by 30% in mice (Filatova et al. 2019). The mutant mice were significantly smaller than the controls and their brain weight was reduced by 41%. The majority (~80%) did not survive past postnatal week 9. Intriguingly,

these effects were not observed in BAF47 heterozygotic knockout mice. BRG1 mutations account for 11% of CSS cases and they cluster in the helicase/SANT-associated domains. Mutations of BRG1 as well as BAF155 lead to defects in neural tube closures and exencephaly, demonstrating the critical role of BAF complexes in neural development (Bultman et al. 2000; J. K. Kim et al. 2001). BRG1 is also involved in both neuronal and glial differentiation and BAF is recruited to cell-type-specific genes through different transcription factors. OLIG2, an oligodendrocyte-specific transcription factor, recruits BRG1 to H3K27Ac rich enhancers for myelination-specific genes(Y. Yu et al. 2013). BAF57 mutations are found in the high mobility group (HMG), a DNA binding domain, and ARID1a mutations are predicted to be truncated. ARID2 mutations have been reported in seven CSS patients (Bramswig et al. 2017; Shang et al. 2015; Van Paemel et al. 2017). DPF2 mutations that cluster in the two PHD fingers were found in eight patients (Vasileiou et al. 2018). These mutations altered DPF2 binding to H3 peptides and are predicted to have a dominant-negative mechanism. In 2019, Nixon et al., identified 5 individuals with *BAF60a (SMARCD1)* (MIM: 618779, CSS11) mutations(Nixon et al. 2019). Patients had some overlapping phenotypes with CSS, however, did not exhibit the same facial features such as thick eyebrows, broad noses and long eyelashes. BAF60a mutations did not disrupt incorporation into the BAF complex. Interestingly, BAF60a is important for recruiting BAF to OCT6 and KROX20 through SOX10 interaction in Schwann cells (Weider et al. 2012).

Mutations in BRM have been shown to be causative for Nicolaides-Baraitser syndrome (MIM:601358), a developmental disorder characterized by short stature, microcephaly, sparse hair, epilepsy, and intellectual disabilities (Van Houdt et al. 2012). Sousa et al. examined 59 patients with 48 missense mutations in BRM and found these mutations cluster in the highly conserved SNF2 ATPase domain and are predicted to cause gain or loss-of-function, rather than truncations (Sousa et al. 2014). Additional BAF subunits are mutated in neurodevelopmental disorders. Machol et al., found 15 patients with BAF170 (SMARCC2) mutations, also exhibiting similar phenotypes to CSS patients, including the lack of the fifth finger nail (Machol et al. 2019). Three novel mutations have also been identified in *Actl6a* (Marom et al. 2017).

A recent study on how BAF assembles demonstrated a sequential addition subunit modules and that the incorporation of the ARID proteins is critical in determining which BAF subcomplex will be formed (Mashtalir et al. 2018). Loss of expression or mutant BAF subunits can alter proper formation or skew the composition of the complex as well as alter the function of the complex. It is likely that the introduction of BAF mutations, disrupt BAF composition as well as altering the switch between npBAF and nBAF. Due to the importance of BAF in neurogenesis and development, this list of mutations will likely grow as we expand sequencing studies of NDD patients.

CHD Family

The CHD family of ATPase helicase remodelers is comprised of nine proteins, CHD1–9, that contain tandem chromodomains, methyl-lysine readers, and SNF2-like ATPase catalytic domain (Marfella and Imbalzano 2007). These proteins are divided into three subgroups: 1) CHD1and CHD2 contain C-terminal DNA domains that bind AT-rich regions, 2) CHD3 and

CHD4 have paired N-terminal PHD zinc fingers, and 3) CHD5-CHD9 featuring Brahma and Kismet domains, CR-domains, SANT domains, and DNA binding domains[25]. In contrast to the other remodelers, many of the CHD proteins act without accessory proteins, however, CHD3, CHD4, and CHD5 can be incorporated in the NURD complex along with HDAC1/2, MBD2 or 3, MTA1,2 or 3, RBAP46, and RBAP48 (Hoffmann and Spengler 2019). The CHD proteins have important roles in development and differentiation. Knockdown CHD1 causes defects in self-renewal and pluripotency in ESCs. During brain development, the CHD4-containing NURD complex is critical in synapse formation by repressing genes to drive synaptogenesis (T. Yamada et al. 2014). This involves deacetylation of histone H3 at residues at K9, K14, and K27 as well as demethylation of H3K4me3. Neural crest cell migration is also mediated through CHD7 and PBAF by regulating gene expression of Sox9, Slug, and Twist (Bajpai et al. 2010; Schulz et al. 2014). Loss of CHD7 decreases the pool of neural stem cells and impairs neuron maturation (K. M. Jones et al. 2015). As sequencing of patients with intellectual disorders becomes standard, the CHD proteins have been identified as culprits in several disorders.

CHD1

CHD1, known to bind H3K4me3/H3K4me3 through its chromodomains, and is predicted to play important roles in pluripotency, transcriptional elongation, and deposition of histone variant H3.3 (Flanagan et al. 2005). CHD1, particularly the N-terminus, is critical in mouse long-term and spatial memory (Schoberleitner et al. 2019). In 2018, Pilarowski et al., identified six female patients with *de novo* heterozygous mutations, most of which were at highly conserved arginine residues. A larger cohort is needed to determine if there is a gender bias for Pilarowski-Bjornsson syndrome (MIM: 617682) patients (Pilarowski et al. 2018). Probands exhibited developmental delays, hypotonia, pointed chins, frontal forehead bossing, and arched eyebrows. Using patient-derived fibroblasts containing CHD1 mutation, global increases in H3K27me3 compare to wild-type cells were observed. Mice with heterozygotic loss of *Chd1* are phenotypically normal(Guzman-Ayala et al. 2015), suggesting a dominant-negative mechanism for CHD1 mutants, leading to the prevention of wild-type CHD1 properly binding to the targets and regulation gene expression (Pilarowski et al. 2018). Further work is needed to determine the role of these mutations.

CHD2

CHD2 mutations have been characterized in patients with neurodevelopmental delays and epilepsy (MIM: 615369). CHD2 was identified as a driver of epilepsy when several seizure patients were identified with chromosome 15 deletions ranging from 5Mb to 511kb (Dhamija et al. 2011; Veredice et al. 2009; M. M. Li et al. 2008; Capelli et al. 2012). The smallest deletion encompassed only two genes, *CHD2* and *RGMA* (Capelli et al. 2012). After adding *CHD2* as a potential target when re-sequenced 500 individuals with epileptic encephalopathy, Carvill et al., identified six patients with CHD2 mutations (Carvill et al. 2013). As of 2021, 139 patients with neurodevelopmental disorders have been found, with ~95% of these individuals being affected by epilepsy, the onset ranging from six months to 12 years old (Carvill et al. 2013; Carvill and Mefford 1993; Suls et al. 2013; Heyne et al. 2018; Ko et al. 2018; Chen et al. 2020; Truty et al. 2019; Fitzgerald et al. 2015). Majority of CHD2 mutations lead to loss of expression or truncations, the few missense mutations

do not appear to cluster in any particular region of the gene (Carvill and Mefford 1993). Mutations are mostly *de novo*, however, several were inherited from unaffected parents (Chen et al. 2020). CHD2 patients exhibited increased photosensitivity compared to other epileptic disorders and have varying degrees of intellectual delays. Though the mechanism of pathology is unknown, it is hypothesized that CHD2 is key in neuron differentiation by keeping bivalent genes active(Semba et al. 2017). Loss of CHD2 leads to increased H3.3 containing nucleosomes as well as elevated levels of the repressive mark, H3K27me3(Semba et al. 2017). In 2018, Kim et al., created a haploinsufficient CHD2 mouse and though this model did not recapitulate seizures, it demonstrated the importance of CHD2 in proliferation of neural progenitors, synapse transmission, hippocampus memory, and cortical synchrony, which appeared to be regulated by changes in expression of genes involved in neurogenesis, chromatin regulation and synaptic transmission(Y. J. Kim et al. 2018).

CHD3

In 2018, Blok et al., published the first report of CHD3 mutations (Snijders Blok et al. 2018). This first cohort of Snijders Blok-Campeau syndrome (MIM: 618205) consisted of 35 patients with 23 distinct mutations. These individuals suffered from ID, hypotonia, developmental delays, and severe speech and language disabilities. Many exhibited macrocephaly, with CT scans showing broad cerebrospinal fluid spaced; one patient presented with microcephaly. These probands have distinct facial features including broad foreheads, wide-spaced eyes sparse eyebrows, low set ears, and pointy chins. The majority of the CHD3 mutations clustered in the ATPase/helicase domain as well as amino acids that are evolutionarily conserved between species and other CHD proteins. Biochemical assays demonstrated several patient mutations caused loss of ATPase and remodeling activity of CHD3. The following year, Drivas et al., reported 24 additional patients with CHD3 mutations (Drivas et al. 2020). Though the majority of these mutations were found in the ATPase domain, nine were found outside of the domain. No phenotypic difference was observed between patients with mutations in or outside of the ATPase domain. Eising et al., found another CHD3 mutation in the helicase domains while genetically screening individuals with childhood apraxia of speech (Eising et al. 2019). Though, loss of catalytic activity is predicted to be the pathogenic mechanism, it is unclear the mechanism for the mutations found outside the ATPase domain.

CHD4

In 2016, two separate studies identified CHD4 mutations in patients. Sifrim et al., found five probands through screening individuals with congenital heart defects (Sifrim et al. 2016). Three patients exhibited Tetralogy of Fallot (defect of ventricular septal, pulmonary valve narrowing, misplaced aorta, and thickening of the right ventricular). In addition to cardiac defects, all five patients exhibited neurodevelopmental disorders and genital abnormalities. Weiss et al., identified an additional five patients exhibiting developmental delay, intellectual disabilities, macrocephaly, facial abnormalities, hypogonadism, hearing loss, bone fusion as well as congenital issues (Weiss et al. 2016). The five mutations were found at highly conserved residues, with four located in the C-terminal helicase domain. A follow-up study of Sifrim-Hitz-Weiss syndrome (MIM: 617159) looked at 32 individuals, and found mutations causing loss of CHD4 had less severe phenotype compared to patients with point

mutations (Weiss et al. 2020). Biochemical investigation of mutations showed that some, but not all the mutations, were able to disrupt ATPase and nucleosome remodeling. Goodman et al., has seen that conditional knockout of CHD4 increases H3K27ac, as well as increasing promoter and enhancer accessibility in mouse brains(Goodman et al. 2020). Additionally, they observed increases in looping and cohesion binding, indicating reorganizing of the genome. It is yet to be determined if mutations of CHD4 will have similar effects as CHD4 knockout (Goodman et al. 2020).

CHD7

CHARGE (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and development, and Ear abnormalities and deafness) syndrome (MIM:214800) is mainly associated with heterozygotic loss of CHD7, causing haploinsufficiency. CHARGE was first described in 1979 by two separate groups (Hittner et al. 1979; Hall 1979), however, the link with CHD7 was not discovered until 2004 by Vissers et al (Vissers et al. 2004). Since then, screening for CHD7 mutations has become standard in diagnosis (van Ravenswaaij-Arts et al. 1993). Patients exhibit an extensive list of symptoms that affect multiple organs. Coloboma is the improper formation of the eye, resulting in a keyhole in the iris, causing photosensitivity (van Ravenswaaij-Arts et al. 1993). Cranial nerve abnormalities lead to loss of hearing, balance issues, swallowing difficulties, asymmetric facial palsy, lack of smell and hypogonadism (van Ravenswaaij-Arts et al. 1993). They also present with heart abnormalities, esophageal atresia, hypotonia, craniofacial abnormalities, and characteristic “CHARGE ears” (short, wide and lacking earlobes) (van Ravenswaaij-Arts et al. 1993). Analysis of expression 10 human fetuses with CHARGE, demonstrated CHD7 was localized to the spinal ganglia, cranial nerves, neural retina, pituitary (important for regulation growth and development), as well as nasal and auditory tissues (Sanlaville et al. 2006). Knockout of CHD7 in mice reduced neurogenesis in the hippocampus, dentate gyrus, which is important for memory, the sub-ventricular zone, and in the inner ear. Examining its role in differentiation, CHD7 is not essential in ESC proliferation or differentiation into neuron progenitor cells and dispensable in many cell-types (H. Yao et al. 2020). However, CHD7 is critical in development of neurons. Specifically, loss of CHD7 leads to decrease in neuroblasts and causes a shift in increases the glial cell, and neurons that are created have fewer branches with reduced length, effecting the number and the quality of neurons (Micucci et al. 2014; H. Yao et al. 2020). CHD7 is important keeping chromatin open and activating neuron differentiation genes and associates with H3K27ac rich super enhanced and cell identify specific transcription factors as well as recruiting DNA Topoisomerase IIb to long neuron genes (Feng et al. 2017; Hnisz et al. 2013). CHARGE and CHD7 has been studied more extensively than other NDDs and Trider et al. has created an extensive checklist of 49 symptoms of CHARGE patients and guidelines for treatment of the individuals as they age (Trider et al. 2017). Though this is an invaluable resource, the treatments focus on management of symptoms. Developing therapeutics to elevate the defects of neurogenesis caused by CHD7 haploinsufficiency are still needed.

HISTONES

All of the disorders previously described originate from germline mutations in enzymes that either catalyze histone post-translational modifications or chromatin remodeling. Recent studies have discovered germline mutations in histone proteins, allowing us to define their roles not only in the context of gene regulation but also development.

HIST1H1E

In 2017, Tatton-Brown et. al. conducted a study with 710 individuals all suffering from overgrowth syndrome and intellectual disability to explore the underlying genetic predispositions (Tatton-Brown et al. 2017). Utilizing exome sequencing, they reported de novo heterozygous germline mutations in the HIST1H1E gene (5/710) which encodes linker histone, histone H1.4 (H1.4). Patients bearing H1.4 mutations suffer from distinct facial features, intellectual disability, and macrocephaly (Tatton-Brown et al. 2017). This syndrome was coined Rahman syndrome (MIM: 617537), with the causative gene being HIST1H1E. Following the 2017 study, 42 patients were discovered suffering from Rahman Syndrome all exhibiting distinct facial gestalt, ID, skeletal, and congenital cardiac abnormalities (Burkardt et al. 2019; Duffney et al. 2018; n.d.). Reported frameshift mutations are centralized to the C-termini of the protein and result in a truncated H1.4 with a charge reduced from +44 to +7. Linker histones play a critical role in regulating higher-order chromatin structure through neutralization of negatively charged linker DNA via its positively charged tails. H1.4 is often sequestered in heterochromatic regions and the truncation of H1.4 ultimately impairs the linker histone's ability to generate higher-order structures (Tatton-Brown et al. 2017; McGinty and Tan 2015; Ponte et al. 2017; Song et al. 2014).

Conducting a robust functional assessment of the HIST1H1E mutations it was determined that these mutants had proper nuclear localization and increased stability compared to wild type (Flex et al. 2019). Normally, the C-terminal tail of H1 undergoes reversible phosphorylation which mitigates chromatin compaction, chromosome segregation, and chromatin decondensation, however, these residues are all lost in HIST1H1E mutants (Flex et al. 2019; Chadee et al. 1997; Ajiro, Borun, and Cohen 1981). Interestingly, patient-derived fibroblasts showed significantly more relaxed DNA as well as a decrease in H3K4me2, H3K9me3, H3K27me3, and HP1β (Flex et al. 2019). Ultimately, the frameshift mutations disrupt chromatin structure, alter nuclear lamina organization, generate a hypomethylated DNA signature, and drive replicative senescene (Flex et al. 2019). Another study determined that the aberrant DNA methylation profile resulted in altered gene regulation, which was exacerbated in post-mitotic cells as genes involved in neural signal transduction were significantly altered (Ciolfi et al. 2020). Overall, there is sufficient evidence to start elaborating on the pathomechanism of H1.4 mutations and the role of this linker histone in neuronal development.

HIST1H4C/J

Histone H4 (H4), which is encoded by 15 distinct genes, is currently the only histone with no functionally distinct variants (Holmes et al. 2005). It is ubiquitously expressed in all cells

and is a critical nucleosomal protein. In 2017, monoallelic missense heterozygous mutations of HIST1H4C were discovered via trio sequencing (Tessadori et al. 2017). These mutations result in substitutions that cause a charge switch (K->E), lose (K->Q) or retain charge (K->R) at residue 91 of H4 (Tessadori et al. 2017). These patients exhibit short stature, microencephaly, intellectual disability, craniofacial abnormalities, and foot ray anomalies. RNA sequencing utilizing patient-derived fibroblasts revealing 115 genes differentially expressed in K91 mutants. Intriguingly, 25 of these genes encoded for histone proteins. Enriched gene ontology (GO) terms for differentially regulated genes related to chromosome organization, DNA packaging, and cell cycle progress (Tessadori et al. 2017).

To assess the functional consequence of these mutations, zebrafish were injected with mRNA encoding mutations and K91R/Q injected embryos exhibited severe developmental defect (Tessadori et al. 2017). These embryos had underdeveloped brains and eyes, defective body axis growth, and dysmorphic tails which recapitulated the phenotype seen in patients (Tessadori et al. 2017). Thus, this *in vivo* model provided sufficient evidence that HIST1H4C mutations were causative in the observed syndrome. Zebrafish larvae expressing H4-K91R/Q exhibited increased accumulation DNA double-strand breaks (DDBs) specifically in the head and tail region and this was determined utilizing a well-known readout for DDBs, γ-H2AX signal (Tessadori et al. 2017). Additionally, these embryos had increased apoptosis in the head and tail regions (Tessadori et al. 2017). K91 is a known PTM site for H4, as acetylation has been linked to chromatin assembly regulation and ubiquitination has been linked to DNA damage response (Ye et al. 2005; Q. Yan et al. 2009; Yang et al. 2011). Co-expression of DTX3L, the E3 ligase responsible for K91 ubiquitination, with K91 mutants alleviated the increase in double-strand breaks and morphological anomalies observed (Tessadori et al. 2017). This study was able to determine that the loss of K91 ubiquitination in the mutants was sufficient to alter cell cycle progression and apoptosis.

Recent work from the Gijs van Haaften lab reported a *de novo* germline missense mutations in HIST1H4J, another gene encoding histone H4 (Tessadori et al. 2019). This patient had a K91E mutation and exhibited intellectual disability, microcephaly, and had dysmorphic facial features, symptoms extremely similar to the previous report HIST1H4C mutations (Tessadori et al. 2017; 2019). Here they hypothesized that the glutamic acid (E) substitution may contribute to genomic instability due to its inability to be modified as well as the addition of a negative charge. This study was critical in showing the importance of K91 residue in H4, as different substitutions at this position can result in distinct phenotypic outcomes.

H3F3A/H3F3B

The most recent discovery of histone germline missense mutations involves the two genes (*H3F3A* and *H3F3B)* encoding Histone H3 variant, Histone H3.3 (Bryant et al. 2020). Bryant et. al discovered 37 unique *de novo* mutations in 46 patients. These patients suffered from a common pattern of neurodevelopmental disorder encompassing microencephaly, craniofacial abnormalities, and intellectual disabilities (Bryant et al. 2020). Unlike Rahman Syndrome and the K91 mutants of H4, these H3.3 mutations are dispersed across the

entire protein affecting, post-translational modification residues, chaperone interaction, protein-protein interaction, and protein-DNA contacts. Bottom-up mass spectrometry of patient lymphoblasts revealed histone PTM changes which were reproducibly altered in patients compared to controls (Bryant et al. 2020). Additionally, RNA sequencing utilizing patient-derived fibroblasts identified 323 differently expressed genes associated with mitosis and cell cycle regulation upregulated (Bryant et al. 2020). Due to the locations of these mutations along *H3F3A* and *H3F3B* it is predicted different biological processes are altered but appear to converge on similar phenotypes. This suggests that the phenotype is due to dysregulation of H3.3 in general and not limited to a single mechanism.

Here we have discussed the recent findings regarding germline variants associated with histone proteins, histone H1, histone H3.3, and histone H4. All of these patients exhibit common dysregulation of neurodevelopment clinically characterized with craniofacial abnormalities, intellectual disabilities, and developmental delay. These histone-related disorders allow a unique perspective on the role of histones specifically in the control of central nervous system development and growth.

CONCLUSION

In this review, we have highlighted the importance of epigenetic factors in neurodevelopment and how disruption of chromatin regulation at multiple levels can drive NDDs. The expansion of next-generation sequencing techniques in the diagnosis of NDD has elucidated many genes mutated in these disorders. Of particular interest are proteins involved in the regulation of DNA organization and gene expression. We have discussed mutations of histones, forming nucleosomes, the smallest unit of chromatin, to the proteins that curate PTM patterns across the genome to megadalton complexes the enforce chromatin structure. Though varying in phenotypical differences and severity, most of these disorders have devastating effects on physical and mental development. Although syndromes, such as RSTS1 and CHARGE, have been defined since the 1970s, the genetic drivers have only begun to be identified in the last couple of decades with the advances in sequencing. Sequencing has not only allowed for better classification of current syndromes; it has expanded our list of known driving mutations. Patients present with chromosomal deletions, resulting in the loss of multiple genes, or frameshift and missense mutations that can cause loss of expression, truncation, or point mutations.

For the most part, these mutations are de novo, with no familial history of the disorder as well as monogenic, indicating these mutations are causative. These disorders' common characteristics include intellectual disabilities, hypotonia, and facial abnormalities with comorbidities such as epilepsy and cardiac abnormalities. It is essential that most of these patients need extensive medical intervention to manage the symptoms and a lifetime of care and will never achieve independence. Therefore, it is imperative that more studies are done to determine the molecular pathways disrupted in these disorders. Thus far, clinical geneticists have determined the driving mechanism of NDD involves either haploinsufficiency, loss or gain-of-function, or dominant-negative. These all point to gene dosage effects, and future studies utilizing heterozygotes will be required to elucidate these pathological mechanisms fully.

Regarding chromatin-modifying enzymes, their genes are heavily regulated as precise regulation is necessary for proper differentiation and cellular identity. Therefore, epigenetic factors are critical for accurate expression or repression and the establishment of distinct chromatin structures. As discussed previously, distinct PTMs indicate active promoters, gene bodies, enhancers, and repressed regions. Neuroepigenetic, a relatively new field, has propelled research into NDDs forward as it focuses on determining how alterations in the epigenome result in neurological disease or disorders. Furthermore, extensive work in understanding neurogenesis has demonstrated the importance of epigenetic machinery as loss of these enzymes results in alterations to precise coordination of proliferation and differentiation in neural stem cells. Deletion of chromatin proteins results in abnormal cortical neurogenesis and defective synaptic plasticity. Due to the post-mitotic nature of neurons, it raises the question of whether neurons exhibit increased sensitivity to point-mutations or deletions of the epigenetic machinery. However, this remains to be fully explored. To date, mouse models of KS1, KLEFS1, RSTS1, SOTOS1, and WVS have been generated, and defects in hippocampal memory were observed in all models (Alarcón et al. 2004; Korzus 2017; Hans T. Bjornsson et al. 2014; M. C. M. Balemans et al. 2013; Monique C. M. Balemans et al. 2014; Harrison et al. 2012; J. Zhang et al. 2014). This suggests a similar disruption to memory formation, retrieval, or overall hippocampal function in these various NDDs. Interestingly, both the RSTS1 and KS mouse model had their hippocampal defects rescued by postnatal treatment with HDAC inhibitors (Alarcón et al. 2004; Hans T. Bjornsson et al. 2014).

Interestingly one of those inhibitors, Vorinostat, is approved by the US Food and Drug Administration (FDA) as cancer therapeutic. Epigenetic therapies, including both HAT and HDAC inhibitors, are currently being studied for the treatment of neurological conditions such as spinal muscle atrophy, bipolar disorder, and Alzheimer's disease ("Histone Acetyltransferase Inhibitors and Preclinical Studies: Expert Opinion on Therapeutic Patents: Vol 19, No 6" n.d.). As of 2021, four HDAC inhibitors are FDA-approved: Vorinostat, Panobinostat, Romidepsin, and Belinostat. These may be fruitful therapeutics in these disorders, especially those with decreased histone acetylation, which highlights the importance of classifying these disorders based on chromatin state and target gene expression. Studies of chromatin regulator proteins will offer keen insight into manipulating the epigenome in the context of disease to develop broad and potentially personalized therapeutics. Despite these promising therapeutics, one limitation remains the number of neural tissue available from patients and the overall rarity of individuals themselves. However, recent advances involving the generation of functional neurons and glia through patient-derived iPSCs or creating a patient-mimic through CRISPR/Cas9 technology allowed a new avenue to explore these etiologies NDDs (Sabitha, Shetty, and Upadhya 2021). This, coupled to the 3D self-assembled structures known as brain organoids, provides a unique opportunity not only to determine the pathways dysregulated but to assess cellular organization, transcriptional and epigenetic landscape in neurodevelopment. Collectively, utilizing both neuroscience advancements, we can begin to understand human neurodevelopment and its dysregulation using patient cells fully.

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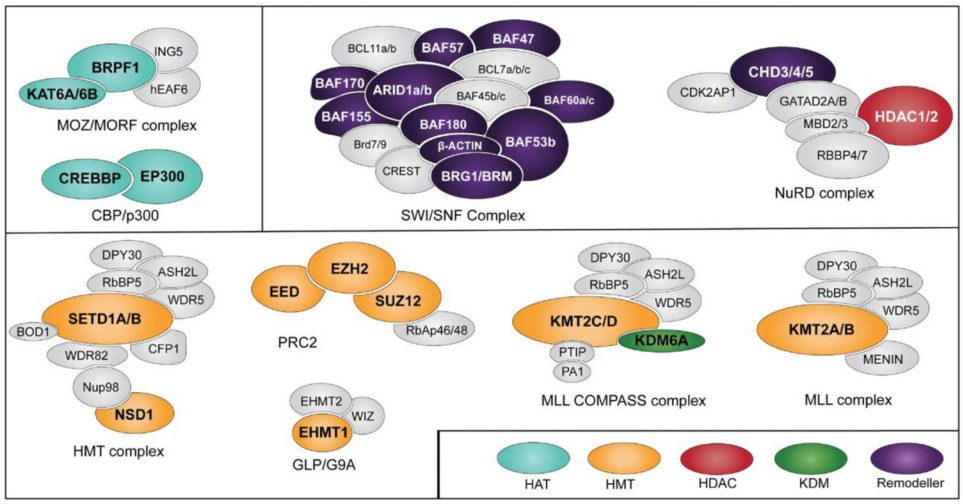

FIGURE 1:

Chromatin-modifying enzymes and the complexes they belong. Proteins mutated in NDDs are shown in color.

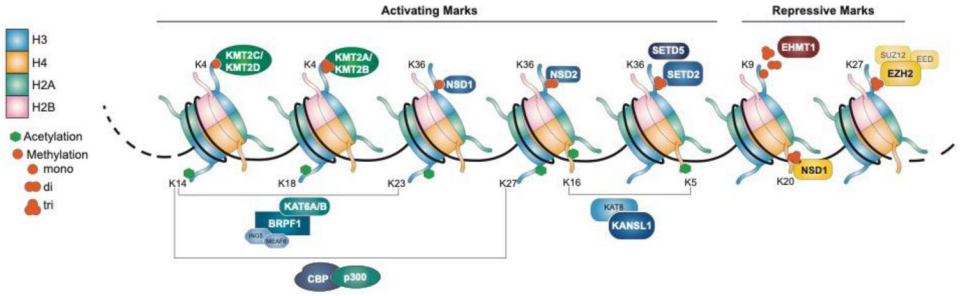

FIGURE 2:

Histone post-translational modifications are classified as activating or repressing depending on the modification site and the degree of modifications. Histone acetylation is primarily activating whereas methylation can play both roles. The HATs and KMTs which are mutated in NDD, as well as their targets, are shown above.

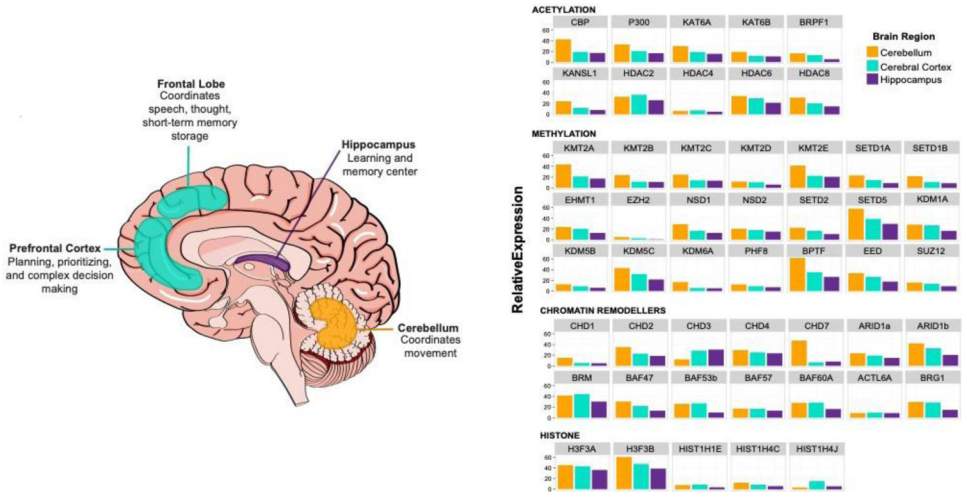

FIGURE 3:

Spatial expression of epigenetic factors dysregulated in NDD. (left) Graphical representation of brain regions in which most genes are highly expressed and their respective functions. (right) Expression in these three regions according to Consensus normalized expression (NX) levels on Protein atlas. This dataset was created by combining two transcriptomic datasets (GTEx and FANTOM5).

Table 1.

Driver mutations of chromatin modifying enzymes in intellectual disability disorders

Gene	Gene OMIM	Syndrome	OMIM	Gene Function
CBP	600140	Menke-Hennekam syndrome 1/Rubinstein-Taybi syndrome 1	618332/180849	Histone acetyltransferase
P300	602700	Menke-Hennekam syndrome 2/ Rubinstein-Taybi syndrome 2	618333/613684	Histone acetyltransferase
KAT6A	601408	Arboleda-Tham syndrome	616268	Histone acetyltransferase
KAT6B	602303	Say-Barber-Biesecker-Young-Simpson / Genitopatellar syndrome	603736 / 606170	Histone acetyltransferase
BRPF1	602410	Intellectual developmental disorder with dysmorphic facies and ptosis	617333	Histone acetyltransferase complex subunit
KANSU	612452	Koolen-De Vries syndrome	610443	Histone acetyltransferase complex subunit
HDAC2	605164	Cornelia de Lange syndrome	n/a	Histone deacetylase
HDAC4	605314	Brachydactyly mental retardation	600430	Histone deacetylase
HDAC6	300272	X-linked dominant Chondrodysplasia	300863	Histone deacetylase
HDAC8	300269	Cornelia de Lange syndrome 5	300882	Histone deacetylase
KMT2A	159555	Wiedemann-Steiner syndrome	605130	Histone lysine methytransferase
KMT2B	606834	Dystonia 28, childhood-onset	617284	Histone lysine methytransferase
KMT2C	606833	Kleefstra syndrome 2	617768	Histone lysine methytransferase
KMT2D	602113	Kabuki syndrome 1	147920	Histone lysine methytransferase
KMT2E	608444	O'Donnell-Luria-Rodan syndrome	618512	Histone lysine methytransferase
SETD1A	611052	Neurodevelopmental disorder with speech impairment and dysmorphic facies / Eariy-onset Epilepsy	619056 / 618832	Histone lysine methytransferase
SETD1B	611055	Intellectual developmental disorder with seizures and language delay	619000	Histone lysine methytransferase
EHMT1	607001	Kleefstra syndrome 1	610253	Histone lysine methytransferase
NSD1	606681	Sotos syndrome 1	117550	Histone lysine methytransferase
NSD2	602952	Wolf-Hirschhom syndrome	194190	Histone lysine methytransferase
SETD2	612778	Luscan-Lumish syndrome	616831	Histone lysine methytransferase
SETD5	615743	Mental retardation, autosomal dominant 23	615761	Histone lysine methytransferase
EZH2	601573	Weaver syndrome	277590	Histone lysine methytransferase
SUZ12	606245	Imagawa-Matsumoto syndrome	618786	PRC2 subunit
EED	605984	Cohen-Gibson syndrome	617561	PRC2 subunit
KDM1A	609132	Cleft palate, psychomotor retardation, and distinctive facial features	616728	Histone lysine demethylase
KDM5B	605393	Mental retardation, autosomal recessive 65	618109	Histone lysine demethylase
KDM5C	314690	Mental retardation, X-linked, syndromic, Claes-Jensen type	300534	Histone lysine demethylase
KDM6A	300128	Kabuki syndrome 2	300867	Histone lysine demethylase
PHF8	300560	Mental retardation syndrome, X-linked, Siderius type	300263	Histone lysine demethylase

Gene	Gene OMIM	Syndrome	OMIM	Gene Function
CHD1	602118	Pilarowski-Bjomsson syndrome	617682	ATP-dependent Chromatin remodeler
CHD2	602119	Childhood-onset Epileptic Encephalopathy	615369	ATP-dependent Chromatin remodeler
CHD3	602120	Snijders Blok-Campeau syndrome	618205	ATP-dependent Chromatin remodeler
CHD4	603277	Sifrim-Hitz-Weiss syndrome	617159	ATP-dependent Chromatin remodeler
CHD7	608892	CHARGE syndrome	214800	ATP-dependent Chromatin remodeler
ARIDIb	614556	Coffin-Siris syndrome 1	135900	ATP-dependent Chromatin remodeler
ARIDIa	603024	Coffin-Siris syndrome 2	614607	BAF subunit
BAF47	601607	Coffin-Siris syndrome 3	614608	BAF subunit
BRG1	603254	Coffin-Siris syndrome 4	614609	ATP-dependent Chromatin remodeler
BAF57	603111	Coffin-Siris syndrome 5	616938	BAF subunit
ARID2	609539	Coffin-Siris syndrome 6	617808	BAF subunit
DPF2	601671	Coffin-Siris syndrome 7	618027	BAF subunit
BAF60A	601735	Coffin-Siris syndrome 11	618779	BAF subunit
BRM	600014	Nicolaides-Baraitser syndrome	601358	BAF subunit
BAF53b	612458	IDD with severe speech and ambulation defects / Developmental and epileptic encephalopathy 76	618470 / 618468	BAF subunit
ACTL6A	604958	n/a	n/a	BAF subunit
BPTF	601819	Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies	617755	Chromatin remodeller
HIST1H1E	142220	Rahman syndrome	817537	Linker Histone
HIST1H4C	602827	unclassified	n/a	Canonical histone
HIST1H4J	602826	unclassified	n/a	Canonical histone
H3F3A	601128	Unclassified	n/a	Histone variant
H3F3B	601058	Unclassified	n/a	Histone variant