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Chromatin remodelling complexes in cerebral cortex development and neurodevelopmental disorders

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Abstract

The diverse number of neurons in the cerebral cortex are generated during development by neural stem cells lining the ventricle, and they continue maturing postnatally. Dynamic chromatin regulation in these neural stem cells is a fundamental determinant of the emerging property of the functional neural network, and the chromatin remodellers are critical determinants of this process. Chromatin remodellers participate in several steps of this process from proliferation, differentiation, migration leading to complex network formation which forms the basis of higher-order functions of cognition and behaviour. Here we review the role of these ATP-dependent chromatin remodellers in cortical development in health and disease and highlight several key mouse mutants of the subunits of the complexes which have revealed how the remodelling mechanisms control the cortical stem cell chromatin landscape for expression of stage-specific transcripts. Consistent with their role in cortical development, several putative risk variants in the subunits of the remodelling complexes have been identified as the underlying causes of several neurodevelopmental disorders. A basic understanding of the detailed molecular mechanism of their action is key to understating how mutations in the same networks lead to disease pathologies and perhaps pave the way for therapeutic development for these complex multifactorial disorders.

Keywords

NuRD complex; BAF (mSWI/SNF) complex; ISWI complex; INO80 complex; Corticogenesis; Neurodevelopmental disorders

1 Introduction

The cerebral cortex is the domain of all higher-order functions in the brain, including motor and sensory activities, cognition and social behaviour. Neurulation commences with the

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establishment of a neural plate from a single sheet of neuroepithelial cells (NECs) that eventually close to give rise to the neural tube (Gotz and Huttner, 2005). These NECs divide symmetrically to self-renew and expand the pool, and at the onset of neurogenesis at embryonic day (E)10.5, give rise to apical radial glia cells (aRGs) (Fig. 1) (Tuoc et al., 2014). aRGs are bipolar cells that line the ventricular zone (VZ) of the neocortex and extend processes towards both the apical and basal surfaces. Similar to NECs, aRGs divide both symmetrically for pool expansion as well as asymmetrically to self-renew and form a differentiating daughter cell (Tuoc et al., 2014). aRGs can directly give rise to neurons upon asymmetric division (direct neurogenesis) or can give rise to basal intermediate progenitors (bIPs) or basal radial glia (bRGs), that line the subventricular zone (SVZ), which then differentiate to form neurons (indirect neurogenesis) (Georgala et al., 2011; Gotz and Huttner, 2005; Govindan and Jabaudon, 2017; Jabaudon, 2017; Molyneaux et al., 2007; Sessa et al., 2008; Tuoc et al., 2014). bRGs are found in both the lateral and medial cortex of mice, albeit at lower proportions as compared to gyren-cephalic mammals. bRGs have been further characterised into separate populations based on the expression of Hopx, a marker for human bRGs (Wang 2011; Vaid 2018). bIPs are fate restricted with a limited self-renewal capacity (Hevner, 2019; Kalebic and Huttner, 2020). Both aRGs and bIPs give rise to neurons, that populate the cortical plate (CP) to form the six-layered neocortex (Agirman et al., 2017; Budday et al., 2015; Florio and Huttner, 2014; Leone et al., 2008; Lodato and Arlotta, 2015; Molyneaux et al., 2007; Mukhtar and Taylor, 2018). For a detailed review on mammalian corticogenesis refer to Florio and Huttner (2014); and Lodato and Arlotta (2015). The neocortex is formed in an inside out fashion, beginning with the formation of layer VI. New-born neurons migrate past the early-born neurons and occupy their positions in the growing cortical plate to create newer layers (Fig. 1). As corticogenesis progresses, aRGs also give rise to astrocytes and oligodendrocytes, which mature postnatally (Guillemot, 2007; Martynoga et al., 2012). An interesting feature of mammalian nervous system is that the same set of progenitors give rise to both neurons and glial cells. Neurogenesis precedes gliogenesis, and this transition from neuron to glia production is termed as the neuron-glia cell fate switch (Gao 2014; Mukhtar and Taylor, 2018).

Corticogenesis involves expression of transcriptional waves of proliferative (P), neurogenic (Ng) and neuronal (N) transcripts sequentially. These P-type, Ng-type and N-type transcripts display enriched localisation in the VZ, SVZ and CP respectively. The P-type transcripts are the first to be repressed as development progresses (Telley et al., 2016) This sequential expression and repression of transcripts at different stages of corticogenesis require dynamic chromatin remodelling to promote/inhibit chromatin accessibility.

Chromatin accessibility is a dynamic and changing process occurring during cortical development wherein nucleosomes are rearranged to bring about gene regulation. A recent study showed that predicted regulatory elements in accessible chromatin at different stages of human cortical development display motifs for various transcription factors known to regulate corticogenesis at that stage (Markenscoff-Papadimitriou et al., 2020). PAX6 motifs on open regulatory elements were observed at 14 gestational weeks (gw), and PBX1 motifs were observed at 19gw. Similarly, the deep layers displayed motifs for TBR1, ETV1, ETV2; whereas the upper layers showed motifs for LHX2, LHX5, BRN1 and BRN2. This accessibility of motifs at the regulatory elements is essential for transcription factor binding.

Transcription factors can then recruit chromatin remodelling complexes to regulate gene expression. For example, the transcription factor LHX2 interacts with NuRD subunits, and specific subunits bind to distal LHX2 binding regions in the genome to repress layer V formation during layer VI neurogenesis (Muralidharan et al., 2017).

Chromatin Remodellers are translocases that alter the chromatin structure to enable access to transcriptional machinery (Clapier et al., 2017). Chromatin remodelling complexes consist of multiple protein subunits. They are ATP-driven and contain a single core subunit belonging to the Sucrose non-fermentable (SNF2) family that acts as an ATPase. Based on the sequence similarity and domain structures of the ATPase subunits, these complexes have been classified into four sub-families - Nucleosome Remodelling and Deacetylase (NuRD), BRG1-or BRM Associated Factors (BAF or SWItch/Sucrose non-fermentable - SWI/SNF), Imitation SWItch (ISWI) and Inositol 80 (INO80) (Hargreaves and Crabtree, 2011; Ho and Crabtree, 2010; Hota and Bruneau, 2016). The subunits of these complexes are expressed in the different zones of the developing cortical primordium (Sokpor et al., 2018) and thus regulate several critical steps of corticogenesis starting from progenitor proliferation to neuronal maturation (Fig. 1).

A key feature of the mammalian genome is the highly compact arrangement of chromatin structure in the form of nucleosomes. This compaction accommodated the genome expansion that resulted from gene duplication and a relative increase in protein-coding and noncoding regulatory elements. In comparison to yeast and flies, mammals underwent only a small increase in the total number of genes, in contrast, the amount of regulatory DNA expanded substantially in the mammalian genome (Alfert et al., 2019; Hajheidari et al., 2019). This led to the proposal that the function of a limited number of proteincoding genes is diversified by establishing a pattern of gene expression mediated by transcriptional regulation.

Therefore, chromatin regulation at different levels, namely DNA methylation, histone modification, and nucleosome remodelling evolved to compact DNA and regulate gene expression (Hajheidari et al., 2019; Ho and Crabtree, 2010; Wu et al., 2009).

The chromatin modifiers have thus expanded and diversified their function. For example, SWI/SNF has changed from a monomorphic complex with a role in transcriptional activation in yeast to a dimorphic complex in invertebrates with two ATPase paralogs that have evolved to activate and repress gene expression transcriptionally. In the vertebrates, SWI/SNF complexes are polymorphic with two ATPase paralogs and multiple variants for most of the associated subunits, permitting a combinatorial assembly of the complex (Hajheidari et al., 2019; Ho and Crabtree, 2010; Wu et al., 2009). The chromodomain helicase DNA-binding (CHD) proteins have diverged and acquired new functions to act through multi-subunit complexes such as NuRD. The ISWI family consists of 2 ATPases, conserved from yeast to mammals. The INO80 complex has acquired new subunits such as YY1, NFRKB, and Uch37 over the course of evolution (Conaway and Conaway, 2009).

Hence, the emergence of ATP dependent chromatin remodelling complexes in parallel with multicellularity and morphological complexity was a quintessential step in the evolutionary trajectory of eukaryotes.

2 Composition of the chromatin remodelling complexes

2.1 Core constituents of the NuRD complex

The NuRD complex possesses dual enzymatic activities of - ATPase and deacetylase. The core components of the complex are CHD3/4/5, HDAC1 and HDAC2, MBD2/3, MTA1/2/3, RBBP4 and RBBP7, GATAD2A/B and LSD1(KDM1A) (Fig. 2); (Kolla et al., 2015; Tong et al., 1998; Wade et al., 1998; Wang et al., 2009; Xue et al., 1998; Zhang et al., 1998, 1999). The chromodomain helicase DNA-binding (CHD) proteins 3, 4 and 5 are ATPases, and form the catalytic core in independent NuRD complexes (Tong et al., 1998; Wade et al., 1998; Xue et al., 1998; Zhang et al., 1998; Nitarska et al., 2016). The PHD fingers of the chromodomain proteins interact with histone H3 tails (Mansfield et al., 2011; Musselman et al., 2009). The Histone deacetylases 1 and 2 (HDAC1 and HDAC2) provide the second catalytic activity to the complex. HDAC1 and HDAC2 belong to class I of histone deacetylases (Gregoretti et al., 2004) and deacetylate both histone and non-histone proteins (Seto and Yoshida, 2014). MBD2 and MBD3 belong to the methyl cytosine-guanosine (CpG)-binding domain (MBD) protein family (Le Guezennec et al., 2006). MBD3 preferentially occupies methylated CpG islands, whereas MBD2 displays localisation on both methylated and unmethylated CpG islands (Cramer et al., 2014). Metastasis associated genes 1 and 2 (MTA1/2) act as scaffolds for the NuRD com-plex and help in complex assembly (Alqarni et al., 2014). The retinoblastoma-binding proteins RBBP4 and RBBP7 are histone chaperones (Murzina et al., 2008). RBBP4 interacts with MTA1 for recruiting both itself and RBBP7 into the NuRD complex (Alqarni et al., 2014). The GATA zinc finger domain-containing D2A and D2B (GATAD2A and GATAD2B) proteins are also known as p66α and p66β, respectively. p66 contains two conserved regions - the CR1 and CR2 domains. The CR1 domain interacts with MBD3, and the CR2 domain is necessary for targeting both p66 and MBD3 to specific nuclear loci (Feng et al., 2002). Both p66α and p66β contain sumoylation sites, and mutants for these sites affect p66α-HDAC1 and p66β-RBBP7 interactions in fibroblasts (Gong et al., 2006). LSD1, lysine specific demethylase is one of the newest additions to the NuRD complex and provides histone demethylase activity (Wang et al., 2009).

2.2 Core constituents of the BAF complex/mSWI/SNF complex

The BAF complexes comprise of up to 15 subunits containing a single catalytic core of either BRM or BRG1 with ATPase activity and exhibit dynamicity in terms of subunit composition at different stages of development in various tissues. BAF45 subunits have PHD fingers which facilitate the interaction with histone tails, wherein BAF45c is known to bind to monomethylated H3K4 and BAF45d interacts with both monomethylated H3K4 and crotonylated H3K14 *in vitro* (Ho et al., 2019).

BAF47 and BAF250a/b have a role in promoting DNA binding at the regulatory sequences (Allen et al., 2015; Ho et al., 2019).

The esBAF (embryonic stem cell BAF), npBAF (neural progenitor-specific BAF) and nBAF (neuron-specific BAF) are the three predominantly studied canonical BAF complexes that play regulatory roles in embryonic development, neural progenitors and neurons respectively (Fig. 3) (Alfert et al., 2019; Ho et al., 2009; Son and Crabtree, 2014).

Multiple variants of BAF subunits are encoded by gene families (DEAD/H Helicase family), but these are mutually exclusive, and only a single variant from each family is recruited in a complex. BAF180, BAF60, BAF250, BAF47, BCL7, β-actin and BAF155 are a few of the core subunits which are present in both npBAF and nBAF. BAF45a/d, SS18 and BAF53a are specific to npBAF of progenitors and are replaced by BAF45b/c, CREST and BAF53b respectively in nBAF of neurons (Alfert et al., 2019; Son and Crabtree, 2014; Staahl et al., 2013) (Fig. 3).

2.3 Core constituents of the ISWI complex

The mammalian homologues of the ISWI proteins are the SNF2H and the SNF2L chromatin remodelling proteins encoded by the *Smarca5* and *Smarca1* genes, respectively (Aihara et al., 1998; Lazzaro and Picketts, 2001). ISWI proteins are ATPase motor proteins. The catalytic ATPase activity is at the N -terminal of the ISWI protein, whereas the C-terminal HAND-SANT-SLIDE (HSS) domain mediates its interaction with the linker DNA and the histone H4 tails. The autoregulatory motifs AutoN and NegC-confer specificity (Clapier and Cairns, 2012; Yan et al., 2016). The ATP-mediated activity of the motor proteins of this complex help in the translocation of the DNA along nucleosomes, thereby leading to the formation of equally distanced nucleosomes (Corona et al., 1999; Ito et al., 1997). The SNF2H or the SNF2L are the catalytic subunits of the 8 mammalian ISWI complexes whose compositions vary depending on the interacting partners namely the BAZ (bromodomain adjacent to PHD zinc finger) domain-containing proteins and may also include partner proteins containing AT hooks or DNA-binding homeobox containing proteins and the different transcription and chromatin remodelling factors (DDT) domains for DNA binding (Table 1) (Goodwin and Picketts, 2018).

The 8 complexes are ACF (ATP-utilising chromatin assembly and remodelling factor), CHRAC (chromatin assembly complex), WICH (WSTF-ISWI chromatin remodelling complex), RSF (remodelling and spacing factor), CERF (CECR2-containing remodelling factor), NoRC (nucleolar remodelling complex), NURF (Nucleosome remodelling factor complex) and SNF2H-cohesin complex (Table 1). Each of the complexes performs a particular function and has been identified in distinct cell types (Goodwin and Picketts, 2018; Manelyte and Langst, 2013).

2.4 Core constituents of the INO80 complex

The INO80/SWR remodeller family consists of 3 complexes, namely INO80, SNF2-related CBP activator protein (SRCAP) and P400/TIP60 (Gerhold and Gasser, 2014). The complexes are named based on the core ATPase subunit, and share the RUVB helicases – RVB1 and RVB2 and actin related proteins (ARPs). The RUVB subunits RVB1 and RVB2 are ATP-dependent helicases, that unwind DNA (Gerhold and Gasser, 2014). Actin and ARPs are involved in histone recognition, with different ARP subunits displaying

differential preferences (Willhoft and Wigley, 2020). The ARP4 subunit which is shared between the complexes, interacts with unmodified and phosphorylated H2A, whereas ARP8 of the INO80 complex interacts with H3/H4 tetramers (Willhoft and Wigley, 2020). The Yin Yang 1(YY-1) subunit of INO80 is a transcription factor and helps target INO80 to gene promoters (Cai et al., 2007). KAT5, previously known as TIP60, is a lysine acetyltransferase and transformation/transcription domain-associated protein (TRRAP) is a co-factor of KATs/HATs (Tapias et al., 2014). The UCH37 protein encoded by the UCHL5 gene is a deubiquitinating enzyme (Burgie et al., 2012). Functions of many subunits belonging to this complex family have not been well characterised.

3 Role of the chromatin remodellers in the developing dorsal telencephalon

The interplay of morphogens and TFs determines the specification of the dorsal neural fate in the developing telencephalon, which goes on to form the neocortex and hippocampus (Tole and Hebert, 2013). Loss of critical subunits of the BAF complex affects this crucial initial step of telencephalic specification.

FoxG1-Cre, which is expressed in the entire telencephalon (dorsal and ventral - from E8.5) (Hebert and McConnell, 2000), mediated removal of both BAF155 and BAF170 resulted in complete loss of cortex and head structures regions suggesting a very early and crucial role for BAF complexes in neural fate specification and perhaps the proliferation of NECs (Bachmann et al., 2016; Narayanan et al., 2015; Nguyen et al., 2016). SRG3 – mouse homologue of human BAF155, heterozygote mutants show exencephaly (defect in neural tube closure leading to the brain growing outside the skull) (Kim et al., 2001).

After dorsal telencephalon specification, the various subunits of the remodelling complexes play key roles in several steps of corticogenesis in order to develop a functional neural network (Fig. 1B). Deletion of the subunits affects major steps of cortical development including progenitor proliferation, progenitor maintenance, bIP generation and localisation, differentiation, neuronal subtype specification, migration, neuron-glia cell fate switch and maturation as delineated below.

3.1 Progenitor proliferation, bIP generation and neuron differentiation

All stem cells, namely NECs, aRGs, aIPs, bIPs, bRGs in the developing cortex are capable of proliferation by symmetric divisions. The intermediate progenitors divide symmetrically fewer times than the aRGs. Thus, progenitor proliferation is important to sustain the stem cell pool required to generate the entire cortex and to produce the proper/correct number of neurons. Asymmetric divisions ensure the generation of bIPs from aRGs and differentiation of neurons from bIPs and aRGs.

3.1.1 Members of the NuRD complex—The different members of the NuRD complex which are expressed in the VZ and show similar role in regulation of the PAX6+ aRGs are HDAC1&2, CHD4, LSD1 and MBD3. HDAC1 and HDAC2 are expressed in the VZ progenitors during neurogenesis. HDAC2 also shows enhanced expression in post-

mitotic neurons in the cortical plate. CHD4 appears early in development around E12.5 in the VZ, with lower expression around E18.5. LSD1 is ubiquitously expressed in the developing cortex, (Fuentes et al., 2012). MBD3 is expressed in the VZ/SVZ and cortical plate, albeit at lower levels as compared to other NuRD subunits (Sokpor et al., 2018).

Central Nervous system (CNS) specific deletion of either *Hdac1* or *Hdac2* did not produce any overt brain phenotypes owing to genetic redundancy. Deletion of both resulted in prenatal and postnatal death depending on whether an CNS-specific early (*Nestin-Cre*) or late acting Cre (*hGFAP-Cre*) was used (Hagelkruys et al., 2014; Montgomery et al., 2009). The brains were smaller in size, and the cortical plate was reduced in thickness due to decreased proliferation and increased cell death (Hagelkruys et al., 2014). Brain-specific complete deletion of *Hdac 1* and a single allele of *Hdac2* (*Hdac 1*$^{-/-}$ and *Hdac2* $^{+/-}$) resulted in no defect. However, deletion of both the *Hdac2* alleles and a single allele of *Hdac 1* (*Hdac 1*$^{+/-}$ and *Hdac2*$^{-/-}$) resulted in reduced proliferation in the cortex and cerebellum eventually leading to neonatal death. Thus, a single allele of *Hdac2* is sufficient to rescue the essential brain development functions of HDAC1 (Hagelkruys et al., 2014). A similar phenotype was observed in heterozygous knock-in mice generated with an amino acid substitution of histidine to alanine (*Hdac 1*-H141A; *Hdac2*-H142A) which codes for an inactive protein. The *Hdac 1* knock-in mice display normal development, whereas the *Hdac2* knock-in mice show severe nervous system defects, including a reduction in the cortical and cerebellar sizes due to a dominant-negative effect. A global increase in the acetylation marks is also observed in the *Hdac2* knock-in mice brain consistent with its role as a histone deacetylase (Hagelkruys etal., 2016).

Cortex specific deletion (*Emx1*-Cre) of *Hdac1/2* at the onset of neurogenesis using *Emx1*-Cre precluded the embryonic and postnatal lethality observed in the other studies and enabled a study of the functions of the two deacetylases specifically in the developing cortical primordium (Tang et al., 2019). The double mutant resulted in a smaller brain and a significant reduction in cortical thickness. The mutant displays a thinner VZ and reduced number of PAX6 + aRGs which are distributed across the entire cortex and later undergo apoptosis (Fig. 4).

Thus, HDAC1 and HDAC2 have partially redundant roles in the proliferation of PAX6+ aRGs in the developing cortex and that HDAC2 has a more specific role in progenitor proliferation.

The intermediate progenitor (IP) cells are generated from apical radial glia and are classified into two subtypes, based on the molecular expression pattern. IPs located in the VZ are bipolar and divide away from the apical surface. IPs localised in the subventricular zone are multipolar and express neuronal differentiation markers such as NEUROD1. Both subtypes express the classical IP marker TBR2 and differentiating IPs produce glutamatergic neurons that occupy all cortical layers (Hevner, 2019).

Besides aRG proliferation, HDAC1/2 temporally regulate the positioning of bIPs in the developing cortex. *Emx1* -Cre mediated deletion of HDAC1/2 causes mislocalisation of bIPs to the VZ. These ectopic bIPs undergo apical cell division, display precocious cell cycle exit

and are prone to differentiation. Newly postmitotic TBR1 + neurons generated by these mutant IPs also mislocalise in the VZ. The mislocalisation affects cortical lamination at E16.5 as seen by reduced upper layers (UL) neurons and mispositioned deep layer (DL)neurons. HDAC1 occupies the *Ngn2* promoter, which has both the H3K9ac active mark and the H3K27me3 repressive mark (Fig. 4). In the mutants, NGN2 expression is diminished coinciding with a reduction in the active mark and an increase in the repressive mark. NGN2 overexpression in HDAC1 and HDAC2 knockdown rescues the ectopic IP localisation, whereas NGN2 knockdown recapitulates the ectopic IP positioning. NGN2 is thus a downstream effector of HDAC1 and HDAC2 in their function of maintaining proper IP localisation. Interestingly, deletion of HDAC1 and HDAC2 post E13.5 still causes reduced cortical thickness but does not affect bIP localisation, suggesting a temporal window for their role in bIP localisation (Tang et al., 2019).

Nestin-Cre mediated deletion of *Chd4* results in death at birth in mice. The *Chd4* mutant mice have a smaller brain, with reduced cortical thickness. Mutant progenitors precociously exit the cell cycle and fail to differentiate, and later become apoptotic. The number of TBR2+ intermediate progenitors is reduced in the mutants, with decreased proliferation. CHD4 occupies the promoters of *Sox2, Pax6* and *Tbr2* at higher levels in progenitors as compared to postmitotic neurons, and the expression of these transcription factors is downregulated in the *Chd4* mutants, providing a mechanism for its action (Fig. 2B). CHD4 is therefore required for bIP pool maintenance, and *Chd4* deletion thus leads to depletion of the bIP pool leading to defective cortical lamination with a specific reduction in the numbers of neurons of the upper layers (Nitarska et al., 2016).

shRNA mediated knockdown of LSD1 in rat cortex or *Nestin*-Cre mediated deletion in LSD1 conditional mutants leads to precocious differentiation of progenitors into neurons. This defect is due to LSD1's role in positively regulating the proliferation of aRGs in the ventricular zone. The knockdown brains show fewer SOX2 + and TBR2 + progenitor cells and a corresponding increase in the number of TUJ1 + immature neurons. Further *Lsd1* knockdown leads to a migration defect wherein the cells are stuck in the intermediate zone (IZ). LSD1 mediates this function via its direct downstream effector *Atrophin1.* Interestingly the authors note that H3K4me2 marks increase in the absence of LSD1 on the LBAL (LSD1 binding site at Atrophin1) locus. This seems to be counterintuitive to the reported activatory function of LSD1 which is mediated by the removal of the dimethyl H3K9 instead of the H3K4. The authors conclude that it is perhaps the first report of LSD1 mediated H3K4 methylation leading to gene activation. *Atrophin1* (*Atn1*) is both necessary like LSD1 and sufficient in progenitor proliferation in the aRGs. LSD1 thus maintains the cortical progenitor pool by regulating *Atn1* by binding to the LBAL locus (Zhang et al., 2014).

CNS specific deletion of Mbd3 using *Nestin-Cre* yields a small cortex and a reduction in the number of TBR2 + bIPS. Decreased asymmetric division of aRGs suggests a role for MBD3 in bIPs generation. An opposing function to that of MBD3 in the progenitor comes from Suppressor of Mek null - *Smek 1/2*. SMEK1/2 polyubiquitinates MBD3 and prevents the repressive binding of MBD3, MTA1, HDAC1/2 (NuRD subunits) to neuronal and proneuronal genes. This leads to progenitors exiting the cell cycle and becoming postmitotic. *Smek1/2* null mutants have decreased TUJ1+, same phenotype as overexpression of MBD3.

Loss of MBD3 rescued the defective neurogenesis in *Smek1/2* mutant. Thus, SMEK1/2 targets MBD3 for degradation at the onset of neurogenesis (Moon et al., 2017).

The Holo-NuRD complex is formed by an interaction of the HDAC and CHD remodeller subcomplexes, mediated by the MBD protein (Basu et al., 2020; Spruijt et al., 2020). MBD3 is expressed in the VZ, SVZ and a subpopulation of post-mitotic neurons (Knock et al., 2015), but is degraded at the onset of neurogenesis (Moon et al., 2017) and is essential for gliogenesis (Knock et al., 2015). MBD2 null mice are viable and show behavioural defects, whereas MBD3 null mice are embryonic lethal (Hendrich et al., 2001). MBD3 perhaps is redundant for MBD2 in the brain, or MBD2 deletion alone is not sufficient to cause a cellular phenotype, indicating the need for a detailed characterisation of MBD2 function in cortical development. All these together suggest that deletion of the MBD2/3 genes should be sufficient to disrupt the Holo-NuRD complex in the neocortex. A complete and comprehensive picture on the function of the NuRD complex could be obtained by deletion of the MBD2/3 genes spatio-temporally in the neocortex, helping identify its functions both in progenitors and post-mitotic cells. Mutants of HDAC1/2, CHD4, LSD1 and MBD3 exhibit a reduction in the number of Tbr2+ bIP cells, suggesting that this cellular phenotype is governed by chromatin remodelling through the NuRD complex. And indeed the functioning of the NuRD complex could be hindered by deletion of the HDAC1/2, MBD3 and CHD4 proteins, as observed by their positioning within the Holo-NuRD complex (Basu et al., 2020). The multiple subunits of the NuRD complex namely HDACs, LSD1, CHDs and RBBPs are known to function individually or as part of other complexes. HDAC1 and HDAC2 are part of the NuRD, SIN3 (switch-independent 3), Mi-DAC (mitotic deacetylase), CoREST (co-repressor of REST), MIER (mesoderm induction early response) and RERE (arginine-glutamic acid dipeptide repeats) complexes (Millard et al., 2017). LSD1 is known to associate with the CoREST complex (Yang et al., 2006). CHDs are known to function both individually as well as part of multimeric complexes like NuRD and ChAHP (CHD4, ADNP, HP1γ) (Nitarska et al., 2016; Tabar et al., 2021). RBBP4 and RBBP7 are a part of both the NuRD complex and NuRF subcomplex of ISWI (Goodwin and Picketts, 2018; Kolla et al., 2015).

Besides, the distinctive developmental and lineage specific expression of the different subunits themselves, it raises the possibility that the complex does not function as holo-NuRD but rather the subunits perhaps come together in a context/site specific manner to dynamically regulate the cortical genome. Sequential ChIP-sequencing will verify the co-occurrence of multiple chromatin regulators on the same gene loci and will clearly be a way forward to understand the function of the NuRD complex in its entirety and its subunits individually.

3.1.2 Members of the BAF complex—The npBAF complex, required to maintain self-renewal and proliferation of neural stem cells, has a different combination of subunits as compared to nBAF that is important for neuron subtype specificity, neuronal maturation, terminal differentiation and dendritic development (Ho and Crabtree, 2010; Sokpor et al., 2017; Son and Crabtree, 2014) (Fig. 3). Both these complexes contain either BRG1 or BRM as the ATPase which is expressed throughout mouse development and in both progenitors and postmitotic neurons (Olave, 2002; Sokpor et al., 2018).

npBAF contains high levels of BAF155 and low levels of BAF170 and vice versa for nBAF (Narayanan et al., 2018; Staahl et al., 2013; Tuoc et al., 2013a, 2013b). As the neurons exit mitosis, subunits BAF53a, BAF45a/d and SS18 of npBAF are switched with BAF53b, BAF45b/c and CREST (Son and Crabtree, 2014; Staahl et al., 2013). The stoichiometry of composition of BAF170 and BAF155 in the two BAF complexes is crucial for modulating the switch between direct and indirect neurogenesis by controlling euchromatin structure (Tuoc et al., 2013a). Consistent with their role, expression of BAF45a and BAF53a is restricted to neural progenitors, while BAF45b, BAF45c and BAF53b are expressed in post-mitotic neurons in the cortex (Lessard et al., 2007). BAF170 and BAF155 are expressed in apical progenitors between E12.5–14.5. At the peak of upper layer neurogenesis (E15.5), they show complementary expression pattern with BAF170 being absent from VZ progenitors and expressed in the cortical plate (Tuoc et al., 2013a).

The mouse mutants for these various subunits divulge the functional role of each of these subunits in maintaining the progenitors in the developing cortical primordium.

Nestin-Cre mediated deletion of BRG1 ATPase subunit leads to a reduced cortex (Lessard et al., 2007; Matsumoto et al., 2006). aRGs show defective proliferation and exit cell cycle to give rise to postmitotic neurons (Lessard et al., 2007).

BRG1 containing npBAF regulates aRG proliferation by activating Notch signalling pathway and repressing Sonic hedgehog signalling pathway by transcriptional regulation of key components of these pathways such as *Patched, Olig1, and Jagged1* (Lessard et al., 2007).

BAF45a, BAF53a and SS18 are a part of npBAF and have characterised roles in aRG proliferation. BAF45a and BAF53a are both necessary and sufficient for aRG proliferation, whereas SS18 knockdown in cultures affects the self-renewal capacity of progenitors (Braun et al., 2021; Lessard et al., 2007; Staahl et al., 2013). Mechanistically, BAF53a containing npBAF regulates the chromatin accessibility of genes required for neural progenitor proliferation and cell cycle maintenance by opposing the PRC2 mediated repression. In the absence of BAF53a in these mutants, there is an increase in the levels of PRC2 mediated H3K27me3 repressive marks on cell cycle genes such as *Ccdn1, Cdk2* (Braun et al., 2021). The switch from BAF53a to BAF53b in BAF complex in post-mitotic neurons is known to be regulated by miR-9 and miR-124 (Yoo et al., 2009). In progenitors, REST and its co-repressors restrict the expression of these miRNAs that have a binding site in the 3'UTR of *Baf53a* (Conaco et al., 2006). Upon differentiation, the expression of these miRNA is derepressed in neurons which in turn promote the substitution of BAF53b in nBAF complex by silencing *Baf53a* expression. Prolonged expression of BAF53a leads to increased progenitor proliferation (Yoo et al., 2009).

For indirect neurogenesis, aRGs undergoes asymmetric division to give rise to bIPs, which then differentiate into neurons. This is a crucial step as it increases the final number of neurons by increasing the progenitor pool and is also considered as the step which contributed towards increased cortical size in primates. BAF complexes regulate this crucial step in corticogenesis. The differential combinatorial stoichiometry of the BAF complex

allows for such distinct regulations of the chromatin landscape in the different cells and expression of cell-type specific genes (Wang et al., 1996).

BAF170 and BAF155 have complementary roles in the cortex.

Deletion of BAF170 from E13.5 cortical progenitors leads to increased IPs with no alteration to Pax6 + aRGs and a larger cortex. Overexpression of BAF170 had an opposite effect of reduced IPs and reduction in cortical thickness and volume. Mechanistically BAF170 competes with BAF155 to recruit PAX6/REST repressor to PAX6 target genes *Tbr2, Cux1,* and *Tle1* which regulate the production of bIPs and late cortical progenitors (Tuoc et al., 2013a, 2013b).

Emx1-Cre mediated knockout of BAF155 in cortex leads to increased conversion of aRGs to bRGS by delamination and depletion of bIPs. BAF155 regulates the production of bIPs by positively regulating the expression of PAX6 dependent genes like CEP4 one of the key players of cytoskeleton remodelling and is reported to regulate progenitor delamination (Narayanan et al., 2018).

To analyse the role for BAF170 in regulating bRGs production, the authors overexpressed BAF170 in E14.5 cortex which also leads to in-creased expression of PAX6 and TBR2 + bRGs in the IZ. This phenotype was reverted by the overexpression of both BAF155 and BAF 170 (Narayanan et al., 2018). Thus, BAF155 and BAF170 have opposing roles in bIPs generation and maintenance. BAF155 works in concert with PAX6 whereas BAF170 has an opposite role. These studies delineate how competing chromatin remodeller subunits balance the generation of bIPs population at specific developmental time points in the developing cortex. Very recently, RBM15-RNA-binding motif protein 15 has been shown to regulate the expression of BAF155 in the cortex. RBM15 has been reported to regulate the progenitor delamination (bRGs) by modulating the stability of *Baf155* mRNA. METTL3 (methyltransferase-like 3), is a core catalytic component of the N6 - methyladenosine (m6A) RNA methylation machinery, together with RBM15, affect the stability of BAF155. *Baf1*55 mRNAs have three m6A methylation sites, RBM15 activates *Baf1*55 mRNA degradation by promoting m6A methylation. Ablation of RBM15 leads to an increased expression of BAF155, whereas, RBM15 overexpression phenocopies *Baf155*cKO mutants (Xie et al., 2019).

A cortex specific deletion of BAF155 and BAF170 at E10.5 resulted in a thin cortex with severely affected progenitor proliferation and complete absence of the BAF complex (Narayanan et al., 2015). A global reduction in active chromatin marks H3K9Ac and increase in repressive chromatin marks H3K27me2 and H3K27me3 was seen in the mutants. BAF155 and BAF170 are critical subunits required to maintain the integrity of the BAF complex and the absence of which leads to the dissolution of the complex (Narayanan et al., 2015; Sohn et al., 2007).

Deletion of both BAF155 and BAF 170 at later stages of corticogenesis using hGFAP-cre (E15.5 onwards in the dorsal telencephalon) leads to genome wide increase in H3K4me2 active marks and specific upregulation of proliferation pathways and associated genes and Wnt/β-catenin signaling (Nguyen H et al., 2018). This was confirmed by a concurrent

increase in proliferation of PAX6+, SOX2+ aRGs. These mutants also showed suppression of neuronal differentiation related genes seen concomitantly with increased H3K27me3 globally. There was a significantly reduced number of TBR2+ IPs, and late born SATB2 +, BRN2+ neurons in dorsal and lateral pallium of the mutants.

Disruption of npBAF subunits - BAF45a, BAF53a, SS18, BAF155 and BAF170 leads to progenitor proliferation defects.

3.1.3 Members of the ISWI complex—The ISWI ATPases SNF2L and SNF2H are both expressed early during neurogenesis in the developing cortex. As neurogenesis proceeds, the levels of SNF2L and SNF2H increase and decrease respectively. The *Snf2l* gene also encodes a brain-specific transcript of 3.7 kb, which starts peaking postnatally (Lazzaro and Picketts, 2001). The complementary expression pattern of *Snf2h* and *Snf2l* in the developing cortex (Banting et al., 2005, Lazarro and Picketts, 2001) is suggestive of the fact that the chromatin remodelling activities of the two ISWI proteins could be required at particular times in specific regions performing distinct functions in cortical development. *Snf2h* is abundantly expressed in the cortical progenitors during development whereas Snf2l is expressed in newly postmitotic neurons (Alvarez-Saavedra et al., 2014; Lazzaro and Picketts, 2001).

Interestingly, when the ATP-binding motif of SNF2L was deleted conditionally the resulting mutant (Ex6DEL) showed increased cortical thickness (Yip et al., 2012). The brain to body mass was also increased by 1.4-fold. The increased cortex size was due to increased proliferation of TBR2+ bIPs resulting in changes in cortical lamination and the timing of neurogenesis was also altered. Mechanistically, SNF2L bound to the *FoxG1* locus and regulated its expression. Transcription factor, FOXG1 positively regulates basal progenitor expansion in the developing cortex (Kumamoto et al., 2013; Martynoga et al., 2005). FOXG1 was indeed downstream to SNF2L and necessary for IP maintenance as evident by the rescue of the bIP proliferation and the increased brain size phenotype when the Ex6Del mutants were crossed with *Foxg1* heterozygous mice to reduce the FOXG1 dosage. Thus, SNF2L represses *FoxG1* expression and thereby keeps the bIP numbers in the cortex at adequate levels and regulates the timing of neurogenesis in the cortex (Yip et al., 2012).

Whereas a cortex specific deletion of the *Snf2h* leads to an opposite phenotype of reduced TBR2+ IPCs and a shrunken cortex. The decreased TBR2+ bIPs resulted in decreased callosal projection neurons leading to partial corpus callosum agenesis. *Snf2h* depletion leads to altered axonal targeting of the corticothalamic projection neurons and neurons that project across the corpus callosum (Alvarez-Saavedra et al., 2019). This role of *Snf2h* is consistent with the study where the loss of *Snf2h* causes proliferation defects observed in the cerebellum granule neuron progenitors (Alvarez-Saavedra et al., 2014).

These results suggest a critical role for *Snf2h* in maintaining progenitor proliferation and contrasts with the role of *Snf2l* – the other ISWI mammalian protein thereby suggesting that the two play distinct roles in the developing cortical primordium and merits further detailed analysis on their molecular mechanisms.

BAZ1 or WSTF target genes identified by ChIP-seq from human fetal neural progenitors and neurons derived from them, distinguished its role in both (Lalli et al., 2016). WSTF regulated stem cell renewal genes in the progenitors vs neural differentiation and synaptic genes in the neurons. Further haploinsufficent levels of WSTF dramatically affected the differentiation of the progenitors into neurons and the progenitors remained proliferative. Transcriptomic profiling of these cells also showed an upregulation of mitotic genes alongwith Wnt-activated receptor genes. Thus WSTF function in progenitors is to regulate the balance between proliferation vs neuron generation.

3.1.4 Members of INO80/SWR1 complex—INO80 is expressed in the forebrain from E11.5 with enhanced expression in the cortical VZ and is observed postnatally as well (Elsen et al., 2018; Keil et al., 2020). INO80 deletion from progenitors using *Emx1*-Cre yields a smaller brain size (Keil et al., 2020). Accumulation of DNAdouble-strand breaks in the progenitors leads to increased apoptosis and loss of aRGs and bIPs in the mutant medial cortex. The cortical lamination is disrupted only in the medial cortex, where *Emx1*-Cre excises *Ino80* specifically from progenitors undergoing symmetric division. The INO80 function in the symmetric progenitors is through its role in DNA repair, but not chromatin remodelling providing an insight into the multifunctional aspects of remodeller subunits. Interestingly, the transcription factor YY1 of the INO80 complex plays an opposite role and is important for neuronal differentiation. Knockdown of YY1 leads to an increase in the progenitors and a concurrent decrease in the number of post-mitotic neurons (Knauss et al., 2018).

MRG15, a subunit of the P400/TIP60 complex, exhibits weak expression in the VZ/SVZ progenitors and enhanced expression in the post-mitotic neurons in the cortical plate at E14.5 (Sokpor et al., 2018). It plays a role in both progenitor proliferation and neuronal differentiation (Chen et al., 2009, 2011). *Mrg15* null mice show a thinner neural tube at E10.5 due to increased apoptosis. Mutant neurosphere cultures are smaller in size and show reduced passaging capacity due to proliferation defects. Mutant neurospheres resist differentiation, with an overall reduction in the number of neurons but not glia.

TRRAP is expressed in all cells at E14.5 but displays the highest expression in basal progenitors consistent with its role in progenitors (Telley et al., 2016).

CNS specific mutants of *Trrap*, another subunit of the P400/TIP60 complex, also show proliferation defects. The mutant brain size and cortical thickness are reduced. Neural progenitors in the mutant show reduced proliferation and precocious differentiation into neurons. Mutant aRGs and bIPs show localisation defects, with a greater number of aRGs differentiating into bIPs and neurons. This phenotype in the mutant is rescued by overexpressing cyclins A2 and B1 (Tapias et al., 2014).

Though the various subunits have overlapping expression patterns in the developing cortical primordium, their roles seem to be in regulating very context-specific aspects of the progenitor proliferation, bIP generation and neuron differentiation thereby highlighting the dynamic nature of the associations leading to temporal control of corticogenesis.

3.2 Neuronal subtype specification

The projection neurons within the cortical layers show diversity in terms of morphology, molecular identity, location, function and synaptic properties (Lodato and Arlotta, 2015). Neuronal subtypes are specified temporally, guided by the spatiotemporal expression of signalling proteins and transcription factors (Molyneaux et al., 2007). Proper specification of neuronal subtypes is essential to form a functional cortex (Mukhtar and Taylor, 2018).

3.2.1 Members of the NuRD complex in neuronal subtype specification—

Transcription factors in concert with chromatin remodellers play a crucial role in neuronal subtype specification. In the developing mice brain, *Satb2* mutant shows an absence of corpus callosum, thicker anterior commissure, and UL migration and genetic programming defects. SATB2 represses CTIP2 expression in the UL neurons by employing HDAC1 and MTA2 on the matrix attachment region (MAR) for the *Ctip2* gene locus. In the absence of SATB2, HDAC1, and MTA2 interaction with the *Ctip2* locus is reduced, and CTIP2 is expressed in the UL neurons which now start projecting subcortically (Fig. 5) (Alcamo et al., 2008; Britanova et al., 2008). Ectopic CTIP2 expression in the developing UL neurons is also observed in *Ski* null mutants. SKI, a transcriptional regulator, interacts with SATB2 and helps recruit HDAC1 to the CTIP2 locus. In the absence of SKI, only MTA2 is recruited to the *Ctip2* locus, and SATB2-HDAC1 interaction is reduced (Fig. 5) (Baranek et al., 2012). CTIP2 is thus a downstream regulator of SKI and SATB2, and NuRD subunits are recruited to suppress ectopic CTIP2 expression in the UL neurons (Baranek et al., 2012; Britanova et al., 2008). Postnatally, there is an increase in the number of CTIP2 and SATB2 co-expressing neurons in the somatosensory cortex. The protein LMO4 competes with SATB2 for HDAC1 in postnatal neurons, thus disrupting the NuRD complex and de-repressing CTIP2 expression (Harb et al., 2016).

Several transcription factors have been characterised, and well-studied as postmitotic determinants of neuronal subtype specification namely TBR1 (Bedogni et al., 2010; Han et al., 2011; McKenna et al., 2011), SOX5 (Kwan et al., 2008; Lai et al., 2008), SOX4 and SOX11 (Shim et al., 2012) and FEZF2 (McKenna et al., 2011), SATB2 (Britanova et al., 2008), BRN1 and BRN2 (Dominguez et al., 2013; Sugitani et al., 2002), but a progenitor specific mechanism was not known. LHX2 is expressed in the progenitors at the time of deep layer neurogenesis but is not detected in the postmitotic DL neurons. Postnatally LHX2 expression comes up in the UL neurons but not in deep layers suggesting a possible role in deep layer neurogenesis. Cortex-specific deletion of *Lhx2* using the *Emx1-Cre* line alters the DL cortical lamination. Mutant cortices exhibit an expansion of layer V at the expense of layer VI, coinciding with an increase and decrease in the number of CTIP+ and TBR1+ neurons, respectively. The expression of layer V markers FEZF2 and SOX11 is enhanced in these mutants within a day of LHX2 removal, with an increase in the active marks H3K4me3 and H3K9ac at the transcription start sites or LHX2 binding regions on the *Fezf2* and *Sox11* gene loci. LHX2 acts by interacting with NuRD subunits HDAC2, RBBP4 and LSD1, which occupy distal LHX2 binding regions and transcription start sites of the *Fezf2* and *Sox11* gene loci and repress their expression during layer VI specification (Figure) (Muralidharan et al., 2017).

A similar progenitor specific mechanism was shown in the CNS specific *Mbd3* deletion mutants exhibiting disrupted cortical lamination. The CTIP2+ CSMNs is expanded in the mutant cortex, which also exhibits intermingling of TBR1, CTIP2 and SATB2 positive cells, with no distinction in the layers (Knock et al., 2015).

In-depth mechanistic analysis exists for few factors where a combination of biochemical techniques combined with genome-wide binding and mouse genetics have established a clear connection starting with gene regulation to phenotypic outcomes. The above studies have elegantly delineated the role of transcription factors and chromatin remodellers on specific gene loci to make epigenetic changes leading to altered gene expression. Cortical lamination defects as seen in the mutants above signify the importance of chromatin remodellers in fine tuning gene expression during cortical development. Further studies to dissect the role of these remodellers in controlling gene expression via epigenetic changes would enhance our understanding of cortical development.

3.2.2 Members of the BAF complex in neuronal subtype specification—

Close relatives, *Ctip1* and *Ctip2* have complementary expression pattern and roles in the developing cortex.

CTIP2/BCL11b/BAF100b is highly expressed in subcerebral projection neurons and cortical spinal motor neurons of layer V (Wiegreffe et al., 2015; Leid et al., 2004) and forms a part of l5-nBAF complex (Narayanan and Tuoc, 2014). *Ctip2* null mice fail to project corticospinal neurons to the spinal cord (Arlotta et al., 2005). FEZF2 is critical for the formation of sub-cerebral projection neurons (Molyneaux et al., 2005) and CTIP2 is a downstream effector of FEZF2 in guiding the axonal tracts to sub-cortical regions (Chen et al., 2008). As previously discussed, its expression is regulated by NuRD subunits, giving an example of how these remodellers perhaps cross-regulate each other.

Whereas CTIP1/BAF100a/BCL11a, highly expressed in Layer VI–CThPN and Layers II-IV, plays a cell-autonomous role in establishing somatosensory area identity and projection neuron subtype identity in developing cortex. *Emx1*-Cre mediated deletion of *Baf100a* showed an abnormal expansion of subcerebral projection neurons at the expense corticothalamic and deep-layer callosal neurons resulting in the formation of an expanded layer V (Woodworth et al., 2016). It controls somatosensory area patterning by suppressing the expression of motor specific genes in sensory areas (Greig et al., 2016). *Ctip1* depletion results in abnormal differentiation of layer IV neurons and causes a subset of them to project to motor thalamic nuclei instead of sensory thalamic nuclei. Further *Ctip1* deletion affects the differentiation of Layer IV granule neurons which affects the integration of thalamocortical inputs to form proper barrel fields. Thus, CTIP1 is a crucial post-mitotic determinant of area identity in the cortex and ensures the specification of somatosensory cortex.

3.3 Neuronal migration

Newborn neurons generated in the ventricular and subventricular zones migrate radially towards the basal surface to occupy their positions in the cortical layers. Early born neurons migrate by somal translocation, whereas the late-born neurons migrate by multipolar

migration up to the IZ. These multipolar cells then become bipolar and migrate further guided by radial glia fibres. As the cortex is formed in an inside-out fashion, late-born neurons migrate past the early-born neurons. This neuronal migration is essential for proper cortical lamination, and defects can lead to cortical malformations (Buchsbaum and Cappello, 2019).

CHD3 and CHD5 display enhanced expression post E15.5 with elevated levels in the cortical plate (Knockdown of CHD5 at E13.5 leads to accumulation of cells in the IZ, whereas a majority of these cells reach the cortical plate in control. The mutant cells fail to transition into bipolar cells and remain multipolar but express the UL markers SATB2 and CUX1, forming an ectopic layer below the cortical plate. CHD5 occupies the promoters of *RhoA* and *Dcx,* which are known to regulate neuronal migration and mutant cells exhibit reduced levels of both. Knockdown of CHD3 at E13.5 leads to retention of cells in the deep layers, with multipolar identity. A majority of these mutant cells expressed TBR1 and SOX5, and only a few expressed UL markers BRN2 and CUX1. CHD3 shows higher occupancy on *Sox2, Pax6* and *Tbr2* promoters in post-mitotic neurons as compared to neural progenitors, and acts to repress them. Ectopic early expression of CHD3 at E13.5 also causes downregulation of protein expression. CHD5 is thus essential for radial migration, whereas CHD3 is necessary for both radial migration as well as layer specification (Fig. 2) (Nitarska et al., 2016). CHD3 is directly activated by TBR1 and TBR2, which supports its expression and function later in neuronal development (Elsen et al., 2018).

A contrasting study by Egan et al., 2013 showed that CHD5 knockdown at E14.5 leads to progenitor accumulation in the VZ/SVZ as these cells fail to undergo terminal differentiation (Egan et al., 2013).

The HDAC2 protein contains two cysteine residues which can be S-nitrosylated on treatment with BDNF or S-nitrocysteine, thus promoting chromatin remodelling. Mutations of the cysteine residues prevent HDAC2 S-nitrosylation (Nott et al., 2008). Electroporation of E14.5 mice cortices with mutated *Hdac2* leads to accumulation of cells in the IZ, whereas these cells reach the cortical plate in the controls. The BAF complex protein BRM is a target of S-nitrosylated HDAC2, and its expression is reduced in mutant HDAC2 cells. Overexpression of BRM in mutant cells rescues the neuronal migration phenotype. S-nitrosylation of HDAC2 is hence necessary for neuronal migration and the BAF complex subunit BRM is its downstream regulator. This study thus identified the interaction between subunits of 2 different remodelling complexes – BAF and NuRD (Nott et al., 2013).

Deletion of *Ctip1* at E14.5 leads to delayed migration of UL neurons and the mutant neurons remain multipolar. UL neurons exhibit specific molecular markers but impaired dendritic morphology. These mutant neurons undergo apoptosis postnatally, giving rise to a thinner cortex and CC. CTIP1 acts by directly repressing the signalling molecule SE-MA3C. Overexpression of SEMA3C recapitulates the *Ctip1* mutant phenotype and knockdown in *Ctip1* mutants rescues the impaired migration (Wiegreffe et al., 2015).

3.4 Neuritogenesis

Neuritogenesis and synapse formation are the building blocks to form a mature neural circuitry. Dendritic size and topology both affect firing (van Elburg et al., 2010).

NuRD complex subunits are expressed throughout development, and thus their roles extend to regulate maturation of neurons (Nott et al., 2008).

LSD1 has four known isoforms – LSD1, LSD1-2a, LSD1-2a/8a and LSD1-8a, wherein the 8a isoforms are neuron-specific (Zibetti et al., 2010).

Knockdown of the neuron-specific LSD1 isoforms in rat cortical cultures causes defects in neuritogenesis, with a reduced number of neurite branches, width and length. Overexpression of the neuro-specific LSD1 isoforms has the opposite effect with increased neuritogenesis (Zibetti et al., 2010). The phosphorylated amino acid threonine within the neuron-specific 8a exon of *Lsd1* is necessary for neuritogenesis. A phosphodefective mutant phenocopied *Lsd1* knockdown phenotype, whereas a demethylase activity inactivating mutant rescued the phenotype in a phospho-defective mutant (Toffolo et al., 2014). The neuro-specific LSD1 isoforms are crucial for neuronal maturation.

S-Nitrosylation of HDAC2 promotes its dissociation from the chromatin, thus facilitating the acetylation of histones H3 and H4. Disrupting this nitrosylation by mutating the two cysteine residues leads to a reduction in the total and average dendritic length in cortical cultures. Short interfering RNA mediated silencing of HDAC2 causes the opposite effect with an increase in the average dendritic length and number of branch points per neuron. These dendritic phenotypes are rescued in the presence of wildtype HDAC2. Thus, HDAC2 S-nitrosylation plays a role in dendritic length and branching (Nott et al., 2008).

Early on cell-intrinsic mechanism drive corticogenesis and later stages of development, namely migration, dendritic maturation are both driven by cell-intrinsic and extrinsic input activity cues. Calcium signalling plays a significant role in dendritic maturation. The down-stream trans-activator of the Calcium signalling is Calcium responsive trans-activator (CREST) and is both a necessary and sufficient regulator of this process.

CREST expression is detected around E18.5 in post-mitotic neurons of the developing cortex, peaks at postnatal P1 and starts to decline after P10 (Aizawa et al., 2004). CREST regulates dendritic architecture and branching both during pre-natal (Staahl et al., 2013) and postnatal development (Aizawa et al., 2004). Absence of CREST and BAF53b impairs calcium-dependent dendritic outgrowth and branching in the cortex (Aizawa et al., 2004; Wu et al., 2007). Mechanistically, BAF53b helps in recruiting nBAF containing CREST to the promoters of key players in axon growth such as *Ephexin1, Gap43.* Moreover, knocking down other neuron-specific subunits of nBAF BRG, BAF57, or BAF45b had similar defects in dendritic morphogenesis (Wu et al., 2007). These highlight the importance of the combinatorial chemistry of the nBAF complex in regulating dendritogenesis.

ARID1B (BAF250b) knockdown leads to dendritic arborization defects in the mice cortex (Ka et al., 2016). shRNA mediated knockdown of *Arid1b* leads to both apical and basal dendritic defects. Apical dendritic length and number are reduced, with fewer dendrites

reaching the pial surface. Basal dendrites in the knockdown are shorter and extend only laterally, as opposed to a lateral and towards VZ orientation of control neurons. The number and length of spines are reduced, leading to impaired excitatory and inhibitory functions. The expression of CFOS, ARC and neurite associated genes (*Stmn22, Gprin11 and Gap43*) is reduced in the knockdown, and overexpression of C-FOS or ARC partially rescues the apical dendritic phenotype.

3.5 Glial fate specification

Astrocytes are essential for neural circuit formation, and play key roles in synaptogenesis (Fossati et al., 2020). Oligodendrocytes are myelinating cells that help propagate action potentials through saltatory conduction (Freeman and Rowitch, 2013; Parras et al., 2020).

Neurogenic mechanisms are actively repressed during gliogenic phase to prevent prolonged neuronal generation in the developing cortex (Hirabayashi and Gotoh, 2010; Miller and Gauthier, 2007; Yao et al., 2016).

MBD3 plays a crucial role in the neuron-glia cell fate switch. *Nestin*- Cre mediated deletion of *Mbd3* leads to enhanced and prolonged-expression of the neurogenic factors NEUROD1, NEUROD2, NHLH1 and NHLH2 in the mutant cortex. Concurrently, the expression of the glial markers GFAP, NEUROD4 and S100B is significantly reduced. MBD3 occupies the gene loci of all four factors and potentially acts by repressing the expression of these genes at the onset of gliogenesis (Knock et al., 2015). MBD3 knockdown cultures also causes an increase and a corresponding decrease in the number of TUJ1+ neurons and GFAP + astrocytes, respectively. A similar reduction in GFAP + glial cells lining the VZ is recapitulated in tamoxifen driven *Emx1-Cre* mediated deletion of MBD3 in mice. MBD3 occupies gene loci of the neurogenic genes *Neurog1, Fezf2, Lef1* and *Tcfap2c* in gliogenic NPCs, but not in neurogenic NPCs. Deletion of *Mbd3* before the gliogenic phase in cortical cultures, leads to enhanced expression of FEZF2 and TCFAP2C and a reduced expression of GFAP (Tsuboi et al., 2018). Thus, MBD3 functions to keep neurogenic genes repressed in gliogenic NPCs to ensure glia production.

In the adult brain, HDAC1 is primarily expressed in glial cells, and HDAC2 is expressed in the neurons (MacDonald and Roskams, 2008; Sokpor et al., 2018).

HDAC1 and HDAC2 play opposing roles in oligodendrogenesis. Knockdown of HDAC1 or HDAC2 in oligodendrocyte precursor cells causes reduced and increased formation of oligodendrocytes, respectively (Egawa et al., 2019). HDAC2 is essential for preventing precocious oligodendrocyte differentiation and acts by inhibiting expression of SOX10, which is required for terminal differentiation (Castelo-Branco et al., 2014). *Hdac1/2* knockout in OLIG1 expressing cells leads to failure in oligodendrocyte differentiation. In the absence of HDAC1/2, the Wnt signalling protein B-Catenin sequesters the oligodendrogenesis protein TCF7L2 (Ye et al., 2009).

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4 Role of chromatin remodellers in neurodevelopmental disorders (NDDs)

Neurodevelopmental Disorders (NDDs) are complex conditions arising due to defects in nervous system development. These conditions affect major aspects of brain function, including speech, cognition, motor skills, language and behaviour (Celen et al., 2017; Homma et al., 2019; Kruszka et al., 2019; Lalli et al., 2016). Childhood NDDs (diagnosis in infancy or childhood) include Intellectual disability (ID), Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) whereas adolescent NDDs (diagnosis in adolescent age) include Schizophrenia and bipolar disorder (Morris-Rosendahl and Crocq, 2020; Stein et al., 2020). The emerging hypothesis in the field is that these conditions which show a wide spectrum of symptoms share genetic and environmental risks factors which lead to overlapping disease mechanisms affecting brain development (Owen et al., 2011; Singh et al., 2017). A comprehensive list of human NDDs caused by mutations in the chromatin remodeller complex subunits with their clinical features is summarised in Table 2. Chromatin regulation plays a critical role and is a fundamental determinant of the generation of the cerebral cortex (Telley et al., 2019). Indeed the long list of mutations in chromatin remodellers comes as no surprise and suggests that chromatin remodelling seems to be at the root of these disorders. Genetic mutations in the remodellers can have a functional impact on their protein activity, which then leads to a cellular impact on neural function, leading to the formation of a dysfunctional neural circuitry ultimately affecting human be-haviour. In this section we discuss known mechanisms of chromatin dysregulation caused by mutations in the subunits of the 4 families of ATP dependent chromatin remodelling complexes followed by a description of overlapping cellular/behavioural phenotypes leading to NDDs.

The mutations in these subunit genes can disrupt protein function in the following ways:

4.1 Disruption of protein binding to histones or DNA

Sifrim-Hitz-Weiss syndrome (SIHIWES) is caused by mutations within the CHD4 gene locus. Variants located within the PHD and chromodomains affect both the ATPase and nucleosome remodelling activities of CHD4 (Weiss et al., 2020). A protein modelling study showed that a few of these mutations affect the binding of CHD4 to H3 or DNA, or disrupt binding of Zn^{2+} to CHD4, thus affecting its activity (Farnung et al., 2020). CHD4 is important for maintenance of bIP pool (Nitarska et al., 2016) and mutations could possibly lead to depletion of the progenitor pool and perhaps be causative of the thin corpus callosum seen in the patients.

4.2 Disruption of protein-protein interaction

GATAD2B-associated neurodevelopmental disorder (GAND) is caused due to mutations in the *GATAD2B* gene. The GATAD2B protein contains 2 conserved regions termed CR1 and CR2, and all identified missense mutations lie within these regions. Mutations located in the CR1 and CR2 domain impaired the ability of GATAD2B to interact with MBD2/MBD3 or CHDs respectively (Shieh et al., 2020).

4.3 Truncated/catalytically impaired enzyme activity

Patients with de novo mutations in *LSD1* exhibit ID and DD, with Kabuki and KBG like syndrome (Chong et al., 2015). Biochemical analysis of three variants – E379K, D556G and Y761H showed that the protein is structurally stable, but enzymatically impaired coupled to a reduced half-life (Pilotto et al., 2016). Chromosome translocation mutation in *ARID1B* is implicated in a patient with ID and corpus callosum agenesis. *De novo* translocation between chromosome chr4 (q25.3) and chr14 (q13.2) results in formation of a fusion transcript of *ARID1B* and *MRPP3.* This fusion transcript is suggested to contribute to disease phenotypes likely by haploinsufficiency (Backx et al., 2011).

Further studies on downstream targets which are mis-regulated due to these mutations and alteration in protein activity will reveal how these mutations affect neurobiological pathways important for cortical development. This will be crucial to establish a cause-and-effect relationship between the mutations and the altered cellular neural development outcomes leading to clinical symptoms in patients with NDDs.

4.3.1 Altered cellular and behavioural phenotypes ––The various steps of neural development are critical for the formation of a functional neural circuitry leading to behaviour. Defects in the neural development processes as outlined below could alter the behavioural outcome manifesting as a clinical disease symptom in patients with NDDs.

Progenitor proliferation defect-Williams syndrome is caused due to microdeletion of ~28 genes within chromosome 7, including *BAZ1B* which encodes the WSTF protein of the ISWI complex. ChIP-seq analysis of genes bound by WSTF in human NSCs showed occupancy on genes implicated in self-renewal and neurogenesis. Transcriptomic analysis of WSTF haploinsufficient neuronal cultures showed bound genes to be misregulated and mirror the transcriptomic profiling from patients with Williams syndrome containing the microdeletion including overactivation of WNT-activated receptor genes. Knockdown of *BAZ1B* inhibits neural progenitor differentiation and cells remain proliferative. Thus, WSTF is crucial for regulating the progenitor proliferation and its haploinsufficiency changes the balance between progenitor proliferation and differentiation leading to reduced neuronal output (Lalli et al., 2016).

Neuronal cell death-Mutations in the *BPTF* gene cause a yet unnamed syndrome. ID, DD, speech, and motor delay have been reported in these patients (Table 2). Zebrafish *bptf* mutant embryos exhibit a smaller head size, and increased apoptosis. These mutants also showed craniofacial patterning defects, with an increase in the angle of the ceratohyal cartilage. The mutants further showed increased apoptosis but not changed proliferation suggesting that microcephaly could possibly be because of increased neuronal cell death (Stankiewicz et al., 2017).

Dendritic impairments-*De novo* mutation in the *CHD5* gene locus has been reported on MyGene2 website in a (http://www.mygene2.org [03 October 2020 accessed]). Genes implicated in ASD are affected in *Chd5* null mice, and *in vitro* cortical neurons exhibit dendritic impairments. These mice are neophobic - prefer familiar spaces and objects, and

show social communication defects. These correlate with known autistic behaviours (Pisansky et al., 2017).

Recessive mutations in *ACTL6B (BAF53b)* have been implicated as a cause of autism. Patient iPSCs showed that ACTL6B is not included in the nBAF complex due to protein destability. Patients display CC hypoplasia and a reduction in white matter, which is recapitulated in a null mutant of *Actl6b.* These null mutants also exhibit characteristic autistic behaviours of hyperactivity and social interaction defects with memory impairment. The non-neuronal isoform ACTL6A is recruited in the mutant nBAF, and chromatin-complex interactions are impaired. Patient mutations in *ACTL6B* rerouted dendrites in the fly olfactory nervous system (Wenderski et al., 2020). ACTL6B regulates dendritic morphogenesis in cortical development (Aizawa et al., 2004; Wu et al., 2007) and thus the autistic behaviours could be a result of the impaired dendritogenesis, CC hypoplasia and reduction in white matter.

Mutations in *ACTL6B (BAF53b)* have been identified to cause Developmental delay, epileptic encephalopathy, Cerebral atrophy and abnormal Myelination (DECAM) syndrome (Yuksel et al., 2019). Loss of dendrites and a large nucleus are observed in both *ACTL6B* knockout in control iPSC derived neuronal cultures and patient iPSC derived neuronal cultures with mutations in *ACTL6B* (Bell et al., 2019)).

Mutations in *ARID1b* are frequently implicated in autism spectrum disorders and non-syndromic ID (Halgren et al., 2012). Loss of function mutations in these patients are suspected to contribute to the disease. *ARID1b* loss of function leads to dendritic defects as it is part of the nBAF complex which functions in postmitotic neurons. Patients with de novo deletions in *ARID1B/BAF250b* have severe speech impairment, and varying degrees of dysmorphic facies (Celen et al., 2017). *Arid1b* heterozygous mice exhibit impaired learning, memory, social interaction and showed anxiety like behaviour. Mutant littermates displayed growth impairment consistent with clinical features of ASD patients (Jung et al., 2017; Shibutani et al., 2017).

Synapse formation defects - RNAi induced deletion of *simj,* the fly ortholog of the GATAD2A and GATAD2B genes causes habituation delay and synapse formation defects - reduced synaptic area, lower number of branches and branch points in Drosophila (Willemsen et al., 2013).

CSS is commonly associated with mutations in multiple members of the BAF complex, including mutations in the *SMARCA2* (BRM), *SMAR-CB1* (BAF47), *SMARCA4* (BRG1), *SMARCE1* (BAF57), *ARID1A (BAF250a)* and *ARID1B* genes (BAF250b) (Tsurusaki et al., 2012). Mutation in *SMARCD1/BAF60a* is associated with syndromic NDDs which share overlapping clinical features of CSS and Nicolaides-Baraitser syndrome (NCBRS) (Table 2). Studies in Drosophila show that Bap60 (Drosophila ortholog of BAF60a) is required for regulation of genes for synaptic development and circuit formation involved in learning and memory (Nixon et al., 2019).

Corpus Callosum defects-The corpus callosum is a white matter tract which serves to connect the two cerebral hemispheres. Callosal projection neurons of the cortex form this

tract, and hence impairments in corticogenesis affect CC formation. Corpus callosum agenesis is seen as a common clinical feature in many patients with mutations in different chromatin remodeller subunits, namely LSD1, BAF250b, BAF200a and GATAD2a and TIP60.

These patients also show developmental delay and Intellectual disability. This suggests that there might exist a correlation between CC agenesis perhaps caused by defective callosal projection neurons subtype identity leading to ID and DD. Indeed, mouse mutant of BCl11a shows partial agenesis of the CC (Woodworth et al., 2016) and in a separate study, *BCl11a* mice heterozygotes mimicking BCL11a haploinsufficiency show ID like symptoms (Dias et al., 2016).

A missense mutation within the *BAZ1A (ACF-1)* gene has been reported to cause ID. The missense mutation causes a change in the conserved amino acid phenylalanine to cysteine. Global RNA seq analysis of patient sample showed enrichment for genes involved in nervous system development, and 25 differentially expressed transcripts that cause ID (Zaghlool et al., 2016). Another patient with *BAZ1A* and *NBAS* (Neuroblastoma amplified sequence) mutations displayed corpus callosum agenesis (Weitensteiner et al., 2018).

Myelination defects-Another commonly observed feature in NDDs is myelination defect seen in patients with mutations in *CHD3, GATAD2* and *LSD1*. The myelin sheath is formed of oligodendrocytes in the CNS. A proper balance in the expression of chromatin remodeller subunits is essential for oligodendrocyte formation, as discussed earlier for HDAC1 and HDAC2. A recent review discusses in detail the role of chromatin remodellers in oligodendrogenesis (Parras et al., 2020). Perhaps some of these mutations lead to defective olidendrocyte generation, and this needs to be probed further at the molecular level in mice and *in vitro* iPSC derived model systems.

Behavioural deficits-Single nucleotide polymorphisms (SNPs) within the *MBD2* and *MBD3* gene loci have been observed in autistic individuals (Cukier et al., 2009; Li et al., 2005). Rodent studies have shown that MBD2 deficient animals display abnormal maternal behaviour, whereas high maternal licking/grooming females show higher MBD2 expression in hippocampal CA1 and DG (Hendrich et al., 2001; Weaver et al., 2014). Human genes associated with ASD are altered in *Mbd2* null mice, suggesting that MBD2 is an upstream regulator of ASD-associated genes. These mice also show behavioural defects, including memory impairment, reduced social-interaction and increased anxiety. Mice with MBD2 knockdown in adulthood also display similar behaviour (Lax et al., 2019). These phenotypes have been previously established in other rodent models of ASD (Edalatmanesh et al., 2013; Sosa-Diaz et al., 2014).

SMARCA2/BRM has been implicated in Schizophrenia in the Japanese population (Koga et al., 2009). A single risk variant allele showed nuclear localisation defect, which hampers protein functions. *Smarca2* null mice show impaired social interaction, a behaviour commonly observed in SZ.

Cohesin mutations cause chromatin architecture defects, leading to transcriptional changes. *Smc3* knockout using *Nestin-Cre* or *Tau-Cre* shows that these mutant mice exhibit

phenotypes associated with CdL syndrome (Cornelia de Lange syndrome. Behavioural analysis showed that low cohesin expression causes high anxiety in these mice (Fujita et al., 2017).

The chromodomain group of proteins are ATPases, that can each function individually as a chromatin remodeller. Several NDDs have mutations within the CHD group of genes (Table 2). We summarise a few known causal pathological mechanisms.

CHD1-Pilarowski–Bjornsson Syndrome (PILBOS) is characterised by speech apraxia, DD, autism and facial dysmorphic features, with patients displaying missense mutations. All these mutations displaced highly conserved amino acids in the CHD1 protein. Fibroblasts from a single patient with R618Q variant showed a global increase in the H3K27me3 mark, suggesting closed chromatin to be plausible cause for chromatin mysregulation (Pilarowski et al., 2018). *Xenopus laevis* embryo morphants of Chd1 display narrower faces and smaller mouths, with reduction in craniofacial cartilages. Increased apoptosis in the head coupled to a reduced expression of the neural crest marker gene tfap-2α is observed in these morphants. The study suggests towards a possible control of CHD1 expression through retinoic acid signals, but further studies need to be conducted to delineate the role of the signalling molecule in CHD1 expression (Wyatt et al., 2021).

CHD2-Mutations in CHD2 causes Developmental Epileptic Encephalopathy-Zebrafish larvae morphants of *chd2* display both developmental and behavioural anomalies, with epileptiform discharges, similar to those observed in mouse model of epilepsy (Suls et al., 2013).

CHD8-Loss of function mutations in *CHD8* are associated with ASD, intellectual disability and macrocephaly (Bernier et al., 2014). CHD8 has several key roles in neurodevelopment beginning from proliferation of progenitors, dendritic arborization, to neurotransmission and synapse development as studied from loss of function mouse models (Hoffmann and Spengler, 2021). The role of pathogenic mutations in CHD8 is not well understood. To mimic the disease mutations, mice with heterozygous frameshift deletion in Chd8 display cognitive deficits, increased brain regional volume and perturbed expression of other ASD associated genes and biological pathways consistent with the clinical traits of ASD patients carrying *CHD8* mutations (Gompers et al., 2017). Katayama et al., reported that haploinsufficiency of *Chd8* led to characteristic ASD like behaviours such as anxiety, repetitive behaviour and altered social behaviour in mice (Katayama et al., 2016).

Knockdown of CHD8 in human NSCs led to dysregulated expression of ASD risk genes involved in neurodevelopment. These NSCs also showed defects in proliferation and differentiation (Cotney et al., 2015). In a similar study using hiPSC derived cerebral organoids, CRISPR/Cas9 mediated disruption of *CHD8* led to upregulated expression of ASD and SZ risk genes indicating the role of CHD8 in neurodevelopmental pathophysiology (Wang et al., 2017).

It is not always unambiguous to establish a linear cause and effect relationship between the genetic mutations, the underlying altered cellular neural development phenotype and the clinical symptoms in NDDs. Reasons include, the dynamic expression and function of the

subunits of the chromatin remodelling complexes throughout development and perhaps postnatally as well, makes it hard to pinpoint the exact stage at which the mutation affects, the polygenic nature of these disorders, the effect of environment in exacerbating the symptoms, to name a few.

One can adequately model aspects of these disorders using a human-specific model system such iPSCs-derived neurons from patients to capture the genetics of the disease and to understand human disease pathological mechanisms.

5 Concluding remarks and future perspectives

Genome organization is crucial for transcriptional regulation and is an emerging property of its function. Dynamic spatio-temporal gene expression programs determine neural cell outcomes during cortical development (Yuan et al., 2020). The timed and cell-type specific expression of transcripts requires specific chromatin configurations which are mediated individually by the different subunits of the chromatin remodelling complexes. Thus, each subunit has a unique function and contributes towards a dynamic genome which is a crucial driver of the process of proliferation and differentiation in the neural cells. Such a cell intrinsic mechanism propels cortical development initially and at later stages acts in concert with extrinsic signaling to make a functional cortical network (Telley et al., 2019). Given several putative risk variants have been identified in the very same chromatin remodellers a basic understanding of their mode of action is imperative to create a framework to study neuropathological mechanisms in NDDs. With the advent of mouse genetics and functional genomics the last several decades have revealed a mechanistic understanding of this process.

Key concepts which have emerged reveal the dynamicity of the process. For instance, the NuRD subunits display varying levels of expression in the developing mouse neocortex (Fuentes et al., 2012; MacDonald and Roskams, 2008; Nitarska et al., 2016; Sokpor et al., 2018). Some like LSD1 is ubiquitously expressed whereas CHDs have distinct zonal expression. It is not clear whether they function as holo-NuRD complex or perhaps have site-specific genome occupancy and function depending on the complex they are a part of at a given location and time. Disruption of NuRD subunits affects all steps of corticogenesis, right from progenitor proliferation to the neuron-glia cell fate switch. Progenitor proliferation defects are observed in mutants of HDAC1/2, CHD4, LSD1 and MBD3 (Hagelkruys et al., 2014, 2016; Moon et al., 2017; Nitarska et al., 2016; Tang et al., 2019; Zhang et al., 2014). Recruitment of HDACs, MTA2, RBBP4 and LSD1 by transcription factors at gene loci is important for regulating neuronal subtype specification (Britanova et al., 2008; Muralidharan et al., 2017). CHD3, CHD5 and S-nitrosylated HDAC2 have been shown to be important for neuronal migration (Nitarska et al., 2016; Nott et al., 2013). Phosphorylated LSD1 and S-nitrosylated HDAC2 play a role in neuritogenesis, exemplifying how post-translational modifications of these remodellers are necessary in cortical development. Disruption of these modifications in both HDAC2 and LSD1 led to impaired neuritogensis (Nott et al., 2008; Toffolo et al., 2014). The neuron-glia cell fate switch is affected in mutants of MBD3 and HDAC1/2 (Egawa et al., 2019; Knock et al., 2015; Tsuboi et al., 2018; Ye et al., 2009).

In the case of BAF complex, cell-type specific expression of different subunit isoforms enables switching and diverse combinatorial assembly of the complex thereby giving rise to the heterogeneous spatiotemporal pattern of gene expression in a tissue-specific manner (Ho and Crabtree, 2010; Sokpor et al., 2018; Wang et al., 1996; Yoo and Crabtree, 2009). Similar to the NuRD subunits, disruption of BAF subunits also affects all steps of corticogenesis. Mutants of BRG1, BAF45a, BAF53a and SS18 exhibit progenitor proliferation defects, as these subunits form an essential part of the npBAF complex (Son and Crabtree, 2014; Staahl et al., 2013; Lessard et al., 2007). However, each of these components seem to control aRG proliferation through different downstream effectors; illustrating how a multimeric complex modulates progenitor proliferation. A stoichiometric ratio of BAF170 and BAF155 is necessary for the controlled production of bIPs. The transcription factors CTIP1 and CTIP2, which form an essential part of the BAF complex, are involved in neuronal subtype specification. ARID 1b and the nBAF subunits – CREST, BAF53b and BAF45b are necessary for regulating dendritogenesis. Thus the combinatorial chemistry of these remodellers enable a probabilistic genome, one as recently proposed (Misteli 2020) which renders it dynamic, allows for quick changes and fine tuning of gene expression in the different progenitor and post mitotic zones of the developing neocortex.

Much attention has been given to the NuRD and the BAF complexes and their role in cortical development. Though the roles of members of the INO80/SWR and ISWI complexes in cortical development has not been well characterised, various studies indicate that the different subunits display varying expression patterns in the developing cortex.

SRCAP and TIP60 show enhanced expression in neurons (Elsen et al., 2018), as compared to INO80 which is enriched in the cortical VZ, suggesting a differential functional role of the INO80 complexes in progenitors and neurons similar to the CHDs (Nitarska et al., 2016). The expression of the cohesins SMC1 and SMC3 peaks in the embryonic brain at E15.5, post which it decreases gradually and peaks again post-natally at day 5 (Fujita et al., 2017). ACF1, CHRAC15 and CHRAC17 show high expression in the aRGs, followed by bIPs and post-mitotic neurons (Telley et al., 2016), suggesting a putative role of the ACF and CHRAC complexes in cortical progenitors. TIP5 and CECR2 are expressed in both progenitors and neurons but are enriched in the bIPs (Elsen et al., 2018; Telley et al., 2016). RSF1 and the three cohesins RAD21, SA1 and SA2 are expressed in all layers, but enriched in the progenitors (Telley et al., 2019). WSTF and BPTF display high expression in the aRGs and moderate expression in the bIPs (Elsen et al., 2018; Telley et al., 2019). More studies using biochemical and genomics approaches and animal models are necessary to unravel the roles of the ISWI and INO80 subunits in chromatin remodelling during corticogenesis. A complete picture of chromatin control of cortical development will emerge once the molecular underpinnings of the function of the above members of the chromatin remodelling complexes is deciphered.

ChIP-seq has been the mainstay to uncover protein-DNA interactions. This method, though very useful to study histone modifications, TF and co-factor binding, is time-consuming and requires a large number of cells (1-10million cells) and is not performed under native conditions. Newer techniques in the field of genomics have paved the way for in-depth characterisation of capturing the dynamicity of protein-chromatin interactions efficiently for

low cell numbers. Cleavage Under Targets and Tagmentation (CUT & Tag) is an enzyme tethering based *in situ* method to capture chromatin accessibility and TF binding sites in the genome with more efficiency. This strategy uses a Tn5 transposase loaded with sequencing adapters to integrate them at the site of cleavage, within the nuclei, thus reducing the efforts of sequence library creation (Kaya-Okur et al., 2019). Cleavage Under Targets and Release Using Nuclease' (CUT&RUN) is an *in-situ* method that employs TF-specific antibodies to interact with target protein (TF) in intact cells, following which protein A-MNase fragments the DNA bound by the TFs and these cleaved fragments diffuse out of nucleus. DNA extracted from the supernatant is used for paired end sequencing (Skene and Henikoff, 2017).

Chromatin integration labelling (ChIL) is an immunoprecipitation free method, wherein DNA sequences interacting with TFs and histone modifications are captured by antibody directed cleavage by Tn5 transposase. Cells are fixed and labelled with a primary antibody, a secondary antibody conjugated to ChIL DNA probe containing T7 promoter sequence, primer sequence for sequencing library preparation and Tn5 transposase binding site is used to integrate the ChIL probe into the genome. The integrated sequence is amplified by T7 RNA polymerase by *in situ* transcription and transcribed RNA is used for sequencing library preparation (Harada et al., 2019).

Assay for Transposase Accessible Chromatin (ATAC-seq) with high-throughput sequencing uses hyperactive Tn5 transposases loaded with sequencing adaptors. Transposase cleaves DNA in the region of open chromatin and tags adaptors to create DNA fragments, which can be used for sequencing (Buenrostro et al., 2013; Sun et al., 2019).

Recently, ATAC-seq was used to reveal accessible chromatin regulatory regions in human brain development and further used to map genetic risk for disease (Trevino et al., 2020).

The limitations to ChIP seq such as the requirement of high input cell size, low mapping resolution and low signal to noise ratio are overcome by these latest techniques. These techniques populate peaks at low sequencing depth with low background noise and high reproducibility with low cell number samples. Besides each of these techniques have their own advantages for example ChIL and CUT &Tag have an advantage of using them for single cell profiling. Given the subunits of the chromatin remodelling complexes have spatio-temporal functions these epigenomic profiling techniques would allow for high resolution of genome-dynamics in the different neural cells across developmental timelines. Such datasets would establish molecular signatures in successive generations of progenitors, neurons and glia.

Chromatin Remodelling complexes play a significant role in cortical development, and mutations in their subunits are perhaps causative of NDDs. Some recent advances in the field could be useful in establishing cause to effect relationships. Hi-coupled MAGMA utilises Hi-C datasets to interpret gene-SNP association and is useful to predict the effect of distal element SNPs on a gene in NDDs (Sey et al., 2020). Engineered chromatin remodelling proteins (E-ChRPs) that were shown to manipulate nucleosome positioning can be employed to study the functional effects of incorrect nucleosome positioning (Donovan et al., 2019).

A majority of the NDDs are polygenic, and the phenotypes observed are due to a combined effect rather than due to a single gene. It is therefore essential to study these NDDs using newer human models – pluripotent stem cells and organoids. Three-dimensional organoids generated from pluripotent stem cells and the advent of gene manipulation techniques such as CRISPR editing have led to a paradigm shift in our understanding of disease mechanisms. These technologies facilitate the creation of disease-associated mutations in cultured iPSC/ESCs and correcting mutations in patient-derived iPSC (Hotta and Yamanaka, 2015). Further advancements in these approaches such as in vivo genomic and RNA base editing (Sinnamon et al., 2020; Yeh et al., 2018), and combining multiple isogenic iPSC lines with various mutations associated with disease and differentiating them into neural lineage allow for better understanding of complex polygenic disorders (Cederquist et al., 2020).

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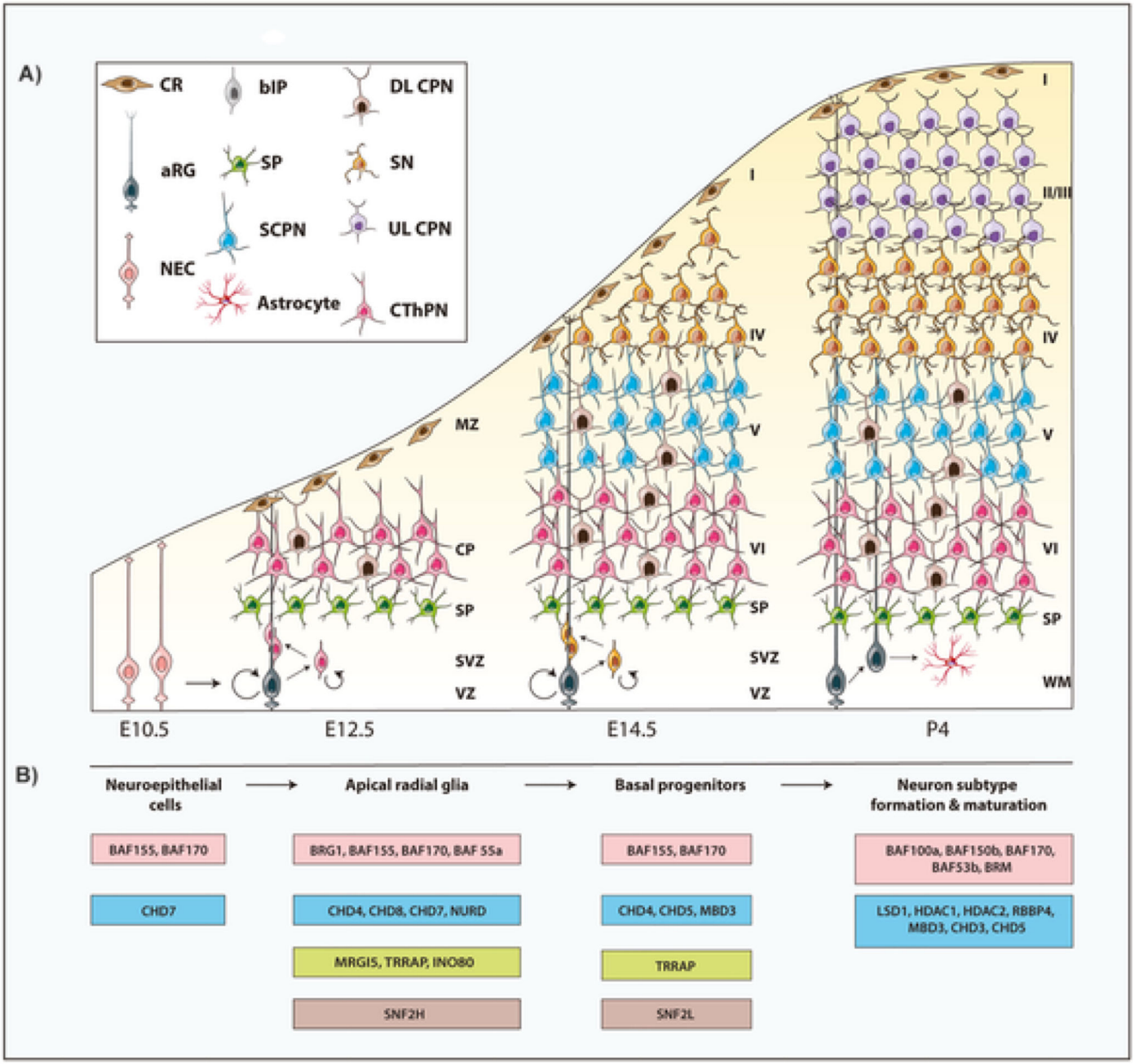

Fig. 1. Snapshot of cortical development and the chromatin remodelling complexes involved in its formation.

Excitatory projection neurons emerge from the progenitors in the dorsal telencephalon which line the ventricle. At early embryonic ages, the dorsal neuroep-ithelium consists of NECs which divide both symmetrically for pool expansion and asymmetrically to give rise to aRGs in the VZ. aRGs self-amplify by symmet-ric division and also give rise to bIPs, bRGs in the SVZ (indirect neurogenesis) and neurons (direct neurogenesis) by asymmetric division. bIPs and bRGs can also self-renew and produce neurons that fill the CP. The CR cells in the MZ do not originate from the cortical progenitor zone. The various PNs of the neocor-tex are generated in a temporally timed manner in an inside out fashion with layer VI generated first followed by V,IV, III and II as development progresses. The newly generated

PNs use the aRGs or bRGs as guidance to migrate and occupy distinct positions in the cortical plate. Chromatin remodellers involved in the various steps of cortical development are depicted. Abbreviations: Neuroepithelial precursors cells (NE or NECs), aRGs-apical radial glia, bIPs-basal inter-mediate progenitors, bRGs-basal radial glia, VZ-ventricular zone, SVZ-subventricular zone, SP-subplate, CP-cortical plate, MZ – marginal zone, WM-white matter, CThPN-corticothalamic projection neuron of layer 6, PN-projection neuron, SCPN-subcerebral projection neuron of layer 5, DL CPN-deep layer callosal projection neuron of layer VI and V, UL CPN-upper layer projection neuron of layers II and III, SN – stellate neuron of layer IV.

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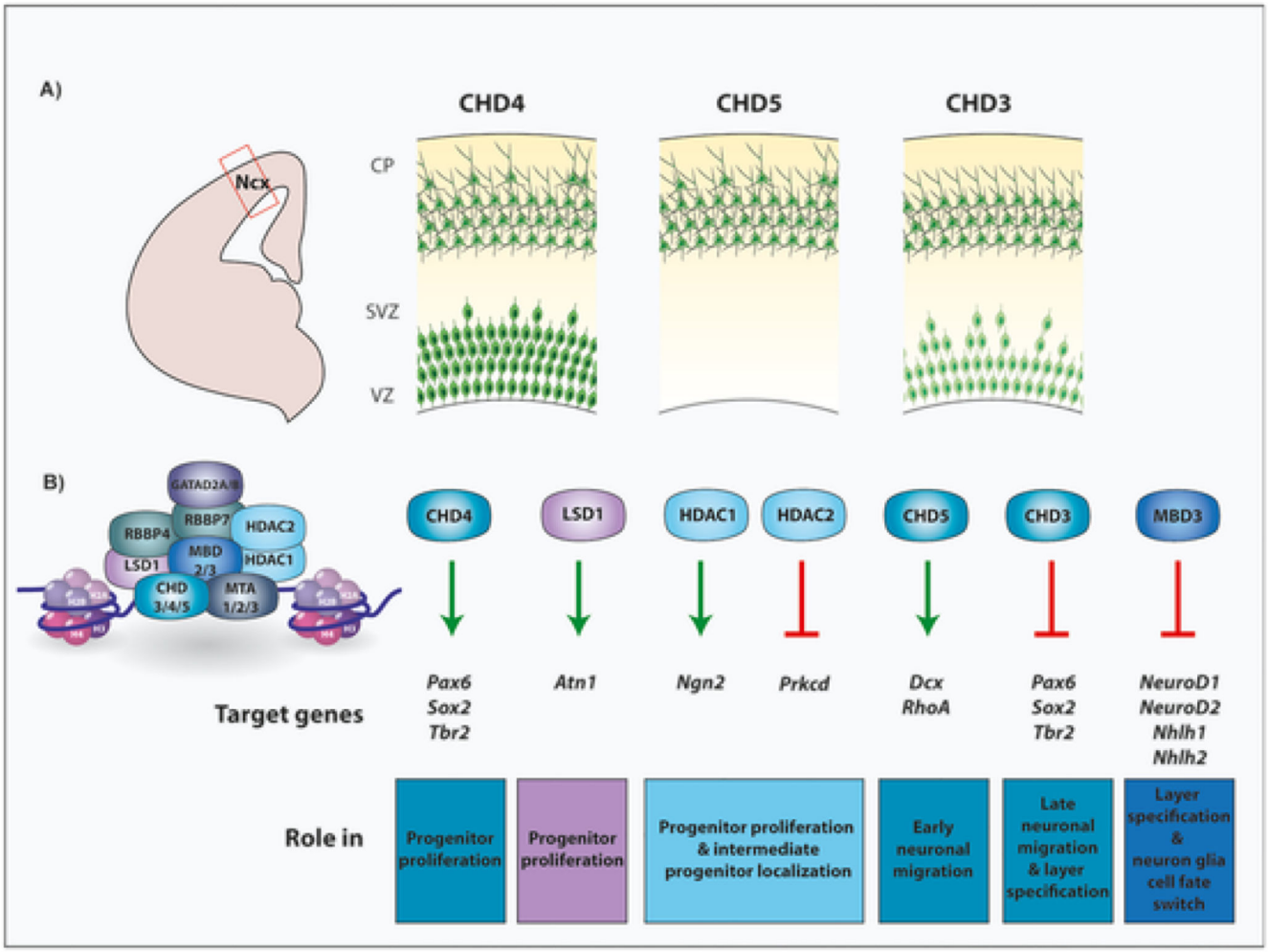

Fig. 2. Members of the NuRD complex mediate different aspects of cortical development.

Diagram illustrating expression pattern of the NuRD ATPases CHD4, CHD5 and CHD3 at the peak of cortical neurogenesis (E15.5) in mice. CHD4 is expressed by the VZ progenitors as well as the post-mitotic neurons of the cortical plate. CHD5 is primarily expressed in the cortical plate. CHD3 exhibits differential expression, with higher expression in the post-mitotic neurons and low expression in the progenitors (top) (Nitarska et al., 2016). Graphical representation of the NuRD subunits, their target genes and their roles in corticogenesis. Deletion of these subunits leads to defects in various steps of corticogenesis. CHD4 positively regulates *Pax6, Sox2* and *Tbr2* to enhance progenitor proliferation. LSD1 activates its effector ATN1 by binding to the LBAL locus downstream of the *Atn1* gene, to maintain the progenitor pool during corticogenesis. HDAC1/2 temporally controls localisation of intermediate progenitors, by activating the HDAC1 target gene *Ngn2*. CHD5 regulates the expression of neuronal migration genes *Dcx* and *RhoA* and promotes early radial migration. CHD3 inhibits the expression of the progenitor genes *Pax6, Sox2* and *Tbr2* and plays a role in both late migration of neurons as well as layer specification. MBD3 plays a role in both layer specification and neuron-glia cell fate switch. It represses the expression

of neurogenic factors *Neurod1, Neurod2, Nhlh1* and *Nhlh2* at the beginning of gliogenesis (bottom) (LBAL: LSD1 binding site at the Atn1 locus).

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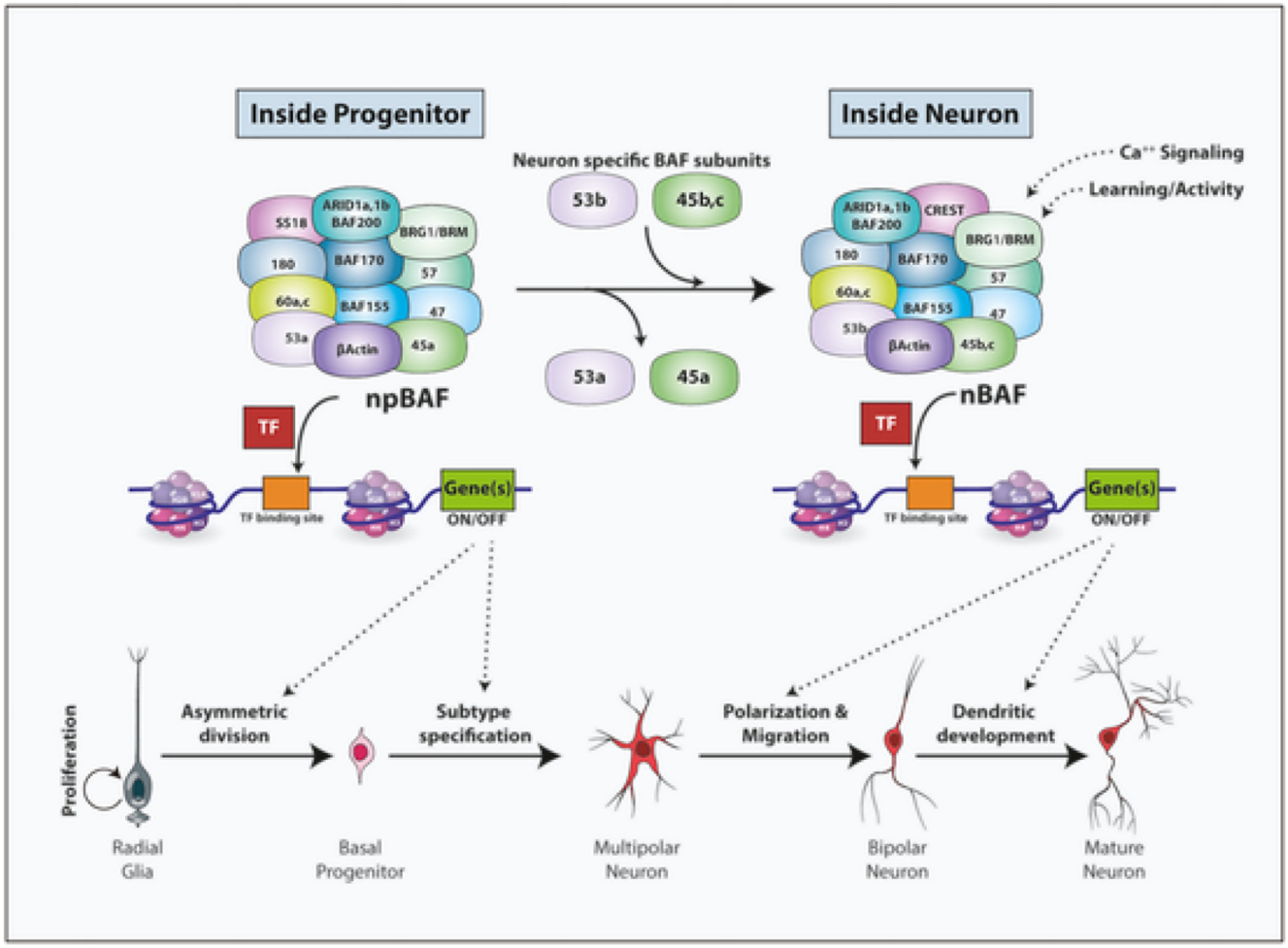

Fig. 3. Differential roles of progenitor and neuron-specific BAF complexes in neurogenesis.

The BAF complexes in the progenitors (npBAF) and neurons (nBAF) share multiple subunits but display a few stage-specific subunits. The progenitor specific subunits BAF53a, BAF45a and SS18 in the npBAF are exchanged for the neuronal-specific subunits BAF53b, BAF45b/c and CREST in the nBAF. The npBAF complex interacts with transcription factors such as PAX6 to regulate gene expression during symmetric and asymmetric progenitor division and neuronal subtype specification. The nBAF, which acts in neurons controls steps of neuronal maturation including polarisation, migration and dendritogenesis.

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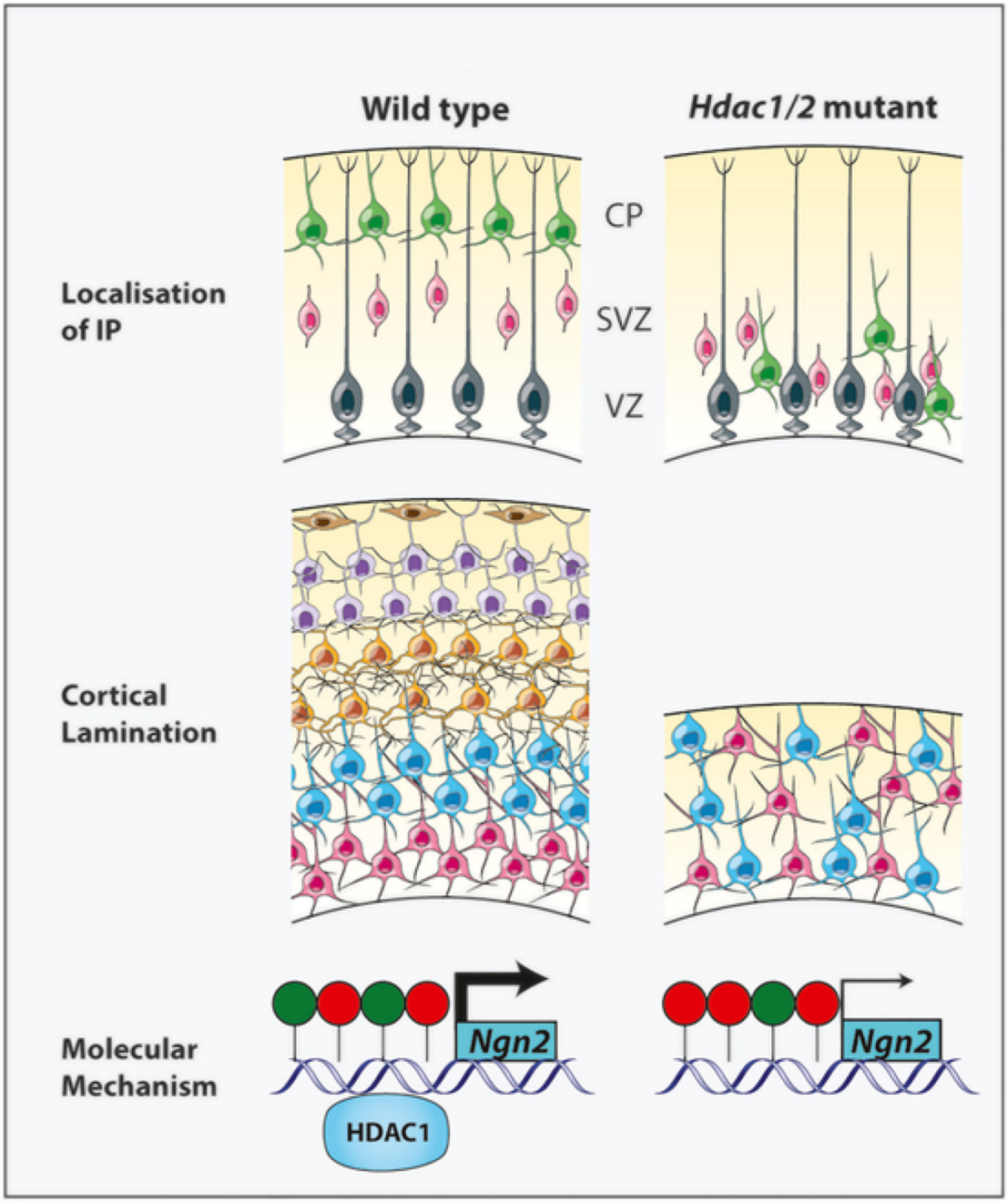

Fig. 4. Regulation of Intermediate progenitor localisation by *Hdac1/2* in the cortex.

Deletion of *Hdac1/2* at E10.5 leads to accumulation of intermediate progenitors in the cortical VZ (top). Analysis at E16.5 shows that the mutant cortex is thinner, and does not display upper layer neurons (middle). *Ngn2* is a target and downstream effector of HDAC1. HDAC1 binds to the Ngn2 promoter, which also displays the H3K9 acetylation (green sphere) and H3K27 trimethylation (red spheres) marks. In the mutant cortex, the H3K9ac mark is reduced, whereas the H2K27me3 mark is increased, thereby repressing NGN2 expression (bottom) (Tang et al., 2019).

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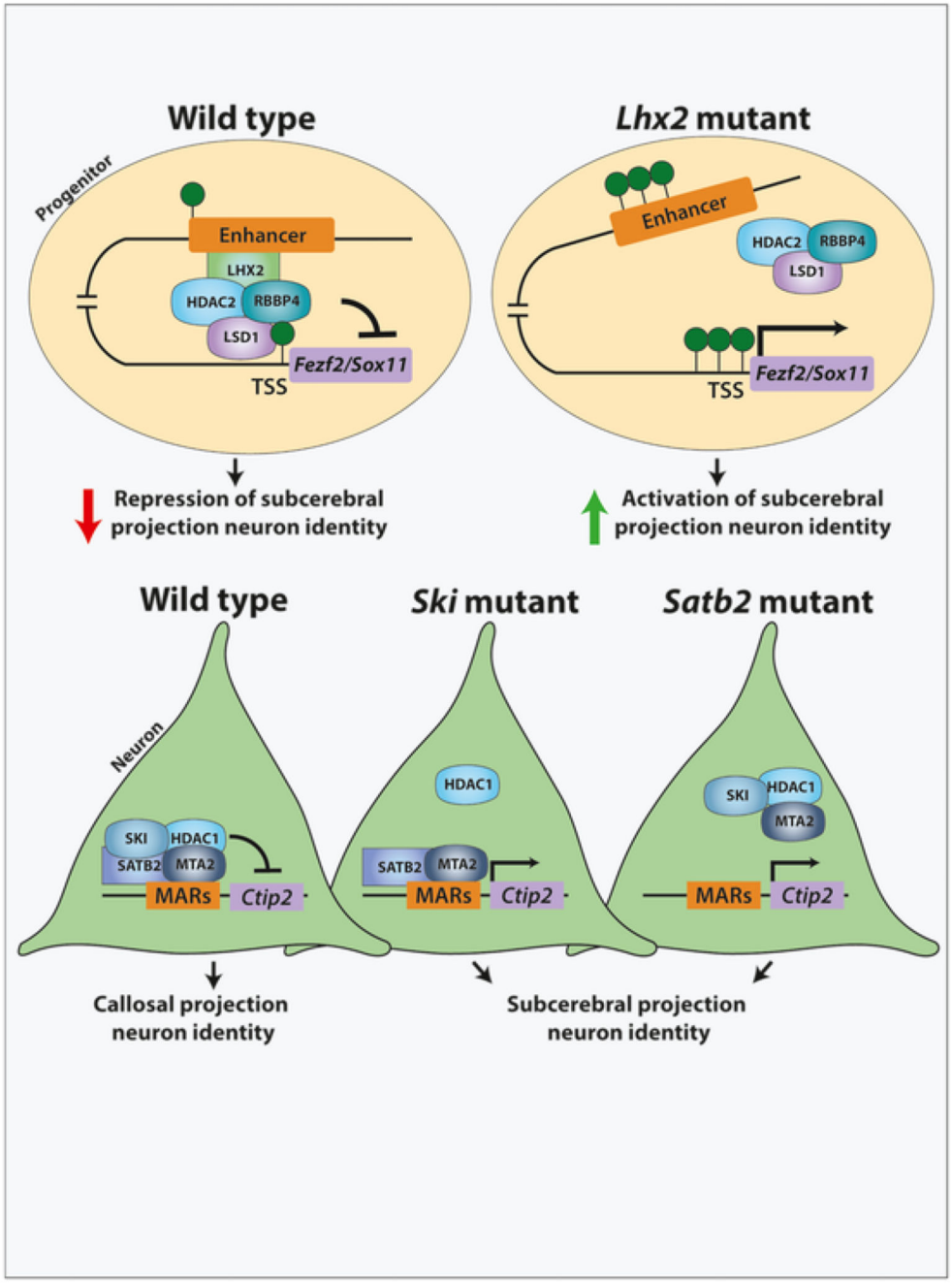

Fig. 5. Interaction between transcription factors and NuRD.

In cortical progenitors, LHX2 putatively recruits HDAC2, LSD1 and RBBP4 and represses FEZF2 and SOX11 expression by removing active marks from their gene loci. The sub-cerebral projection neuron identity of layer V is hence suppressed during layer VI formation. In the absence of LHX2, the NuRD subunits possibly cannot interact with the gene loci, thus retaining the active marks and precocious formation of layer V sub-cerebral projection neurons (Muralidharan et al., 2017). In post-mitotic neurons, transcription factor SATB2 and transcription regulator SKI repress CTIP2 expression in callosal projection neurons by

recruiting HDAC1 and MTA2 to the matrix attachment region (MAR) upstream of the *Ctip2* gene locus. In the *Ski* mutant, HDAC1 is not recruited to the MAR locus whereas, in the *Satb2* mutant, the SKI-NuRD complex is not recruited to the MAR locus. CTIP2 expression is thus facilitated in the *Ski* and *Satb2* mutants, providing a subcerebral projection identity to the neurons (Britanova et al., 2008; Baranek et al., 2012).

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Table 1

ISWI Complex	ISWI Protein	Other partner proteins
CERF	SNF2L	CECR2
NURF	SNF2L	BPTF, RBBP4, RBBP7
ACF	SNF2H	ACF-1
CHRAC	SNF2H	ACF-1, CHRAC15, CHRAC17
NoRC	SNF2H	TIP5
WICH	SNF2H	WSTF
SNF2H-Cohesin	SNF2H	RAD21, SMC1/2/3, SA1/SA2 and NuRD complex proteins
RSF	SNF2H	RSF-1

Table 2

Family	Subunit		Syndrome/NDD	Mutations	Clinical brain Phenotypes	References
	Gene	Protein				
NuRD	*CHD3*	CHD3	Snyders Blok-Campeau Syndrome	Missense, nonsense, frameshift, deletion, splice-site variant	ID, DD, delayed myelination, macrocephaly/ microcephaly	Drivas et al. (2020); Snijders Blok et al., 2018
	CHD4	CHD4	Sifrim-Hitz-Weiss syndrome (SIHIWES)	Missense, in-frame deletions, nonsense	ID, DD, macrocephaly, hydrocephalus, thin corpus callosum,	Farnung et al. (2020); Weiss et al. (2020)
	CHD5	CHD5	Autism-like	Missense	DD, cerebral palsy, speech impairment	http://www.mygene2.org [03 October 2020 accessed]
	MBD2/3	MBD2/3	Autism	SNPs		Cukier et al. (2009); Li et al. (2005)
	HDAC1/2	HDAC1/2	Schizophrenia, Angelman syndrome	–	ID, DD	Jamal et al. (2017); Schroeder et al. (2017); Sharma et al. (2008)
	GATAD2B	GATAD2B	GATAD2B-associated neurodevelopmental disorder (GAND)	Deletion, frameshift, nonsense, splice-site, missense	ID, DD, macrocephaly, thin corpus callosum, widened CSF spaces, hypomyelination	de Ligt et al. (2012); Hamdan et al. (2014); Luo et al, 2017; Shieh et al. (2020); Ueda et al. (2019); Willemsen et al. (2013)
	KDM1A	KDM1A	Kabuki and KBG-like syndrome	Missense, nonsense, splice-variant, nonsense	ID, DD, thin corpus callosum, delayed myelination, cerebellar defects	Chong et al., 2015; Rauch et al. (2012); Tunovic et al. (2014)
BAF	*ARIDla*	BAF250A	Coffin Siris Syndrome	Nonsense, frameshift indel, missense	CNS structural abnormalities	Bramswig et al. (2017); Tsurusaki et al. (2012); Wieczorek et al. (2013)
	SMARCA4	BRG1				
	SMARCE1	BAF57				
	ARID2	BAF200				
	SMARCA2	BRM	Coffin Siris syndrome, Nicolaides-Baraitser syndrome, Schizophrenia	Partial deletion, missense, intronic alteration, duplication	CNS structural abnormalities, ID, microcephaly, behavioural problems and seizures, delusions, thought disorder, cognitive dysfunction	Ejaz et al. (2016); Miyake et al., 2014; Sousa et al. (2014); Wolff et al., 2012
	SMARCB1	BAF47	Coffin Siris Syndrome, Kleefstra syndrome	In-frame deletion, missense	CNS structural abnormalities, ID, behavioural anomalies	Kleefstra et al., 2012; Santen et al., 2013; Tsurusaki et al. (2012); Wieczorek et al., 2013
	ARIDlb	BAF250B	Coffin Siris Syndrome, ID, Hirschsprung's disease, Schizophrenia, Autism, 6q25 Microdeletion Syndrome	Missense, nonsense, frameshift indel, translocation, microdeletion, interstitial deletion	CNS structural abnormalities, developmental delay, epilepsy, and hypoplasia of the corpus callosum and cerebellum, delusions, thought disorder, cognitive dysfunction, defects in social and communication skills, restricted and repetitive behaviour, corpus callosum agenesis	Backx et al. (2011); Halgren et al. (2012); Santen et al., 2013; Takenouchi et al. (2016), Ronzoni et al. (2016)

Family	Subunit		Syndrome/NDD	Mutations	Clinical brain Phenotypes	References
	Gene	Protein				
	SMARCD1	BAF60	Coffin Siris Syndrome, Nicolaides-Baraitser syndrome	Missense, nonsense	CNS structural abnormalities, ID, microcephaly, behavioural problems and seizures	Machol et al. (2019); Nixon et al., 2019
	SMARCC1	BAF155	Autism	Missense	Defects in social and communication skills, restricted and repetitive behaviour	Neale et al. (2013); O'Roak et al. (2012)
	PBRM	BAF180a	Autism	Missense		
	ACTL6b	BAF53b	Autism	Missense	Defects in social and communication skills, restricted and repetitive behaviour	Bell et al. (2019); Wenderski et al. (2020)
	ACTL6b	BAF53b	DECAM syndrome	–	Developmental delay, Epileptic encephalopathy, Cerebral atrophy and abnormal Myelination	Bell et al. (2019); Yuksel et al. (2019)
	BCL11a	BAF100a	Autism, Schizophrenia, p15–16.1 Microdeletion syndrome, Intellectual Disability	Microdeletion, missense, frameshift	Defects in social and communication skills, restricted and repetitive behaviour, delusions, thought disorder, cognitive dysfunction, developmental delay, hearing and visual impairment and corpus callosum agenesis	Basak et al. (2015); Bagheri et al. (2016); Chen et al. (2020); De Rubeis et al. (2014), Korenke et al. (2020)
	SMARCC2	BAF170	Coffin Siris Syndrome, Nicolaides-Baraitser syndrome like, Autism	Splice site mutation	CNS structural abnormalities, ID, microcephaly, behavioural problems and seizures, defects in social and communication skills, restricted and repetitive behaviour	Machol et al. (2019)
ISWI	*SMARCA1*	SNF2L	Coffin-Siris like syndrome; Schizophrenia	Nonsense, missense	ID, microcephaly with cortical atrophy, spasticity, dysmorphic features	Homann et al. (2016); Karaca et al. (2015)
	BAZ1A	ACF-1	Intellectual Disability	Missense	ID, corpus callosum agenesis	Zaghlool et al. (2016)
	BAZ1B	WSTF	Williams Syndrome	Microdeletion	Anxiety, ADHD	Lalli et al. (2016)
	BPTF	BPTF	Unnamed syndrome; Silver-Russell syndrome	Nonsense, missense, frameshift, CNV deletion, splice-variant	ID, DD, microcephaly, dysmorphic facial features; pre- and postnatal growth retardation	Stankiewicz et al. (2017); Wakeling et al. (2017)
	RAD21	RAD21	Cornelia de Lange (CdL)	LOF	Microcephaly, holoprosencephaly	Goel 2020; Kruszka et al. (2019)
	SMC1	SMC1	Cornelia de Lange syndrome and holoprosencephaly	Nonsense, missense	Holoprosencephaly	Kruszka et al. (2019)
	SMC3	SMC3	ID and holoprosencephaly	Missense, nonsense, in-frame deletion/ duplication	Holoprosencephaly	Kruszka et al. (2019)
	STAG2	SA2	STAG2-related X-linked Intellectual	LOF	Moderate ID, language and hearing defects,	Kruszka et al. (2019); Soardi et al. (2017)

Family	Subunit		Syndrome/NDD	Mutations	Clinical brain Phenotypes	References
	Gene	Protein				
			Deficiency and holoprosencephaly		developmental delay, microcephaly, characteristic facial features, holoprosencephaly	
INO80/ SWR1	*INO80*		Intellectual Disability and Global developmental delay	–	ID, DD, microcephaly	Alazami et al. (2015)
	SRCAP		Floating Harbor Syndrome	Nonsense	ID, ADHD, speech delay, cranio-facial features	Greenberg et al. (2019); Homma et al. (2019); Zhang et al. (2019)
	TIP60/ KAT5		Unnamed syndrome	Missense	ID, DD, corpus callosum agenesis/dysgenesis, characteristic facial features	Humbert et al. (2020)
Other CHDs	*CHD1*	CHD1	Pilarowski-Bj ornsson Syndrome, 5q15-q21.2 deletion, ASD	Missense, deletion	Speech apraxia, DD, autism, craniofacial dysmorphism, motor delay	Neale et al. (2013); Pilarowski et al. (2018); Zepeda-Mendoza et al., 2019
	CHD2	CHD2	Developmental Epileptic Encephalopathy, Epilepsy with myoclonicatonic epilepsy, ASD	Nonsense, missense, deletion	Photosensitivity, myoclonic seizures, ID	Angione et al. (2019); Carvill et al. (2013); Neale et al. (2013); Trivisano et al. (2015)
	CHD7	CHD7	CHARGE Syndrome, ASD	Missense, nonsense, frameshift, microdeletions, translocation, intronic SNV	Developmental delay, hearing impairment, defects in social and communication skills, restricted and repetitive behaviour	Johnson et al. (2006); O'Roak et al., 2012; Vissers et al. (2004); Zhang et al. (2020)
	CHD8	CHD8	14q11.2 microdeletion, Zahir Friedman syndrome, Schizophrenia	de novo deletion, Microdeletion, CNVs, missense, frameshift, nonsense, single amino acid deletions, duplications, point mutations	Developmental delay, cognitive impairment, dysmorphic features, ASD/DD/ID, macrocephaly, speech defects, defects in social and communication skills, restricted and repetitive behaviour, hallucinations, persecutory delutions and catatonic behaviors	Bernier et al. (2014); Kimura et al., (2016); McCarthy et al., (2014); Merner et al., 2016; Stessman et al. (2017); Talkowski et al., 2012; Yasin et al. (2019); Yasin et al., 2020; Zahir et al., 2007