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The chromatin basis of neurodevelopmental disorders: Rethinking dysfunction along the molecular and temporal axes

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A B S T R A C T

The complexity of the human brain emerges from a long and finely tuned developmental process orchestrated by the crosstalk between genome and environment. Vis à vis other species, the human brain displays unique functional and morphological features that result from this extensive developmental process that is, unsurprisingly, highly vulnerable to both genetically and environmentally induced alterations. One of the most striking outcomes of the recent surge of sequencing-based studies on neurodevelopmental disorders (NDDs) is the emergence of chromatin regulation as one of the two domains most affected by causative mutations or Copy Number Variations besides synaptic function, whose involvement had been largely predicted for obvious reasons. These observations place chromatin dysfunction at the top of the molecular pathways hierarchy that ushers in a sizeable proportion of NDDs and that manifest themselves through synaptic dysfunction and recurrent systemic clinical manifestation. Here we undertake a conceptual investigation of chromatin dysfunction in NDDs with the aim of systematizing the available evidence in a new framework: first, we tease out the developmental vulnerabilities in human corticogenesis as a structuring entry point into the causation of NDDs; second, we provide a much needed clarification of the multiple meanings and explanatory frameworks revolving around "epigenetics", highlighting those that are most relevant for the analysis of these disorders; finally we go in-depth into paradigmatic examples of NDD-causing chromatin dysregulation, with a special focus on human experimental models and datasets.

1. Introduction

Neurodevelopmental Disorders (NDDs) constitute a broad spectrum of diseases originated during the development of the central nervous system (CNS). They are characterized by an early childhood onset leading to varying degrees of neuropsychiatric impairment, often in combination with a plethora of accompanying manifestations, whose specific configurations represent both a diagnostic and therapeutic challenge.

In this review we focus on NDD caused by genetic alterations of high, usually complete penetrance and characterized by often overlapping phenotypes. Importantly, the causative mutations target several convergent molecular axes, with genes either belonging to the same class (e.g. lysine demethylases) or operating in the same molecular pathway (e.g. Polycomb-mediated chromatin regulation). The genetic causes of a major NDD class, such as the Autism Spectrum Disorders (ASD), provide an examplary case. The Simons Foundation Austim Research Initiative (SFARI) currently lists 910 genes whose mutations lead to syndromic and non-syndromic ASDs. Following a Gene Ontology (GO) analysis of these genes (Fig. 1), a strong statistical enrichment emerges for many categories related for neuronal activity and function as well as for gene expression control. Indeed, 87 out of 910 genes are involved in molecular functions such as “demethylase activity”, “transcription coactivator activity”, “transcription factor activity”, “direct ligand regulated sequence-specific DNA binding”, and “chromatin binding”, which highlights the pivotal role of the gene expression regulation in mediating common Gene Regulatory Networks (GRNs) in vulnerable cell types, thus constituting the basis of widespread genetic dysregulation and its overlapping phenotypical manifestations.

As the distinctively human features affected in NDDs, in terms of cognition and behaviour, are arguably linked to the mechanisms engaged in cortical expansion (Rakic, 2009), we first focus on the specific susceptibilities of human cortex development. Next, we mobilize the most rigorous and productive notions of epigenetics and clarify their importance for NDD, considering the relevance of gene expression

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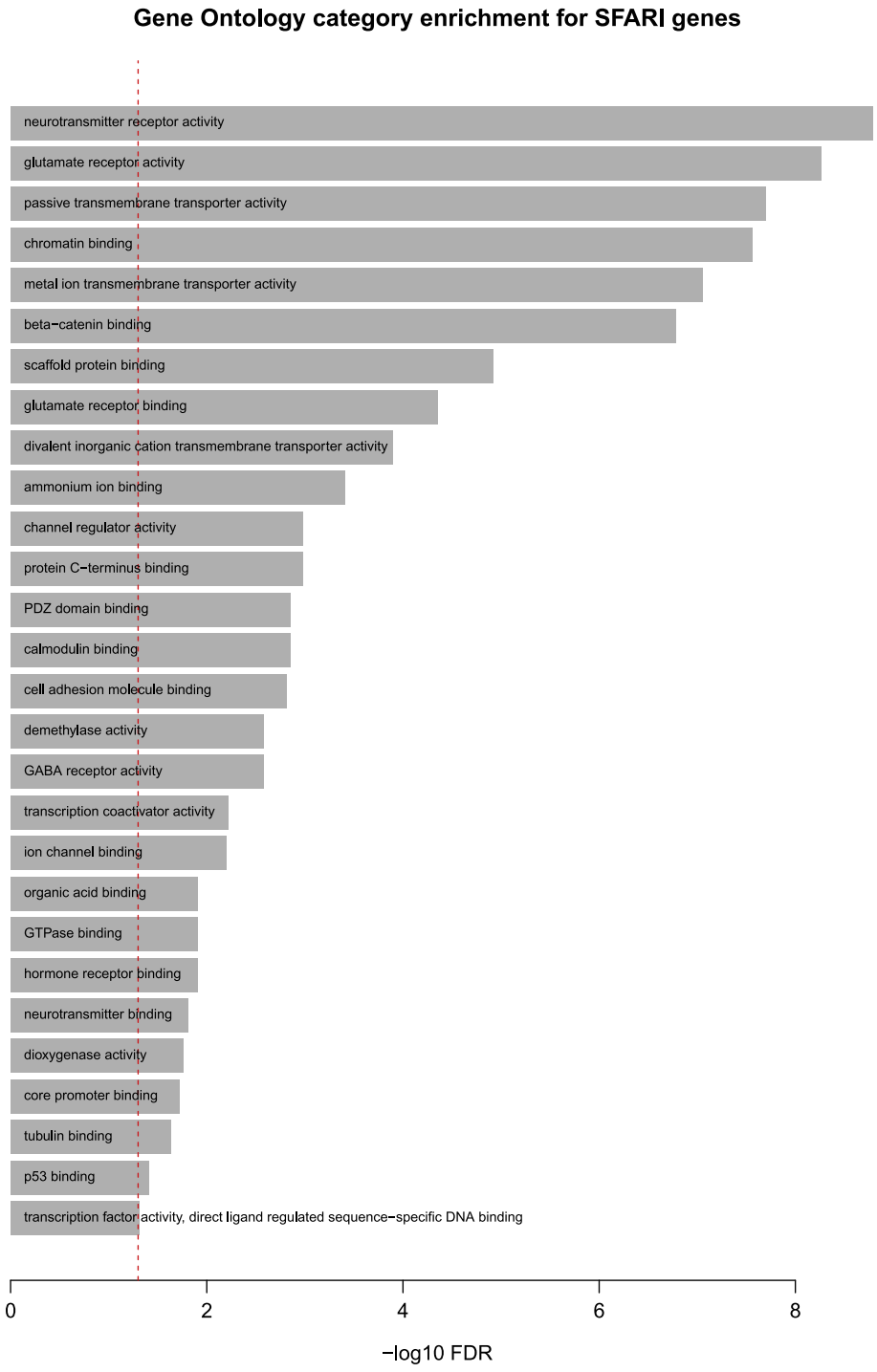

Fig. 1. Gene Ontology analysis of SFARI genes responsible for ASDs. The GO was performed using the WEB-based GEne SeT AnaLysis Toolkit (http://www.webgestalt.org/) with an Overrepresentation Enrichment Analysis. Gene ontology was used as a functional database. The gene list contains 910 user IDs in which 902 user IDs are unambiguously mapped to the unique Entrez Gene IDs and 8 user IDs are mapped to multiple Entrez Gene IDs or could not be mapped to any Entrez Gene ID. The GO Slim summary are based upon the 902 unique Entrez Gene IDs. Among the 902 unique Entrez Gene IDs, 694 IDs are annotated to the selected functional categories and also in the reference gene list, which are used for the enrichment analysis. The analysis was performed with the following parameters: Minimum number of Entrez Gene IDs in the category:1; Maximum number of Entrez Gene IDs in the category:2000; FDR Method:BH; Significance Level: FDR $<$ 0.05.

control in their pathogenesis. On the basis of this framework, we then undertake an exhaustive review of the mechanisms of gene expression regulation whose derangements have been causally linked to NDDs. Specifically, to help the reader appreciate how the interplay of epigenetic mechanisms underlies the molecular-phenotypical convergence, we review the molecular functions and physiological roles of histone methylation, acetylation, phosphorylation, DNA methylation, and nucleosome remodeling, and we underscore the importance of the dynamic balance of each of these mechanisms in the NDDs associated to them.

1.1. Vulnerable stages of human neural development

The human cortex depends on two waves of cell proliferation. First, symmetrical divisions at the ventricular and subventricular areas, 10 times more prolonged in humans than in rodents, are responsible for the expansion of the progenitor pool, resulting in the enlarged subventricular zone (SVZ) in the cortex and subgranular zone (SGZ) in the hippocampus. Later, a stage of asymmetric neurogenic divisions, 20 times longer in humans, determines the number of neurons in the different cortical layers (Florio and Huttner, 2014). Human cortical neurogenesis occurs predominantly during gestation from week 5-6 post-conception, but may continue up to 2.5 years of age (Florio and Huttner, 2014). The prolonged unfolding of neurogenic potential, along

with the highly vascularized nature of the developing SVZ and SGZ, have both been invoked as reasons for the vulnerability of the developing human brain (Baburamani et al., 2012). These proliferative stages are particularly prone to the accumulation of genetic lesions associated with DNA replication and repair, including Single Nucleotide Variations (SNVs) and insertions-deletions (indels) (Ernst, 2016). Also, due to the prolonged nature of corticogenesis, the precise stage at which environmental or genetic insults hit has a discernible impact. In broad terms, the stage of impact influences the phenotypic outcomes in two possible ways: defects occurring during the early phase produce a cortex with a small surface area but normal or enlarged thickness (lissencephaly); conversely, defects during the phase of formation of radially aligned columns of cortical progenitors, (i.e., ontogenetic columns) produces polymicrogyria with thinner cortex and relatively normal or larger surface (Geschwind and Rakic, 2013). This stage-specificity may be due to the timing of expression of the affected gene, or the time at which the buffering effects of compensatory circuits ceases.

After the progenitor pool is established, differentiating neurons rapidly multiply their synaptic connections. In humans, synapse production begins at around 20 weeks of gestation and increases quickly after birth, peaking at 2 years of age. By this stage, the number of synapses is approximately 50% higher than that seen in adults, followed by a process of synaptic pruning that continues well into adolescence (Petanjek et al., 2011). Environmental and genetic factors affecting these processes contribute to functional abnormalities, such as increased filopodia-to-spine ratios and abnormal protrusion densities, a common feature in many NDDs during early childhood (Govek et al., 2005).

The vast majority of neuropsychiatric disorders and intellectual disabilities are linked to improper synaptic pruning (Paus et al., 2010) underlying the biomedical and behavioral implications of the synaptic establishment phase. Moreover, a prolonged synaptic pruning and remodeling are characteristic of areas heavily involved in complex cognitive tasks such as the human prefrontal cortex (Paspalas et al., 2009), increasing the chance that the impact of even minuscule early impairments of the mechanisms regulating synaptic connectivity gets magnified upon development.

1.2. Genetic susceptibilities

Despite the considerable variation in brain sizes across healthy individuals, ranging up to 1.7 fold in the same gender, as well as microstructural variation often found in the neocortex (Toro et al., 2008), the general anatomical distribution and connectivity between regions is highly conserved, suggesting that a substantial proportion of the genetic underpinnings for this architecture is conserved across the human population. Furthermore, when considering only protein coding sequences, the differences between human and chimpanzee genomes is about 1% (Varki and Altheide, 2005). Although there is a significant amount of neutral and non-coding variation, it is estimated that the total SNVs, indels, and structural chromosomal changes make up about 4% of this divergence, with only a few of them resulting in functional alterations to proteins (Sudmant et al., 2013). This evidence suggests that differences in coding sequences alone may not account for the substantial phenotypic and functional complexity observed in humans, instead differences in the rate at which genetic variants are fixed in the human population, copy number polymorphisms as well as epigenetic regulation all contribute to a phenotypic “plasticity” and species-specific differences between humans and great apes (Varki et al., 2008). This accumulation of genetic variation has been associated to a pronounced incidence of genomic disorders affecting brain development. In general, the increased presence in humans and other great ape lineages of complex loci, such as those in which germline structural mutations in many different ancestors have given rise to complex patterns of variation, has created species-specific hotspots prone to copy number variation (Boettger et al., 2012). The accumulation of these hotspots during evolution has contributed to the emergence of human-specific disorders of genetic origin including dyslexia, intellectual disability (ID), attention-deficit hyperactivity disorder (ADHD), Autism spectrum disorders, and schizophrenia, as well as neurodegenerative conditions such as Alzheimer's disease (Geschwind and Rakic, 2013).

In addition to germline genetic variation, the combination of prolonged proliferation of neural progenitors and the extended lifespan of mature neurons make the human brain particularly prone to somatic mosaicism, leading both to higher neuronal diversity (with its possible functional correlates) but also to increasing likelihood of disease (Wei et al., 2016; Weissman and Gage, 2016). In fact, within the same individual, neuronal populations may harbor structural variants in the range of several megabases, including copy number variants (CNVs), inversions, translocations and even whole-chromosome gains or losses (McConnell et al., 2013). Genome-wide analyses performed in brains from autistic individuals revealed the existence of convergent molecular abnormalities in ASD, among which several high confidence genes provide a molecular neuropathological basis for the disease (Voineagu et al., 2011). Recent evidence indicates that postzygotic mosaic mutations may underlie a significant proportion of ASD cases, adding further complexity in terms of the stage-specific impact of mutational burden. Recent efforts, such as the Brain Somatic Mosaicism Network (BSMN), aim at eliminating the bias of typical genome-wide association studies and exome sequencing, which rely on assuming a fixed nature of the genome throughout time, while simultaneously trying to weigh the contribution of cumulative variation across development (McConnell et al., 2017). Preliminary findings of the BSMN have identified a list of well-defined mosaicisms, which cause a broad spectrum of disorders (Freed et al., 2014; McConnell et al., 2017). Altogether, somatic mosaicism may significantly contribute to the enormous range of phenotypical manifestations observed in NDDs.

1.3. Epigenetic susceptibilities

Recently, chromatin regulation has been recognized as one of the two domains most affected by genetic lesions causative of neurodevelopmental disorders (De Rubeis et al., 2014; Lasalle, 2013; Pinto et al., 2014; Ronan et al., 2013a). This allows to reframe the impact of epigenetic dysregulation on human neural development along with a first structuring classification: i) neurodevelopmental disorders caused by mutations in chromatin regulators (in which epigenetic disruption is originally encoded in a genetic lesion); and ii) neurodevelopmental disorders caused by environmentally-induced epigenetic dysfunction. The two possibilities are not mutually exclusive, as genetically encoded epigenetic vulnerabilities may enhance sensitivity to environmental disruptors and, *viceversa*, the environmentally-induced epigenetic disruption may alter DNA management processes and usher into genetic lesions.

Regardless of which of the two scenarios is prevalent (or exclusive) for a given neurodevelopmental condition, both benefit from a clarification of what epigenetics refers to and of which aspect of its multifaceted meanings is most relevant for investigating neurodevelopmental disorders. We thus refer the reader to recent theoretical systematizations of the concept of epigenetics, including a historical reconstruction of their changes in meaning, which can be briefly summarized as follows (Boniolo and Testa, 2012; Meloni and Testa, 2014). In Waddington's original definition, the epigenotype referred to the intermediate phenomena linking genotype to phenotype, a notion that was couched from the outset in developmental terms, with the graphical rendering of the epigenetic landscape in which differentiation was plotted over a map of progressively restricted and irreversible cell fates induced by developmental cues. This integration of the classical view of embryological epigenesis with genetics paved the way to modern epigenetics (Waddington, 1942). However, over the years, the term has adopted several meanings and nuances, among which three

are the most relevant for our analysis. The first is what we refer to as the 'strong' meaning of epigenetics, defining those phenomena that are inherited across generations of cells (or organisms) independent of underlying changes in DNA sequence. The second is an extension of the first, which makes it relevant also for non-dividing cells or for organisms that do not reproduce and considers as epigenetic those phenotypes that are stably maintained across the lifespan of cells or organisms long after their initial trigger has waned (Beck et al., 2010). Finally, the third is the currently most prevalent but also the shallowest meaning of the word, anchored to a literal reading of the etymology of the term, from the greek επί, epì = "above" and γεννετικός, gennetikòs = "genetics". In this nearly all-encompassing sense, epigenetics is widely and increasingly used as synonymous of gene regulation and de facto equated with chromatin, a discursive move that has proceeded to engulf all of the transcription regulation (and possibly beyond) independent of whether its features show any stability or inheritance (Ptashne, 2007).

Indeed, at least four main domains of chromatin regulation (DNA methylation, histone post-translational modifications, chromatin remodelling and nucleosome positioning) are usually welcomed under the rubric of epigenetics, though only for few of them exists *bona fide* evidence or even just a plausible hypothesis or indeed a rationale for stability and/or inheritance. A case in point is the notion of the histone code itself, which was initially proposed to endow the repertoire of histone post-translational modifications (HPTMs) with the same degree of functional cogency borrowed from the genetic code (Allis and Jenuwein, 2016). The realization of the striking diversity of patterns of co-occurring modifications (Wang et al., 2008) made it however increasingly problematic to pursue the code-based simplification of such a rich array of chromatin functions, ushering into more nuanced but still to be settled explanatory frameworks for the palimpsest of HPTMs, especially given the rapidly evolving knowledge on the degree of their inheritability (Heard and Martienssen, 2014; Probst et al., 2009). While a full account of the debate on what counts as epigenetic is beyond the scope of this work, we consider it essential to clarify the multiplicity of its meanings for a heuristically productive investigation of NDD. Specifically, we argue that for NDDs pathogenesis the most relevant definitions are the first and the second, given the vulnerability and sensitivity of CNS development. Indeed, given the extensive phases of cell proliferation that uniquely characterize human CNS, whether dysregulation in the genome-wide occupancy of a given chromatin mark can be transmitted across development is key, especially depending on what stage the dysregulation becomes manifest. Similarly, also the other strict criterion for adjudicating the epigenetic nature of biological phenomena, namely whether a given phenotype, for example chromatin configuration or transcriptional state, is stably maintained in non-dividing cells even long after the initial trigger has removed, is also paramount, given the protracted, oftentimes life-long survival of neurons generated during embryonic life.

Finally, one last word of critical scrutiny concerns the widespread if inadvertent conflation of the role of histone modifications with that of the enzymes that catalyse them. Given the number of histone gene clusters in mammals (Banaszynski et al., 2010), strict functional experiments that probe the effect of a specific modification by disabling the histone aminoacid targeted by the modification are still unfeasible. The function of a given modification is usually inferred by the phenotype observed upon mutation of the effector enzyme. While this assumption is clearly warranted in many cases, it implies that the impact of mutations in a histone modifier is primarily if not exclusively linked to its downstream consequences on histones. Several lines of evidence point however to a more complex situation. For instance, an elegant study that used Crispr/Cas9 to uncouple the enzymatic from non-enzymatic functions of KMT2C and D found that both enzymes promoted enhancer RNA (eRNA) synthesis and promoter transcription largely independent of their contribution to H3K4 monomethylation (Dorighi et al., 2017; Rickels et al., 2017), inviting caution in the acritical attribution of neurodevelopmental phenotypes to the histonic consequences of mutations in chromatin regulators. Similarly, mice homozygous for a KMT2A allele lacking the catalytic domain are viable and recapitulate only a minor fraction of the major developmental phenotypes (including embryonic lethality per se) observed upon full gene ablation (Terranova et al., 2006).

For these reasons in this review, whenever possible, we highlight the cases in which the first and the second definition of epigenetics apply. However, given the widespread use of the third meaning, whose rubric encompasses many causative genes of NDD, we also discuss its relevance in depth, especially given the fact that chromatin as a whole is a critical domain of dysregulation enriched in ASD and ID causative genes.

2. Histone post-translational modifications

2.1. H3K4 methylation

The overall relevance of lysine 4 of histone H3 methylation (H3K4me) for physiological human brain development is underscored by its significant genome-wide redistribution in neurons from the prefrontal cortex during the first year of life (Cheung et al., 2010) as well as by its remarkable locus-specific redistribution in prefrontal cortex neurons of individuals affected by ASD (Shulha et al., 2012). Several lines of evidence spanning multiple models support the heritability of H3K4 methylation: i) H3K4me is required for the inheritance of the rate of transcription across cell division in *Dictyostelium* (Muramoto et al., 2010); ii) enzymatic complexes of the Trithorax and Polycomb group families remain associated to DNA and re-impose the H3K4me (along with the antagonistic H3K27me) modification patterns that had been erased through DNA replication in Drosophila (Petruk et al., 2012); iii) also in human cells, KMT2A engages in mitotic bookmarking, remaining stably associated to promoters within condensed mitotic chromatin whereby it accelerates their transcriptional reactivation following mitotic exit (Blobel et al., 2009); iv) finally, genetic evidence has shown that mutations in the Trithorax family prevent the maintenance of patterns of gene activation, indicating their key role in sustaining expression programs during lineage specification (Kennison, 1995). Thus, mutations of the enzymes controlling the H3K4 methylation are candidates to have a transgenerational impact, thereby allowing to consider H3K4me as a *bona fide* epigenetic mark, borrowing from the 'strong' definition of epigenetics outlined in the introduction.

In mammals, H3K4 can be mono-, di- or tri-methylated and is associated to different genomic regulatory elements. The deposition of these marks has been linked to the activity of the following ten enzymes displaying different specificities, both regarding the level of methylation and the genome-wide distribution of the modification: KMT2A/B/C/D/F/G, ASH1L, SMYD3, SETD7, and PRMD9. In mammals, the KMT2 family of methyl-transferases is composed by 6 members (KMT2A-G, excluding the catalytically inactive KMT2E), which arose from duplication events during evolution and constitute the catalytic cores of the COMPASS (COMplex of Proteins ASsociated with Set1) complexes (Schuettengruber et al., 2011). These complexes are mainly responsible for H3K4 methylation at promoters and enhancers (Allis et al., 2007). In metazoans, the COMPASS complexes can be grouped in three pairs of paralogs based on their methylase catalytic core: the KMT2A/B, KMT2C/D and KMT2F/G. COMPASS complexes share in fact a set of core subunits (ASH2L, RBBP5, WDR5 and DPY30) while each also contains a set of specific ones (Dou et al., 2006; Wysocka et al., 2005). Moreover, COMPASS complexes contain one of the two lysine demethylases KDM6A and KDM6B (also known as UTX and JMJD3, respectively) (Hong et al., 2007; Xiang et al., 2007) which act as counterpart for the post-translational modifications performed by the Polycomb Repressive Complex 2 (PRC2), H3K27me3 (Czermin et al., 2002).

2.1.1. KMT2A and KMT2B

In vitro, recombinant KMT2A and KMT2B are proficient at mono- and di-methylating H3K4, whereas they display low trimethylation activity. It has been shown, however, that the substrate specificity and activity of holocomplexes can differ significantly from that of bacterially expressed subunits, indicating that *in vivo* the presence of cofactors and/or post-translational modifications of the KTM2 enzymes is likely critical to determine their enzymatic output. This is shown in the paradigmatic example of the oocyte, in which KMT2B is solely responsible for the deposition of bulk H3K4me3 (Andreu-Vieyra et al., 2010). The assessment of H3K4me status upon selective and/or combinatorial KMT2s inactivation is thus a more cogent measure of their cell type-specific function.

Mutations in *KMT2A* and *KMT2B* cause two sharply distinct disease phenotypes, pointing to an only partial degree of redundancy between these two paralogs, a feature that is supported by several lines of evidence: first, mutations in either of the two genes resulted in embryonic lethality with non-overlapping developmental phenotypes (Glaser et al., 2006; Yu et al., 1995); however, KMT2B displayed a surprisingly specific and narrow window of requirement for normal development (Glaser et al., 2009). Second, in embryonic stem cells, KMT2B is selectively required for performing H3K4me3 at bivalent promoters, while KMT2A is redundant (Denissov et al., 2014; Hu et al., 2013). Third, conditional ablation of *Kmt2a* in the murine adult subventricular zone revealed its essential role in neurogenesis (Lim et al., 2009). However, the key neurogenic genes that fail to be expressed upon loss of Kmt2a, such as *Dlx2*, retained normal H3K4me3 but also H3K27me3. Therefore the key function of the KMT2 COMPASS complex, in this instance, is not *per se* the trimethylation of lysine 4 (compensated presumably by KMT2B), but the resolution of the bivalent status instantiated by the demethylation of H3K27me3 (Park et al., 2014). Fourth, depletion of Kmt2a from either mouse postnatal forebrain or the adult prefrontal cortex (PFC) resulted in increased anxiety and impaired working memory, due to failure to sustain the immediate early wave of gene expression required for synaptic plasticity (Jakovcevski et al., 2015). Of note, while the loss of *Kmt2b* in the same CamkII-expression domain also resulted in learning phenotypes (Kerimoglu et al., 2013), its selective ablation from the adult PFC caused only minor cognitive impairment. Instead, loss of *Kmt2b* in the hippocampus impaired memory function, suggesting a brain area-specific action for these enzymes.

In human, mutations in *KMT2A*, previously known as *MLL1*, cause Wiedemann-Steiner syndrome (WSS), characterized by individuals with facial dysmorphysms, intellectual disability, hypotonia, ASD, and developmental delay (Jones et al., 2012; Sun et al., 2017). In an interesting example of phenotypic and genotypic convergence, WSS cases have also been reported harbouring mutations in *KMT2A* and subunits or regulators of the cohesin complex *SMC1A* and *SMC3*, which are responsible for a subset of cases of Cornelia De Lange Syndrome (CdLS), a multisystemic NDD defined by intellectual disability, facial dysmorphism, pre- and post-natal delay, microcephaly, heart defects, upper limb abnormalities, and genitourinary anomalies (Yuan et al., 2015). Specularly, *KMT2A* was found mutated in an individual diagnosed with CdLS. Wiedemann-Steiner syndrome is usually caused by nonsense and frame-shift mutations; nevertheless, some missense mutations were also reported both in the CXXC domain and in the PHD finger domain, the latter being a mediator of protein-protein interactions. Subjects affected by missense mutations have a more severe clinical phenotype, featuring seizures, microcephaly, and immunodeficiency featuring low levels of immunoglobulins. Taken together, these findings suggest that haploinsufficiency of the catalytic activity is not the only mechanism through which a mutation in *KMT2A* can cause a developmental phenotype, as missense mutations in other domains might also impair specific GRNs involved in hematopoiesis and the immune system (Stellacci et al., 2016).

Although KMT2A and KMT2B perform the same histone modification, they have different physiological roles. This is reflected by the fact that mutations in *KMT2B* also cause an early-onset dystonia, accompanied by microcephaly, and mild-to-moderate ID in two thirds of the affected individuals; brain anomalies such as symmetrical hypointensity in the globus pallidi were reported as well (Meyer et al., 2016; Zech et al., 2016).

It is now evident that mutations in *KMT2A* or *KMT2B* yield clearly different phenotypes, pointing to the notion that H3K4me3 dysregulation is not *per se* pathological; it is rather the lack of either protein that affects the deposition of the mark at enzyme-specific genomic regions, thus affecting different, specific GRNs.

2.1.2. KMT2C and KMT2D

KMT2C and KMT2D perform H3K4 monomethylation (H3K4me1), a hallmark of enhancer regions (Kaikkonen et al., 2013; Lee et al., 2013), through their SET domain. The COMPASS complex containing KMT2C and D also includes KDM6A (already known as UTX), whose demethylase activity counteracts the PRC2 axis and renders the H3K27 substrate available for p300/CBP-mediated acetylation (Wang et al., 2016). Consequently, the combined action of the mono-methylation deposition and UTX activity was shown to control cell fate transitions of macrophages and ESCs through enhancer activation (Kaikkonen et al., 2013; Wang et al., 2016)

KMT2C and KMT2D also have partially redundant roles. The deletion of either gene affects global H3K4me1 deposition only marginally. The resulting phenotypes in mouse models are remarkably different: *Kmt2c* depleted mice die after birth without morphological alterations, whereas *Kmt2d* KO mice die during embryonic development, at embryonic stage E9.5, due to defects in heart development, adipogenesis, and myogenesis. In addition, the conditional depletion of *Kmt2d* in somatic precursors showed decreased brown adipose tissues formation and muscle mass levels, causing the death of pups by breathing dysfunction (Lee et al., 2013), thus indicating a tissue-specific action for each enzyme.

The effects of KMT2C and D on gene transcription are not solely caused by their catalytic activity: it was recently shown that the absence of both KMT2D and C has an impact on Pol II occupancy at enhancers and on enhancer RNA (eRNA) transcription, resulting in the downregulation of target genes. On the contrary, the presence of two catalytically inactive genes leads to the loss of H3K4me1 and reduction of H3K27Ac with minor effects on eRNA and target genes transcription. Therefore, KMT2C-D mediate long-range interactions between enhancer and target genes independently of their catalytical activity (Dorighi et al., 2017; Rickels et al., 2017).

Mutations in KMT2D cause 60-70% of Kabuki syndrome (KS), whereas 10% of KS are linked to mutations in KDM6A. KS is a rare multisystemic NDD first described in 1981 (Kuroki et al., 1981; Niikawa et al., 1981) and it is mainly characterized by stereotypical facies, mild to moderate ID, congenital heart defects, microcephaly, immunological disorders and endocrinological alterations (Lederer et al., 2012; Ng et al., 2010). The remaining 20% of cases are caused by mutations in unidentified genes (Miyake et al., 2013). Given the involvement of KMT2D and KDM6A in the deposition of enhancer-defining marks, KS was defined as enhanceropathy (Smith and Shilatifard, 2014). Studies in a catalytically inactive *Kmt2d*$^{+/\beta Geo}$ mouse model demonstrated genome-wide deficiency of H3K4me3, impaired adult neurogenesis in the dentate gyrus (DG), and hippocampal memory defects, all of which were rescued by the inhibition of histone deacetylases (Bjornsson et al., 2014). More recently, quantitative imaging of adult neurogenesis in *Kmt2d*$^{+/\beta Geo}$ mouse models revealed alterations in neural stem cells (NSCs) and neural progenitor cells (NPCs). Single-cell expression profiling of adult NPCs revealed divergent maturation trajectories that mirror the bifurcation of proliferation pathways, suggesting that the pathophysiological basis of ID in KS involves aberrations in NSC cell cycle, as well as proliferation, maturation, and integration defects of NPCs in the adult hippocampus (Benjamin et al., 2017). However,

according to the last discoveries made by Dorighi and Rickles, since these studies employed a mouse model which does not mimic the haploinsufficiency, it is possible that it might not completely recapitulate KS pathogenesis, as the complete removal of the entire gene product leads to a more severe phenotype when compared to the inactive enzyme (Dorighi et al., 2017; Rickels et al., 2017). Knockdown experiments in *D. rerio* underlined the involvement of KDM6A and KMT2D in the development of brain and heart and recapitulated the cranio-facial anomalies typical of KS (Van Laarhoven et al., 2015). Although KMT2C and D have a partially redundant effect (Lee et al., 2013), only KMT2D-dependent effects are responsible for KS, as *KMT2C* has never been found mutated in this syndrome. Instead, *KMT2C* was found mutated in 4 out of 9 patients with Kleesftra Syndrome (see below), who lacked an *EHMT1* mutation (Kleefstra et al., 2012). Additionally, copy number variants of *KMT2C* were associated with ASD risk (Sanders et al., 2015). The first enzyme discovered to be able to demethylate lysine residues was *KDM1A* (aka LSD1), which can remove H3K4me1 and H3K4me2 but does not demethylate H3K9, H3K27, and H4K20 (Shi et al., 2004). Notably, *KDM1A* mutations have been linked to a clinical phenotype related to the KS and KBG syndromes, usually caused by *ANKRD11* mutations (Chong et al., 2016; Tunovic et al., 2014), as well as to severe non-syndromic intellectual disability (Rauch et al., 2012). In addition, *KDM5B*, which removes H3K4me1, me2, and me3, has not been found mutated itself but represses *FOXG1* and *HOXA5*. Respectively, *FOXG1* was found to be causative of the Rett syndrome, while *HOXA5* is a deregulated gene both in Kabuki and CHARGE (see below) syndromes (Tan et al., 2003; Yamane et al., 2007).

2.1.3. KMT2F and KMT2G

Recombinant KMT2F (known as *SETD1A*) and G deposit all three combinations of H3K4me *in vitro*, but *in vivo* they are responsible for the bulk deposition of H3K4me3, which is found at transcription start sites (TSSs) (Deng et al., 2013; Shilatifard, 2006). Both KMT2F and G have an essential role in the early embryonic development and KMT2F depletion is embryonic lethal (Bi et al., 2011; Bledau et al., 2014; Tusi et al., 2015).

KMT2F mutations are associated with schizophrenia (Takata et al., 2014, 2016). Regarding *KMT2G*, it is included with 30 other genes in a region on 12q24.31, whose microdeletion causes a syndromic NDD characterized by ID, developmental delay, seizures and dysmorphic features. By focusing only on deleted regions shared among individuals, the range of responsible genes was restricted to five genes, among which *KMT2G* was suggested as a key actor (Palumbo et al., 2015). Moreover, a noncoding regulatory region of *HCFC1*, which is a mediator of both KMT2F/KMT2G and KMT2A (Wysocka et al., 2003; Yokoyama et al., 2004), is mutated in in individuals with a Non-syndromic ID (Huang et al., 2012).

2.2. H3K9, H3K36, and H4K20 modifications

Other less well-studied histone methylation residues are H3K9, H3K36, and H4K20. Their degree of inheritability is still undetermined. Although it has been shown that H3K9me is quickly restored after mitotic division (Steffen and Ringrose, 2014) virtually nothing is known about the inheritability of H3K36 and H4K20. In *C. elegans*, it was found that MES-4 is responsible for H3K36me3 deposition (Rechtsteiner et al., 2010). Moreover, it was shown that H4K20me is not properly inherited while it is restored during the cell cycle (Pesavento et al., 2008; Scharf et al., 2009). H3K36me3 is deposited throughout the gene body of active genes to prevent spurious transcription initiation. H3K36me3 recruits both the RPD3S complex, which catalyses deacetylation of transcribed regions, and DNMT3B, which catalyses DNA methylation (Carrozza et al., 2005; Li et al., 2007; Neri et al., 2017). H3K9 methylation displays a wide range of functions in the genome. H3K9me1 is found at the TSS of transcribed genes (Barski et al., 2007), H3K9me2 is associated with X-inactivation and transcriptional repression (Rougeulle et al., 2004; Wang et al., 2008), whereas H3K9me3 is associated with gene silencing and heterochromatin through the recruitment of DNMT3B and HP1 (Lehnertz et al., 2003). Likewise, H4K20 methylation is associated to different chromatin statuses. H3K20me1 and H4K20me2 are found on active genes, and they are relevant for the cell cycle, though they have different distribution (Beck et al., 2012; Kuo et al., 2012; Wang et al., 2008). In contrast, H4K20me3 is associated to gene and transposone silencing (Schotta et al., 2004; Wang et al., 2008). Mutations in the genes capable of performing these three HPTMs are causative of NDD.

EHMT1 catalyses mono- and di-methylation of H3K9 and it is able to recruit PRC2 (Mozzetta et al., 2014); additionally, it is capable of activating gene expression via an enzyme-independent mechanism (Koemans et al., 2017). In humans, it is mainly expressed in the fetal and adult brain, kidney, spleen, and thymus (Kurotaki et al., 2001).

Mutations on *EHMT1* cause Kleefstra syndrome (KLS), which is defined by severe ID, distinctive facies, hypotonia, microcephaly, seizures and heart defects (Iwakoshi et al., 2004; Kleefstra et al., 2006). KLS has also been linked to mutations in *SMARCB1*, *MBD5*, *NR1I3*, and *KMT2C* (Kleefstra et al., 2012) thus constituting another example of phenotypic convergence. Such a convergence is conserved across evolution, as the *D. melanogaster* paralogs of EHMT1 and KMT2C/D, *G9a* and *Trr*, have common direct targets (Koemans et al., 2017). Nevertheless, observations regarding the function in CNS development of Ehmt1 in rodents are nuanced: *Ehmt1*$^{+/-}$ mice displayed cognitive deficits such as learning and memory issues, and, at the synaptic level, the dendritic arborisation and the number of mature spines were reduced in hippocampal CA1 pyramidal neurons (Balemans et al., 2013). However, more recently, learning and memory tasks assessed in the same *Ehmt1*$^{+/-}$ mice in a low-stress and unaversive environment showed unhindered general learning deficits. The authors suggested that the previous result could be due to enhanced anxiety in *Ehmt1*$^{+/-}$ mice and only to a lesser extent to impaired cognitive ability. Furthermore, an increase in proliferation in the subgranular zone of the dentate gyrus (assessed by BrdU incorporation) and a simultaneous improvement in spatial learning (assessed by location discrimination tasks) were observed in this model (Benevento et al., 2017), thus making the link between EHMT1 and cognitive defects less obvious in mice.

EHMT1-deposited methylation is counteracted by the PHF8 demethylase, which removes the H3K9-me1, me2, and H4K20me1 marks. *PHF8* is known to be important for brain and craniofacial development in *D. rerio* (Qi et al., 2010), and it is altered in an X-linked mental retardation syndrome associated with cleft lip and palate (Laumonnier et al., 2005; Siderius et al., 1999).

The family of NSD enzymes (coded by *NSD1*, *NSD2*, and *NSD3*) is responsible for a variety of H3 and H4 modifications, and their mutations cause Sotos syndrome and Beckwith Wiedemann syndrome (*NSD1*), Wolf-Hirschhom syndrome (*NSD2*) and hereditary acute myeloid leukemia (*NSD3*).

In the presence of nucleosomal H3, NSD1 performs H3K36 and H4K20 methylation (Li et al., 2009). Moreover, disruption of the SETD2 enzyme, which deposits H3K36me3 (Sun et al., 2005), causes Luscan-Lumish syndrome (LLS) and a Sotos-like syndrome. LLS is also an overgrowth syndrome, featuring ID, ASD, developmental delay and seizures (Lumish et al., 2015; Luscan et al., 2014). Despite the involvement in the deposition of the same histone modifications, loss of function murine models for *Nsd1* and *Nsd2* exhibit different phenotypes. *Nsd1* depleted mice do not complete gastrulation (Rayasam et al., 2003), while *Nsd2* knockout mice display anomalies typical of WHS but die after 10 days (Nimura et al., 2009).

Sotos syndrome and Beckwith-Wiedemann syndrome (BWS), caused by mutations in NSD1, both feature overgrowth. Sotos syndrome is characterized by rapid growth, ID, macrocephaly, cerebral, gigantism and increased risk of tumor formation (Le Marec et al., 1999;

Maldonado et al., 1984; Nance et al., 1990). BWS instead is highly heterogeneous and can be caused also by alterations to the imprinted regions 11p15.5 and 11p15.4 loci, which encompass *ICR1*, *H19*, *KCNQ1OT1*, and *CDKN1C* (Shuman et al., 1993). Both BWS and Sotos syndromes are associated with a predisposition to cancer (Mussa et al., 2016).

Conversely, NSD2 preferentially performs H3K36me2, and individuals with Wolf-Hirschhom syndrome (WHS) are affected by severe growth retardation, ID, microcephaly, severe craniofacial anomalies and cardiac septal defects (Battaglia et al., 2015).

2.3. H3K27and H2A119 modifications

The activating histone modifications described above are counteracted by the Polycomb Group of proteins (PcG), mainly through monoubiquitination of Lys 119 of histone H2A (H2AK119Ub) and trimethylation of H3K27 (H3K27me3). These two HPTMs are catalysed by Polycomb Repressive complex 1 (PRC1) and Polycomb Repressive complex 2 (PRC2), respectively. H3K27me3 is a paradigmatic example of inherited modification across cell generations. Epigenetic memory was discovered in *D. Melanogaster* uncovering a mechanism through which Polycomb and Trithorax mediate the inheritance of the GRNs established during embryo development through the antagonistic repression and activation of homeotic genes. The marks regulated by these two axes allow the maintenance of cell identity through development and in the adult, long after the initial stimulus (Hathaway et al., 2012; Steffen and Ringrose, 2014), thus ascribing this regulation to the strong epigenetic definition.

2.3.1. PRC1

PRC1 is a heterogenous complex which can have both a canonical composition and a non-canonical one. The core of PRC1 comprises four components: RING, CBX, PCGF1 and HPH. There are two catalytical homologues, RING1 and RING2, although RING2 is more prevalent (Wang et al., 2004). Moreover, there are three HPH homologues (HPH1, HPH2, HPH3); five CBX (CBX2, CBX4, CBX6, CBX7, CBX8); and six PCGF (PCGF1-6). The CBX proteins are able to bind to the H3K27me3 deposited by PRC2, thereby enabling the recruitment of PRC1 on PRC2 targets. The lack of a CBX protein defines the non-canonical PRC1, which was instead proved to undergo H3K27me3-independent recruitment (Gao et al., 2012; Tavares et al., 2012; Vandamme et al., 2011).

PRC2-associated mutations and effects constitute a good example of convergence as characterized by the network of effects. Although no dominant germline mutations have been described for the catalytic components of PRC1, autosomal recessive mutations of *PHC1* (previously known as *HPH1*) cause a form of microcephaly with short stature, reported in two Saudi siblings (Awad et al., 2013). Moreover, HPH1 depletion was associated with decreased histone H2A ubiquitination and Geminin overexpression (Awad et al., 2013). Geminin mutations are in turn associated with Meier-Gorlin syndrome, an autosomal dominant disorder featuring dwarfism (Burrage et al., 2015). Another PRC2 component, *PCGF4* (also known as *BMI1*), was shown to be essential for the development of the cerebellum (Leung et al., 2004). The network of vulnerability also extends to interactors of PRC1 such as *AUTS2*, whose mutations are responsible for an autosomal dominant form of syndromic mental retardation. Individuals carrying *AUTS2* mutations have ID along with microcephaly, ASD, short stature, cerebral palsy, and facial dysmorphisms (Beunders et al., 2013; Nagamani et al., 2013). The PRC1-AUTS2 complex acts as positive gene expression regulator, especially for genes expressed in the central nervous system, thus expanding the repertoire of functions for PRC1 beyond repressing transcription. Within this complex, the component Casein Kinase II (CK2), a key element of the Wnt signaling (Gao and Wang, 2006), inhibits PRC1 activity. Upon binding to chromatin, AUTS2 recruits CBP/p300,which acetylate histone tails in the target region (Gao et al., 2014). Moreover, mutations in the gene *CSNK2A1*, which codes for CK2, cause the Okur-Chung syndrome, characterized by ID, microcephaly, cortical malformations, and variable facial dysmorphisms (Okur et al., 2016).

2.3.2. PRC2

PRC2 is composed of the catalytically active and mutually exclusive EZH1 and EZH2, the two enzymes capable of depositing H3K27me3 (Czermin et al., 2002; Kuzmichev et al., 2002), and the subunits EED and SUZ12 (Laible et al., 1997; Margueron et al., 2008). The two catalytic components have a different distribution, as EZH2 is mainly expressed in undifferentiated cells and during embryogenesis, while EZH1 is more ubiquitously expressed in adult and quiescent cells. Moreover, EZH2 has stronger catalytic activity than EZH1 (Margueron et al., 2008; Shen et al., 2008). Accordingly, the catalytic subunit EZH2 together with EED and SUZ12 are essential for development, as null mutations result in embryonic lethality, displaying severe developmental and proliferative alterations (O'Carroll et al., 2001; Pasini et al., 2004).

The propagation of H3K27me3 through cell divisions is mediated by the association of the PRC2 complex to the Polycomb-responsive elements (PREs) in the S-phase, during which it recognizes previously methylated histones through EED, and modifies the new ones (Hansen et al., 2008; Margueron et al., 2009). In a way that indicates the most literal definition of epigenetics, H3K27me3 has a primary role in the inheritance of the repressed transcriptional states, as shown in *D. melanogaster* where the repressed state of HOX genes is maintained even after the excision of the PREs from the genome (Coleman and Struhl, 2017).

The fine regulation of the PRC2 axis, mediated by the deposition and removal of H3K27me3, is a key feature in neurodevelopment (Burgold et al., 2008, 2012; Fragola et al., 2013; Park et al., 2014; Testa, 2011). The two enzymes that counteract the PRC2 axis are KDM6A and KDM6B. They are mutated in Kabuki Syndrome (see above), and in individuals with an autosomal recessive form of mental retardation (Kuss et al., 2011; Najmabadi et al., 2011) respectively. In addition, both *KDM5B*, *KDM6A* and *KDM6B* copy variants are associated with ASD risk (Sanders et al., 2015). In particular, EZH2 has a clear role during neurodevelopment, as its knockdown during neurogenesis causes alterations in the migration of the maturating neurons, due to the de-repression of Reelin (Zhao et al., 2015). Moreover, the knockdown of *EZH2* in the neural tube of chicken embryos leads to defects in the apicobasal polarity of neuroblasts, thus causing impaired neural tube organization, which is mediated by the cell cycle regulator $p21^{WAF1/CIP1}$ (Akizu et al., 2016). This evidence hints to a role of EZH2, and more broadly of PRC2, in neurodevelopment, but an exhaustive picture of how its fine regulation occurs throughout human neurogenesis still needs to be drawn. More recently, an elegant study using mouse ESCs proposed a potential mechanism for this global regulation by showing that poised enhancers establish physical interactions with their target genes in a PRC2-dependent manner (Cruz-Molina et al., 2017). Loss of PRC2 in undifferentiated mESCs led to neither the activation of poised enhancers nor the induction of their putative target genes in undifferentiated ESCs. Instead, upon mESC differentiation, the loss of PRC2 severely and specifically compromised the induction of major anterior neural genes, representing poised enhancer targets. The authors suggest that polycomb proteins facilitate neural induction by providing major anterior neural loci accessibility through a permissive regulatory topology, which may constitute a “default” model of neural induction (Cruz-Molina et al., 2017).

Mutations in *EZH2* cause Weaver Syndrome (WVS), an overgrowth syndrome characterized by ASD and accelerated osseous maturation, developmental delay and characteristic facies (Gibson et al., 2012; Weaver et al., 1974).WVS differs from Sotos syndrome (see above) by the typical facies and for an advanced carpal bone development. Moreover, individuals with WVS, negative for *EZH2* mutations, harbour mutations in the essential subunits *SUZ12* and *EED* (Cohen and Gibson,

2016; Cooney et al., 2017; Imagawa et al., 2017; Tatton-Brown et al., 2017). According to the overgrowth and macrocephaly phenotypes observed in the Weaver syndrome, conditional KO of *EZH2* induces an accelerated proliferation of neuronal precursor in the cerebral cortex, which results in a premature increase of neuron numbers and differentiation to astrocytes, at the expense of the number of neurons at birth (Pereira et al., 2010).

2.4. Histone Acetylation

Histone acetylation is regulated by the dynamic balance between Histone acetyltransferases (HATs), and Histone deacetylases (HDACs) (Haberland et al., 2009). The negative charge of the acetyl group can neutralize the lysine positive charge, thus relaxing the nucleosome structure that becomes more accessible to the transcriptional machinery (Zhang et al., 2015). Moreover, the acetylated lysines can be "read" by the bromodomain-containing proteins, that are therefore able to mediate the interaction with other chromatin remodelling complexes and transcription factors (TFs). Lysine acetylation is associated with active promoters and active enhancers (Lawrence et al., 2016; Pradeepa, 2017) and with transcriptional memory as shown in *S. pombe*, in which gene expression can be triggered and maintained by transient exposure to HDAC inhibitors (Ekwall et al., 1997). Human HATs can be divided into two major groups based on their sub-cellular localization: i) Type A HATs, which contain a bromodomain and reside in the nucleus, where they acetylate nucleosomal histones, and which are further subdivided in three classes based on their homology, Gcn5/PCAF, MYST and p300/CBP; ii) Type B HATs, which lack the bromodomain and reside in the cytoplasm where they acetylate newly synthesized histones (Bannister and Kouzarides, 2011). In humans, 18 HDACs deacetylate histones and non-histone proteins and they are divided in four sub-classes (I-IV) (Seto and Yoshida, 2014).

CBP and p300 associate in the CBP/p300 complex, responsible for H3K27, H3K56, H3K64 and H3K122 acetylation (Bannister and Kouzarides, 1996; Das et al., 2009; Di Cerbo et al., 2014; Ogryzko et al., 1996; Tropberger et al., 2013). Mutations in *CREBP* and *EP300* are responsible for Rubinstein–Taybi syndrome (RSTS). Mutations in *CREBP* explain around 50–70% of RSTS cases. RSTS main features are ID, microcephaly, growth deficiency, dysmorphic facies, and broad thumbs and halluces. Moreover, RSTS individuals have an increased risk of developing cancer (Hennekam, 2006; RUBINSTEIN and TAYBI, 1963). Due to the high pleiotropy of CBP/p300, the human molecular pathogenesis mechanism is not clear. The first study on human samples showed hypoacetylation of H2A and H2Bin lymphoblastoid cell lines, which could be rescued by HDAC inhibitors (Kazantsev et al., 2008).

A prominent interactor of p300/CBP is YY1 (Lee et al., 1995), a multifunctional Zinc Finger able to repress or promote gene expression depending on the interactors present in each cell state, and mediates long-range DNA interactions (Atchison, 2014). YY1 has a fundamental role in development since its deletion results in embryonic lethality (Donohoe et al., 1999). Moreover, YY1 mediates gene activation interacting with the chromatin remodeling complex INO80 (Cai et al., 2007; Vella et al., 2012; Wu et al., 2007). Recently, YY1 mutations have been identified as responsible for Gabriele-DeVries syndrome (GADVES), a syndromic intellectual disability characterized by growth retardation, various congenital malformations, and feeding problems (Gabriele et al., 2017). In human cells, YY1 haploinsufficiency leads to a widespread loss of H3K27Ac, and gain of H3K27me3 selectively in enhancer regions that were occupied by YY1. These observations suggested GADVES to be an enhanceropathy caused by a defect of long-range enhancer-promoters interaction mediated by YY1 (Gabriele et al., 2017). Accordingly, research has recently shown that YY1 directly regulates enhancer-promoter looping (Weintraub et al., 2017). Moreover, YY1 interacts with CTCF, they co-occupy genomic regions (Schwalie et al., 2013), and, along similar lines of evidence, an independent study has showed that YY1, together with CTCF, mediates interaction between enhancers and promoters of target genes involved in neuronal differentiation (Beagan et al., 2017). Consistently with this role and YY1 interaction with CTCF, mutations in the latter cause intellectual disability with microcephaly, growth retardation and heart defects (Gregor et al., 2013).

Regarding the MYST family, KANSL1 acts as a scaffold in the Non-Specific Lethal (NSL) complex, in which MYST1 performs both H4K5, H4K8, and H4K16 acetylation (Su et al., 2016), and acetylation of non-histonic proteins such as p53 (Sykes et al., 2006). Moreover, KANSL1 interacts with the COMPASS subunit WDR5 (Dias et al., 2014), and H4K16Ac promotes H3K4me2 deposition by activating the COMPASS/KMT2A complex (Zhao et al., 2013). In humans, mutations in *KANSL1* cause Koolen-de Vries syndrome (KDVS). The main features of KDVS are hypotonia, moderate to severe ID, distinctive facies, and a friendly behaviour (Koolen et al., 2012). Interestingly, a microduplication of the same region is associated with ASD, a phenotype opposed to the microdeletion causing KDVS (Grisart et al., 2009).

HDAC8, a Class I deacetylase, whose *in vitro* substrates are H3 and H4 (Hu et al., 2000), is responsible for a variant of Cornelia de Lange syndrome (see above). However, *in vivo*, HDAC8 is now known to deacetylate non-histone proteins (Wolfson et al., 2013). In addition, the phenotype of the KBG syndrome is thought to be mediated by the ability of *ANKRD11* to interact and activate HDAC3 (Gallagher et al., 2015).

2.5. Histone phosphorylation

Like histone acetylation, histone phosphorylation is highly dynamic. Hydroxyl- containing aminoacids, such as serine and threonine, can be phosphorylated and dephosphorylated. The best-characterized phosphorylation site on histones is the serine 10 of H3 (H3S10), which is associated with gene activation (Ivaldi et al., 2007; Zippo et al., 2007). A complete review of this modification and its role in the CNS can be found elsewhere (Banerjee and Chakravarti, 2011; Maze et al., 2013). So far, only a few NDDs have been associated to this histone modification. Mutations in *RPS6KA3*, which codes for a H3S10 kinase (RSK2), cause Coffin–Lowry syndrome, a rare X-linked condition associated with severe mental retardation, skeletal and cardiac defects, movement alterations, growth retardation, craniofacial, dental and digital abnormalities, auditory and visual defects (Marques Pereira et al., 2010). In addition, mutations in the gene for RSK4, another H3S10 kinase, have been associated to an X-linked form of mental retardation, though the original observation awaits further confirmation (Yntema et al., 1999).

3. Chromatin remodelling

There are four main families of ATP-dependent chromatin remodeling complexes: the SWI/SNF (known as the BAF complex in human, from Brg/Brm-associated factor), INO80, ISWI and the CHD family. These families use ATP to move nucleosomes laterally on DNA, to exchange nucleosomes and to reduce the DNA-nucleosome interaction. Chromatin remodelers target specific nucleosomes close to promoter regions where they control both gene repression and activation (de Dieuleveult et al., 2016), and are involved in the inheritance of the chromatin state and the maintenance of transcriptional memory. As a pivotal example, experiments in yeast showed that the maintenance of the expression of GAL genes is mediated by the incorporation of H2A.Z, mediated by SWI/SNF (Margueron and Reinberg, 2010). Mutations in the above-mentioned chromatin players highlight their importance in early development and cell cycle control. In mice, homozygous mutations in SWI/SNF components such as *Brg1* or *Brm* are embryonic lethal or lead to increased cell proliferation, respectively; ablation in the ISWI and CHD components results in death before birth (de la Serna et al., 2006). Chromatin remodelling is also involved in the control of long-range chromatin interactions, as there is strong evidence for the

involvement of ISWI components in mediating cage-like structures crucial for IL-2Rα silencing in T-Cell development (de la Serna et al., 2006).

Several chromatin remodelling complexes have key roles in the formation and function of the brain. Among the best-studied ones are the BAF complexes, which regulate neurite axonal maturation and arborization. Many BAF complex subunits are involved in the nervous system development in processes such as axonal differentiation, pyramidal layer-specific identity acquisition, gliogenesis and oligodendrogenesis repression, and in the establishment of learning and memory (Ronan et al., 2013b; Sokpor et al., 2017). Moreover, during early phases of development, the SMARCA4 complexes maintain the stemness of neuronal progenitors through the inhibition of genes responsible for neuronal differentiation, mediating the interaction of repressor element 1-silencing transcription factor (REST) with chromatin (Ooi et al., 2006). In addition, a targeted deletion in the nervous system of *Brg*, the ATPase subunit of SWI/SNF, causes defects in neural tube closure and smaller brains with cerebellum agenesis (Lessard et al., 2007).

As a notable example of convergence, heterozygous mutations identified in several components of the BAF complex (SMARCA2, SMARCA4, SMARCB1, SMARCE1, ARID1A and ARID1B) lead to distinct but largely overlapping intellectual disability syndromes referred to as"SWI/SNF-related ID syndromes" (Kosho et al., 2013; Santen et al., 2013). The overlap is evident when considering that haploinsufficient mutations lead to severe intellectual disability and developmental abnormalities regardless of the affected subunit, pointing to a critical role of this complex in early stages of brain development (Vogel-Ciernia et al., 2013; Vogel-Ciernia and Wood, 2014). Specifically, mutations of *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1* and *SMARCE1* cause Coffin-Siris syndrome (CSS) which is a multisystemic disorder characterized by ID, dysmorphic facies, microcephaly, development delay, congenital heart defects, sparse scalp hair, hypoplasia of the fifth digit, and spinal anomalies (Vergano and Deardorff, 2014; Wieczorek et al., 2013). Moreover, mutations in the TF *SOX11*, which is regulated by PAX6-SMARCA4, have been found in a cohort of CSS individuals with a milder phenotype (Ninkovic et al., 2013; Tsurusaki et al., 2014). *SOX11* is expressed exclusively in fetal and adult human brain and adult human heart (Tsurusaki et al., 2014), thus potentially explaining the clinical manifestations of these patients.

SMARCA2 mutations cause Nicolaides-Baraitser syndrome (NBS), which resembles some clinical features of CSS. Individuals affected by the NBS are characterized by severe ID, microcephaly, seizures, short stature, sparse scalp hair and dysmorphic facies (Sousa et al., 2009). NBS can be distinguished from the CSS by the lack of hypoplasia of the fifth digit and the presence of swelling of the finger joints, broad terminal phalanges, short metacarpals and less common internal organ malformation (Sousa et al., 2009).

ADNP, an interactor of the SWI/SNF complex, is mutated in the SWI/SNF-related autism syndrome. ADNP C-terminal domain binds the fundamental components SMARCA4 and SMARCA2, which are the two core ATPase-subunits, and ARID1A (Mandel and Gozes, 2007). This syndrome encompasses ASD and mild to severe ID, along with several other clinical manifestations such as hypotonia, feeding problems, dysmorphic facies, short stature, hand abnormalities, recurrent infections and a range of cardiac defects (Helsmoortel et al., 2014; Vandeweyer et al., 2014). In mice, the depletion of Adnp is embryonic lethal, and the heterozygous model is affected by cognitive deficits and neurodegeneration (Vulih-Shultzman et al., 2007).

Mutations in *CHD7* are responsible for CHARGE syndrome (Sanlaville et al., 2005). The acronym "CHARGE" describes the most recurrent clinical phenotypes: Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia, Ear abnormalities (Källén et al., 1999). CHD7 interacts with active enhancers to modulate cell-specific gene expression (Schnetz et al., 2010). Given the common embryological origin of affected tissues, CHARGE syndrome is thought to be caused by abnormalities in Neural Crest Stem Cells development (NCSC). Accordingly, CHD7 is required for NCSC differentiation and its knockdown impairs NCSC migration (Bajpai et al., 2010). Moreover, using NCSCs differentiated from CHARGE patients-derived iPSCs, it has been described both a transcriptional and migratory phenotype that supports the NCSCs involvement in CHARGE pathogenesis (Okuno et al., 2017).

Moreover, CHD7 was shown to interacts with three of the COMPASS complexes core subunits (WDR5, ASH2L, and RbBP5) (Schulz et al., 2014) which supports a link between histone methylation and chromatin remodeling during neurodevelopment. Consequently, although CHARGE syndrome and KS are two different pathologies, their clinical overlap is mirrored by a molecular link that suggests common downstream GRNs. Moreover, DNA-methylation analysis from whole blood of KS and CHARGE individuals identified a shared gain of DNA methylation at *HOXA5*, which can justify a part of the clinical overlap between the two syndromes (Butcher et al., 2017). This molecular and clinical overlap suggests a NCSCs alteration also in KS pathogenesis.

More recently CHD8 has been associated with ASD (O'Roak et al., 2012). After a "*genotype first*" investigation in a cohort of children with ASD or developmental delay, *CHD8* was found mutated in a subset of children with similar clinical features. Individuals with *CHD8* mutations had macrocephaly, ASD, high stature, hypertelorism, prominent supraorbital ridge, down-slanted palpebral fissures, ID, attention deficits, sleep and gastrointestinal problems (Bernier et al., 2014). Studies in *D. rerio* suggest that the neurological features may be related to a reduction of post-mitotic enteric neurons following *CHD8* disruption.

In a human model of neural precursor cells, *CHD8* was shown to regulate pathways associated with ASD (Sugathan et al., 2014). More recently, two studies described the differentiation in early cortical neurons, neural progenitors, and cortical organoids derived from induced Pluripotent Stem Cells engineered to carry CHD8 mutations, to address the effect of *CHD8* homozygosity (Wang et al., 2015, 2017). A Gene Ontology analysis performed on the sets of differentially expressed genes revealed a significant enrichment in categories related to neurodevelopment. In particular, the authors identified some recurrently upregulated genes, relevant for neurodevelopment, such as the non-coding RNA *DLX6-AS1*, *DLX1*, and *TCF4*. Notably, *DLX6-AS1* regulates GABAergic interneurons development (Berghoff et al., 2013). The transcription factor *DLX1*, together with its homologous *DLX2*, had already been associated with ASD (Liu et al., 2009). Also, *TCF4* is a TF already known for a corneal dystrophy and the Pitt-Hopkins syndrome, another severe NDD (Zweier et al., 2007).

Microcephaly is a feature of both CSS and NBS. This phenotype is thought to be caused by a premature depletion of the neuronal precursor, as a consequence of the deletion of the BAF subunits. As opposed to the PRC2 axis and the role of CDH8, BAF complexes are negative regulators of the Wnt/β-catenin pathway. This molecular asymmetry is also present at the clinical level: Weaver syndrome individuals and *CDH8* mutation carriers have macrocephaly (Ronan et al., 2013b), which is also a hallmark feature of Okur-Chung syndrome, caused by mutations in CK2 (see above). Thus, the direction of cephalic abnormalities seems to be tightly linked to the direction of the derangements in the regulation of the Wnt/β-catenin pathway, underscoring how the fine regulation of transcriptional programs orchestrated at different layers of epigenetic regulation, such as chromatin architecture and histone modifications, is crucial for proper development.

Recently, YY1AP1, a component of the INO80 complex and interactor of YY1, was reported as the cause of Grange syndrome and a fibromuscular dysplasia-Like vascular disease that encompasses arterial and heart defects, bone fragility, brachydactyly, learning disabilities, and borderline ID (Guo et al., 2017).

4. DNA methylation

DNA methylation (DNAm) was the first epigenetic modification identified (HOTCHKISS, 1948) and constitutes the best example of hereditable epigenetic mark. The methylation of cytosine to 5-methyl-Cytosine (5mC) is propagated to daughter cells thanks to the semi-conservative DNA replication, and fully restored by the maintenance enzyme DNMT1 which preferentially methylates hemimethylated sites (Hermann et al., 2004). *De novo* methylation is performed DNA methyltransferases DNMT3A and DNMT3B (Bestor, 2000; Okano et al., 1999). Several lines of evidence underscore the fundamental role of these enzymes: Dnmt1 depletion in mice leads to embryonic lethality; Dnmt3a and Dnmt3b depleted mice die several weeks after birth and in utero, respectively (Margueron and Reinberg, 2010; Okano et al., 1999). Classically, 5mC was thought to be deposited only at CpG nucleotides. However, the existence of non-CpG DNAm, which becomes the prevalent methylation mark in the mature nervous system (Guo et al., 2013; Lister et al., 2009, 2013), is now well established. The removal of 5mC is mediated by a sequential oxidation process performed by a class of dioxygenases collectively named TET (ten-eleven translocation) (Tahiliani et al., 2009), which oxidate 5mC to 5-hydroximethylcytosine (5hmC), to 5-formilcytosine (5fC), and 5-carboxylcytosine (5caC). The restoration of an unmodified cytosine is performed by the Base Excision Repair (BER) mechanism in the presence of 5fC or 5caC (He et al., 2011; Maiti and Drohat, 2011). The recognition of methylated DNA is independent of the sequence and is mediated by methyl-(mCpG)-binding domain (MBD) proteins (Zhang et al., 1999). The first discovered MBD protein is MeCP2 (Meehan et al., 1989), also able to bind 5hmC, which is enriched in active genes (Guo et al., 2013; Mellén et al., 2012). Nevertheless, also TFs lacking an MBD are able to interact with methylated-DNA (Bartke et al., 2010; Spruijt et al., 2013). In the classical view, CpGs in the genome are globally methylated and DNAm is associated with transcriptional repression and gene silencing (Razin and Riggs, 1980). Accordingly, un-methylated CpG islands are associated with promoter regions of active genes (Bird et al., 1985; Deaton and Bird, 2011). In addition to the repressive role, DNAm has a key role in enhancer activation (Charlet et al., 2016) mediated by the formation of 5hmC at enhancer sites following the action of DNMT3A and DNMT3B (Rinaldi et al., 2016). Additionally, gene body methylation performed by DNMT3B induces gene expression (Yang et al., 2014).

Mutations in virtually all the components of the DNA-methylation machinery result in NDDs. Mutations in *DNMT1* are responsible for a hereditary neuropathy characterized by progressive peripheral sensory loss, progressive hearing impairment and early-onset dementias as well as with a neurological disorder associated with cerebellar ataxia, deafness, and narcolepsy (Klein et al., 2011). In contrast to many syndromes described until now, these two are neurodegenerative disorders with adult onset. Mutations in *DNMT3A* give rise to the Tatton-Brown-Rahman syndrome, an overgrowth syndrome associated with a distinctive facies and ID (Tatton-Brown et al., 2014). Finally, mutations in *DNMT3B* cause a recessive “immunodeficiency-centromeric instability facial anomalies” syndrome (Bestor et al., 1999). A recent study which employed human embryonic stem cells (Liao et al., 2015), to study the role of the DNA methylases, described that the deletion of *DNMT1* causes rapid cell death; while in a conditional model it causes a massive loss of DNA methylation. The separate or combined deletion of *DNMT3A* and *DNMT3B* induces viable cells capable of differentiating in the three germ layers, but with different patterns in DNAm alterations, including a milder impact following the deletion of only one of the two genes. Consequently, these results suggest that DNMT3A and DNMT3B have both shared and unique targets. The presence of specific targets might explain the fact that only mutations *DNMT3B* have a recessive inheritance (Liao et al., 2015).

Mutations in *MeCP2 are the main* cause of Rett syndrome (RTT), (Zoghbi et al., 1999), with mutations in *FOXG1* accounting for a minor fraction of the cases (Van der Aa et al., 2011). Since *MeCP2 is located* on the X chromosome, its loss-of-function mutations give rise to distinct phenotypes in males and females. Males are affected by a severe form of encephalopathy with early lethality within usually 1 year of age. Females instead, owing to the expression of the normal allele in about half of the cells, are spared from encephalopathy but go on to develop the defining hallmarks of Rett syndrome (Zoghbi, 2016), which has become one of the best studied NDDs, due to its high prevalence and severe phenotype. In RTT, initial development is normal but it is arrested between 6 and 18 months of age. The onset is characterized by regression of intellectual and motor capabilities. Indeed, loss of speech, regression of motor skills, hands stereotypic movements, ID, seizures, and delayed head growth resulting in microcephaly are all observed in these patients. A post-mortem study showed that RTT brains have a consistently decreased expression of presynaptic markers, and an increased expression of glial markers involved in neuropathologies (Colantuoni et al., 2001). Several human iPSC-based models have been established, and the first human neuronal characterization of an RTT iPSC-based model unveiled a reduction in synapses, dendritic spines, and neuron body size (Marchetto et al., 2010). Many other studies corroborated these results (Ananiev et al., 2011; Cheung et al., 2011; Kim et al., 2011). Additionally, *MeCP2* mutated individuals have a higher susceptibility to L1 retrotransposition (Muotri et al., 2010). The analysis of gene expression in neural precursors and mature neurons obtained by the differentiation of iPSCs derived from individuals with mutations in *MeCP2* or *CDKL5*, whose mutations cause an epileptic encephalopathy with phenotypic overlap with RTT (Guerrini and Parrini, 2012), showed a downregulation of glutamate receptor subunit *GRID1* in iPSCs and upregulation in neuronal precursor for both backgrounds when compared to an healthy control (Livide et al., 2015). *GRID1* codes for GluD1, which is necessary for synapse development but dispensable for channel function (Mayat et al., 1995; Yasumura et al., 2012). Further experiments in neurons differentiated from iPSCs of *FOXG1*-mutated individuals showed that GluD1 alteration leads to an unbalanced increase in inhibitory synapsis (Patriarchi et al., 2016). In addition, neurons derived from iPSCs of *CDKL5* mutated individuals showed that CDKL5 localizes at excitatory synapses, where contributes to dendritic spine development and synapses activity. In particular, VGLUT1 and PSD95 puncta were significantly reduced in mutants (Ricciardi et al., 2012).

DNAm is also responsible for the process of the imprinting, a genetic mechanism that ensures the expression of some genes only from the maternal or paternal allele. The molecular mechanisms of imprinting and the diseases caused by a defect of DNAm or the deletion of the expressed allele are extensively reviewed elsewhere (Buiting et al., 2016; Elhamamsy, 2017; Mackay and Temple, 2017).

5. Multiple genes dosage imbalance

Except for few diseases with a recessive inheritance, most NDDs addressed until now are dominant and caused by deletion, frameshift, missense or nonsense mutations of one allele. Therefore, genes involved in these haploinsufficiency syndromes have a pivotal role and the balance of their stoichiometry is essential to maintain the equilibrium in their GRNs. Sometimes, deletions or duplications can affect entire chromosomes, such as in aneuploidy syndromes (Hutaff-Lee et al., 2013), or encompass large chromosomal regions with multiple genes. The understanding of the molecular cause of these syndromes is more complex since the phenotype is the result of the gain or loss of several genes, and each of the genes involved can be responsible for a specific portion of the clinical manifestation. Well known examples of gene dosage imbalance caused by the complete gain or loss of a chromosome are the Down, the Klinefelter, and the Turner syndrome. Given the complexity of these syndromes, we refer the reader to specialised reviews (Antonarakis, 2016; Bonomi et al., 2017; Morris, 2017).

In contrast, microduplication and microdeletion syndromes

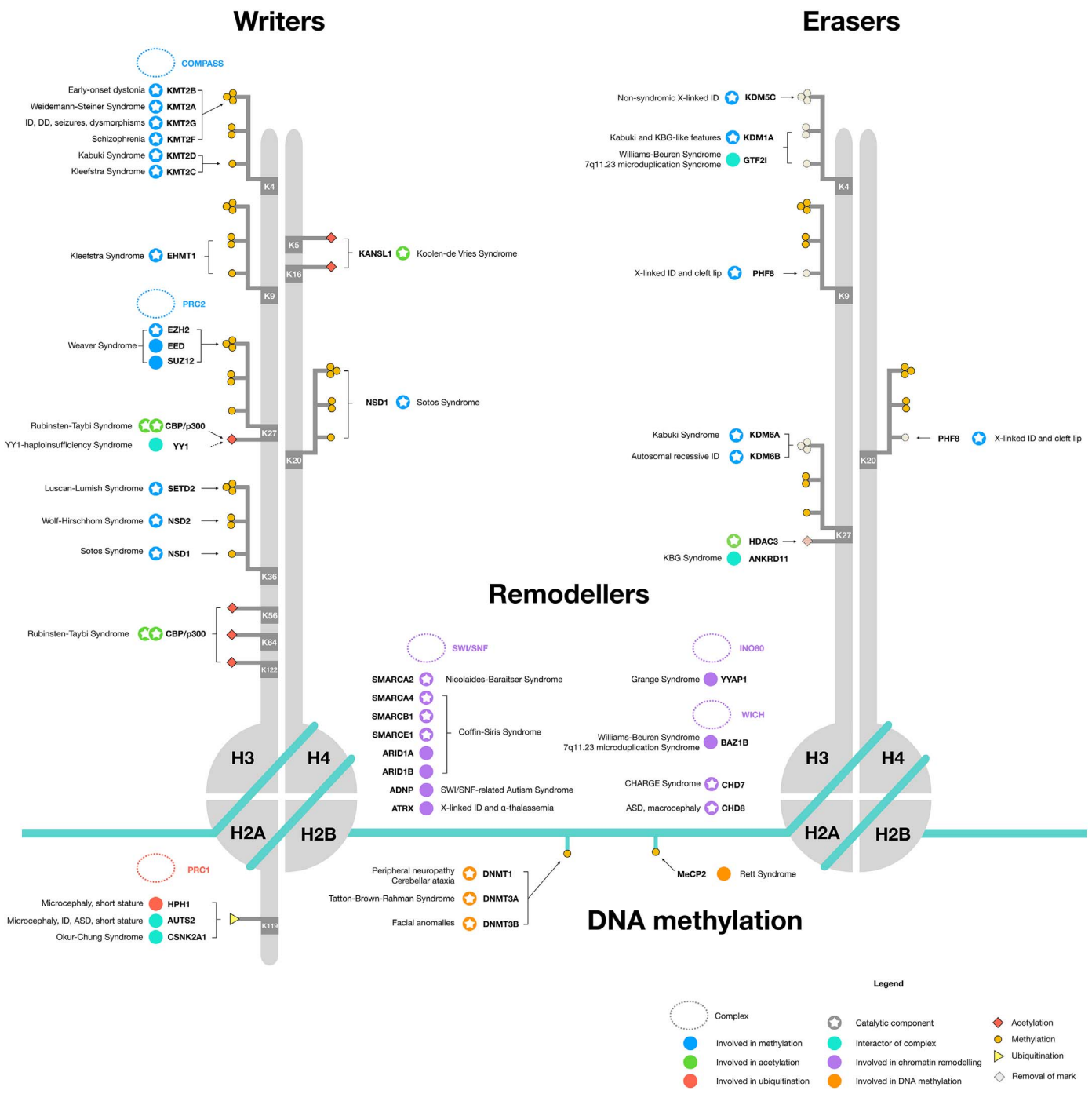

Fig. 2. Transcription regulation is controlled by DNA methylation, nucleosome remodeling, and histone modifications. The deposition of histone markers, performed by histone methyltransferases (HMTs) and histone acetyltransferases (HATs), is counterbalanced by the removal achieved by histone demethylases (HDMs) and histone deacetylases (HDACs). Nucleosome positioning and DNA accessibility are regulated by ATP-dependent chromatin remodeling complexes. Cytosines are modified with methyl groups by DNA methyltransferases. The balance between activating and repressive markers and nucleosome positioning is responsible for the fine tuning of time and space specific gene expression. The alteration of such regulation during individual development leads to various Neurodevelopmental Disorders (NDDs) highlighting the vulnerability of gene regulatory networks (GRNs).

involving far fewer genes, make it possible to dissect their specific contribution to a given pathogenesis. Two well-known examples of microdeletion and microduplication syndromes which appear to have a dosage-dependent phenotype are Williams Beuren Syndrome (WBS), caused by the deletion of the region 7q11.23, which contains 28 genes, (BEUREN et al., 1962; WILLIAMS et al., 1961), and its counterpart, 7q11.23 duplication syndrome (7dup) (Van der Aa et al., 2009). Both syndromes display opposite and shared clinical manifestations. Among the shared ones are ID, craniofacial dysmorphisms, heart defects, metabolic alterations and genitourinary anomalies. Conversely, the opposite phenotypes include WBS hyper-sociability behaviour in WBS, while 7dup individuals are usually affected by ASD, which indicates the existence genes in the region that participate in pathways regulating aspects of neurodevelopment that later influence social behaviour.

To understand the role of each of the 28 genes in the pathogenesis of the two syndromes, some studies have used phenotypes in patients with atypical deletions, which spare some of the interval's genes, causing milder and/or more selective clinical manifestations. Notably, individuals with an atypical 7q11.23 deletion that spares GTF2I retain their neuro-cognitive abilities (Antonell et al., 2010; Dai et al., 2009;

Edelmann et al., 2007; Ferrero et al., 2010). *GTF2I* codes for the General Transcription Factor II-I, a component of histone deacetylase-containing complexes which contain HDAC1, HDAC2 and KDM1A (originally calledBHC110) (Hakimi et al., 2003). Further underscoring the importance of *GTF2I,* independent studies described single nucleotide polymorphisms (SNPs) in *GTF2I* associated with ASD, social anxiety, reduced social communication skills and amygdala activation by aversive stimuli (Crespi and Hurd, 2014; Malenfant et al., 2012; Swartz et al., 2017). The first WBS and 7dup disease modelling study demonstrated that about 30% of differentially expressed genes observed in iPSCS across both syndromes are linked to GTF2I regulation (Adamo et al., 2015). Additionally, this study showed that GTF2I is associated substoichiometrically with KDM1A and HDAC2, implying a dual role in both directly and indirectly in transcriptional regulation. In keeping with the copy number variation of regulators of gene expression, the transcriptional dysregulation observed at the pluripotent stage was propagated and amplified in the neuronal precursor, neural crest stem cells, and mesenchymal stem cells (Adamo et al., 2015). Another human model study corroborates the transcriptional findings of Adamo et al. and focuses on *FZD9*, a receptor of the Wnt pathway in the 7q11.23 region, showing that it is essential to prevent cell death in neuronal precursors (Chailangkarn et al., 2016). Additionally, the authors differentiated iPSCs in cortical neurons, with a particular emphasis for cells expressing cortical markers for layers V/VI, given their involvement in ASD (Hutsler and Zhang, 2010). Following differentiation, data showed an increase in dendritic length and spine number, in accordance with observation made from WBS post-mortem brains individuals, suggesting that this phenotype may generate the altered network activity implicated in the neurocognitive features (Chailangkarn et al., 2016). In another study, blood cells of WBS, 7dup and healthy individuals were profiled for their DNAm content, which reflected gene dosage (Strong et al., 2015). Another example of chromatin regulator contained in the 7q11.23 region is *BAZ1B*, a bromodomain protein which interacts with SMARCA5 (Bozhenok et al., 2002). BAZ1B haploinsufficiency was found to contribute to WBS through transcriptional dysregulation of neurodevelopmental pathways (Lalli et al., 2016).

6. Conclusions

Our aim has been to provide a temporal and developmental framing for the rapidly accumulating knowledge on the derangement of epigenetic regulation that underlies neuropsychiatric disorders. A clarification of the epistemic reach of epigenetics has been integral to this approach, ushering in a review of the field that clearly distinguishes, within the expanding list of chromatin pathways causally linked to NDD, those mediating *bona fide* epigenetic inheritance of cell states from those affecting gene expression more dynamically (and whose pathogenic mechanism is thus not necessarily linked to strictly defined epigenetic alterations). The comprehensive extent of this classification is summarized in Fig. 2 and Table 1 with the list of NDDs caused, respectively, by mutations in epigenetic regulators and related transcription factors. Importantly, we have brought to the fore, whenever possible, both the numerous NDDs that are already related at the molecular mechanistic level and those in which a clear molecular link is still lacking but that display nonetheless significant phenotypic convergence, hinting at convergent downstream pathways. One example of similar phenotypes caused by molecular convergence is the common occurrence of overgrowth in multiple NDDs caused by mutations in repressive chromatin modifiers, such as in *DNMT3A*, *EED*, *EZH2*, *CHD8*, *NSD1*, and *SETD2*. On the other hand, mutations in molecular pathways associated with gene activation such as *SMARCA2*, *SMARCA4*, missense mutations in *KMT2A*, *KMT2B*, *KMT2D*, *EHMT1*, are often causative of microcephaly. One common convergent mechanism responsible for this phenotype is the Wnt/β-catenin pathway, which plays a pivotal role in the balance of progenitor proliferation in the developing cortex and whose impairment leads to macrocephaly or microcephaly. However, there are other cases of microcephaly and macrocephaly with no clear link to wnt/β-catenin pathway, such as for NSD2 or CTCF, highlighting the pleiotropy of the phenotypes.

In order to provide a visual summary of what is discussed here, we have portrayed a spatial mapping of the distribution of the expression of epigenetic modifiers across the adult brain according to the GTEx dataset (Carithers et al., 2015; GTEx Consortium, Laboratory, et al., 2017). This highlights the cortex as the area with the highest levels, with particular emphasis in the Brodmann area 9 (BA9), which is involved in various higher cognitive functions often disrupted in multiple NDDs and ASD, including empathy and processing of pleasant and unpleasant emotions(Carlén, 2017; Lane et al., 1997) (Fig 3A, B). Likewise, an analysis of their relative expression throughout development and adulthood within the BrainSpan atlas RNA-seq dataset (Oldre et al., 2014), highlights the fact that most of the genes commonly mutated in NDDs display an expression pattern increased in the gestational period, which agrees with the concept of early development as a particularly susceptible window in which mutations in these genes result in their highest phenotypical impact.

It is plausible to think that the function of these genes is highly required at the beginning of the development, during differentiation and the acquisition of cell identity, when dramatic changes in chromatin structure happen to prime the expression of differentiation and function-specific genes. Consequently, mutations in these genes have their most substantial impact during the most fragile developmental phase. Nevertheless, the same genes are still required also in adult neuronal tissues, since it is well known that histone modifications and DNAm are involved in processes as neuronal plasticity, learning and memory acquisition (Kaang and Kim, 2017). In Fig. 3C we also highlight the expression profile in the cortex and the amygdala, a site that has been considered important in Williams-Beuren syndrome and other ASDs (Binelli et al., 2016) given its involvement in the regulation of the emotional response.

Further supporting a common downstream pathway, multiple NDDs caused by mutations in epigenetic regulators have a recurrent presence of clinical features such as craniofacial dysmorphisms, immunological defects, heart abnormalities, and other Neural Crest-derived organs malformations, indicating that neural crest cells, along with the CNS-originating neurectoderm from which they emerge, define a cell lineage hub highly vulnerable to chromatin perturbation during development. Consequently, tissues and organs derived from neural crest are often affected in these categories of NDDs.

Although somatic mutations in many of the genes responsible for NDDs are also linked to cancer (Crawley et al., 2016), only a small portion of the NDDs are associated with cancer predisposition (Cross, 2010; Rao and Dou, 2015; TATTON-BROWN and RAHMAN, 2013). Since also cancer is being increasingly understood as an inherently developmental disorder, in which the differentiated cell identity is reprogrammed back to an earlier or at any rate altered developmental stage (Flavahan et al., 2017), the apparent misalignment between NDD and cancers caused by – often equivalent - mutations in the same pathways raises an interesting hypothesis. The NDD-causing mutations, by operating from the onset of development, might trigger downstream (and possibly compensatory) mechanisms that would make somatic cells resistant to the oncogenic side of their impact, which would instead unfold in normally developed cells

The phenotypical convergence between multiple NDDs of varied molecular origin underscores the importance of identifying shared GRNs, whose further functional dissection could afford much greater resolution in genotype-phenotype relationships and define the core hubs on which to develop new therapeutic inroads.

Authors' contribution

MG, ALT, and GT conceived the review. GT developed the

Table 1
Genes involved in chromatin remodeling and transcription regulation causative for Neurodevelopmental disorders. The OMIM column represents the associated phenotype, or gene when followed by *.

Gene	Function	Associated syndrome	OMIM
ADNP	Transcription factor and chromatin remodelling	Helmsmoortel-van der Aa syndrome, ADNPassociated autism spectrum disorder	615873
ARID1A	Chromatin remodeling	Coffin-Siris syndrome	614607
ARID1B	Chromatin remodeling	Coffin-Siris syndrome	135900
ARX	Transcription factor	Mental retardation with or without seizures	300419
ATRX	Chromatin remodeling	α-Thalassemia mental retardation syndrome X-linked and mental retardation-hypotonic facies syndrome	301040, 309580
AUTS2	PRC1-AUTS2 activates transcription	Association with Mental Retardation	615834
BAZ1B	Chromatin remodeler involved in transcriptional regulation, DNA damage response, DNA replication	Williams-Beuren syndrome, 7q11.23 duplication syndrome	605681*
BCOR	Transcriptional repressor	Syndromic microphthalmia 2	300166
BRD1	Transcription factor	Schizophrenia/bipolar	604589*
BRD2	Transcription factor	Autism spectrum disorder	601540*
BRD3	Transcription factor	Mental retardation	601541*
BRWD3	Transcription factor	Autism spectrum disorder	300659
CDKL5	Serine-threonin kinase	Infantile Epileptic encephalopathy	300672
CECR2	Chromatin remodeling	Anencephaly	607576*
CHD2	Chromatin remodeling	Epileptic encephalopathy, childhood-onset	615369
CHD7	Chromatin remodeling	CHARGE syndrome	214800
CHD8	Chromatin remodeling	Autism spectrum disorder, CHARGE syndrome	615032
CREBBP	HAT	Rubinstein–Taybi syndrome	180849
CTCF	Chromatin remodelling	Mental retardation	615502
DNMT1	DNMT	Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant and Neuropathy, hereditary sensory, type IE	604121, 614116
DNMT3A	DNMT	Tatton-Brown-Rahman syndrome	615879
DNMT3B	DNMT	Immunodeficiency-Centromeric Instability-Facial Anomalies syndrome	242860
EBF3	Transcription factor	Hypotonia, ataxia, and delayed development syndrome	617330
EED	PRC2 complex	Cohen-Gibson syndrome	617561
EHMT1	HMT of H3K9	Kleefstra Syndrome	610253
EP300	HAT	Rubinstein-Taybi syndrome	613684
EZH2	HMT of H3K27	Weaver Syndrome	277590
GCN5L2	HAT	Neural tube defects	602301*
GTF2I	Transcription factor	Williams-Beuren syndrome, 7q11.23 duplication syndrome	194050
GTF2IRD1	Transcription factor	Williams-Beuren syndrome, 7q11.23 duplication syndrome	194050
HDAC8	HDAC	Cornelia de Lange syndrome	300882
HPH1	PRC1 Complex	microcephaly and short stature	615414
JARID1C	HDM	Syndromic Mental retardation, Claes-Jensen type	300534
KANSL1	Scaffold of NSL complex, HAT of H4K5 and H4K16	Koolen-de Vries syndrome	610443
KDM5C	HDM of H3K4	Mental retardation	300534
KDM6A	HDM of H3K27	Kabuki syndrome	300867
KMT2A	HMT of H3K4	Wiedemann-Steiner syndrome	605130
KMT2C	HMT of H3K4	Kleefstra Spectrum Syndrome, Autistic Spectrum Disorders	606833*
KMT2D	HMT of H3K4	Kabuki syndrome	147920
KMT2F	HMT of H3K4	Linked to Schizophrenia	611052*
MBD5	Methyl DNA binding protein	2q23.1 microdeletion mental retardation syndrome	156200
MECP2	Methyl DNA binding protein	Rett syndrome	312750
MED12	Bridging of transcription factors/cofactors and RNA polymerase transcriptiona regulator	Lujan–Fryns syndrome, Opitz–Kaveggia syndrome	309520, 305450
NBEA	kinase anchoring protein	Autism spectrum dysorder	604889*
NSD1	HMT of H3K36 and H4K20	Sotos syndrome	117550
NSD2	HMT of H3K4 and H3K36	Wolf–Hirschhom syndrome	194190
PHF21A	Component of histone Deacetylase	Potocki-Shaffer syndrome	601224
PHF6	Transcription factor	Borjeson–Forssman–Lehmann syndrome	301900
PHF8	HDM, Transcription factor	Mental retardation syndrome Siderius type	300263
POLR1C	Core components of the transcriptional machinery	Treacher-Collins Syndrome, Leukodystrophy, hypomyelinating	248390, 616494
POLR1D	Core components of the transcriptional machinery	Treacher-Collins Syndrome	613717
RNASEH2C	Ribonuclease H subunit	Aicardi-Goutieres syndrome	610329
RPS6KA3	Serine-threonin kinase	Coffin–Lowry syndrome	303600
RPS6KA6	Serine-threonin kinase	X-linked mental retardation	300303*
SATB2	Chromatin remodelling	Glass syndrome	612313
SETD2	HMT of H3K36	Luscan-Lumish syndrome, Sotos-like syndrome	616831
SMARCA2	Chromatin remodeling	Nicolaides-Baraitser syndrome	601358
SMARCA4	Chromatin remodeling	Coffin-Siris syndrome	614609
SMARCB1	Chromatin remodeling	Coffin-Siris syndrome	614608
SMARCE1	Chromatin remodeling	Coffin-Siris syndrome	616938
SOX11	Transcription factor	Mental retardation	615866
SOX3	Transcription factor	Mental retardation with isolated growth hormone deficiency	300123
TAF1	Transcription initiation factor	X-linked Dystonia-parkinsonism, Mental retardation	314250, 300966
YY1	Transcription factor	Gabriele-de Vries syndrome	617557
ZBTB20	Transcriptional repressor	Primrose syndrome	259050
ZNF41	Transcription factor	Mental retardation	314995*

(*continued on next page*)

Table 1 (*continued*)

Gene	Function	Associated syndrome	OMIM
ZNF674	Transcription factor	Mental retardation	300573*
ZNF711	Transcription factor	Mental retardation	300803
ZNF81	Transcription factor	Mental retardation	314998*

HAT: histone acetyl transferase; HDAC: histone deacetylase; KDM: lysine demethylase; KMT: lysine methylase; HDM: histone demethylase; DNMT: DNA methyltransferase.

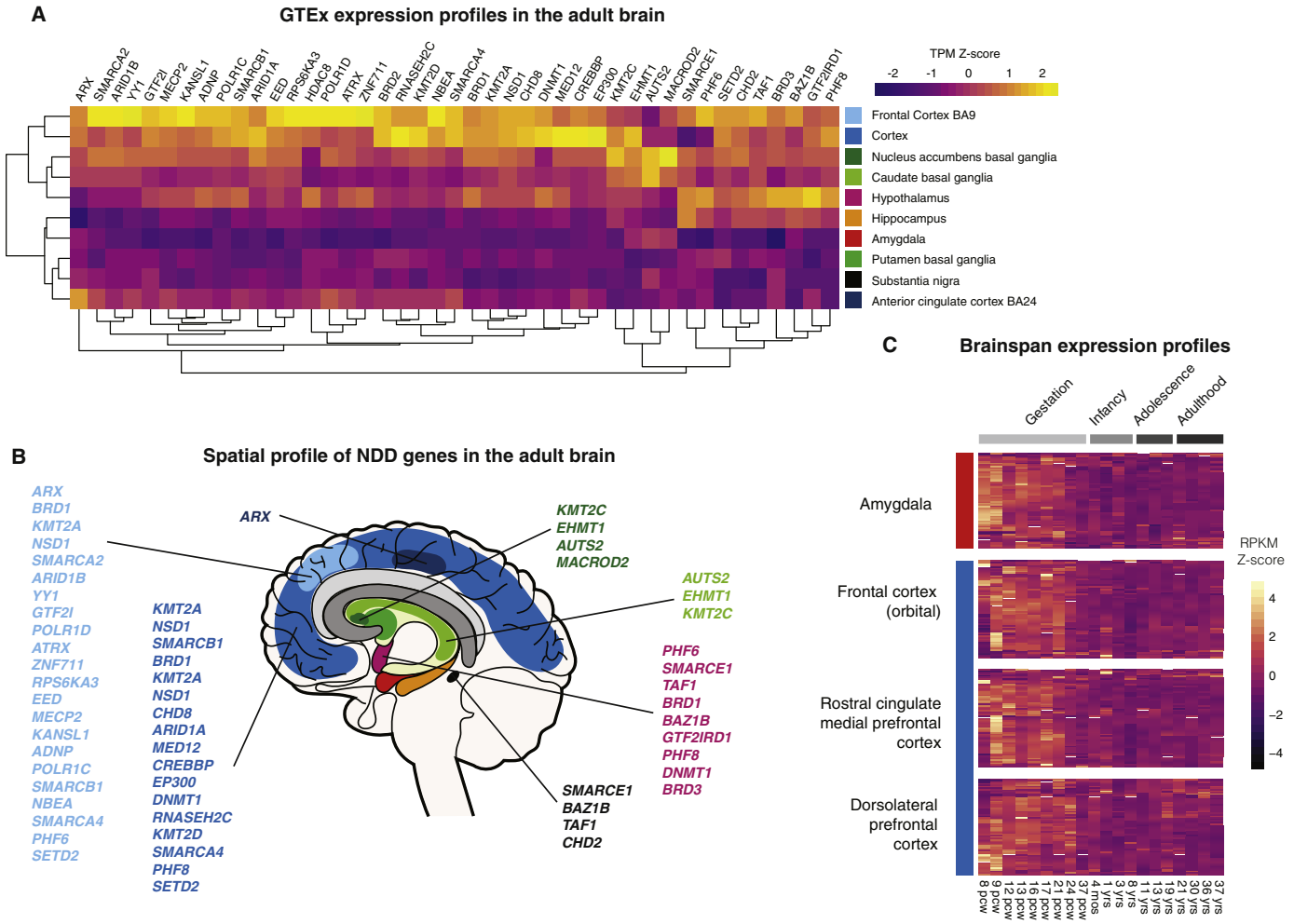

Fig. 3. Spatial and temporal expression of NDD-related epigenetic factors. A: Heatmap of NDDs genes expression in the GTEx brain tissues, using median TPMs from the GTEx dataset. B: Graphical representation of the tissues in which genes are the most expressed. Some of the genes are shared between areas. Graphical reference of A. C: Expression in different brain regions to which the BrainSpan atlas, which offers the possibility to inspect expression profiles in several timepoints of life stages such as gestation, infancy, adolescence, and adulthood, assigns genes in different developmental timepoints. According to the BrainSpan atlas, the NDDs genes shortlisted in Table 1 have a high expression during gestation, and they are downregulated after birth. This observation reflects the "window of vulnerability" hypothesis, exhaustively discussed in the introduction, in which the early stages of brain development are the most sensitive to perturbation. Z-scores calculated for rows; TPM: transcripts per million; BA: Brodmann area; RPKM: reads per kilobase per million mapped reads.

theoretical backbone and argumentative structure of the review. MG, ALT, and GT drafted the initial versions of the various sections. GD reanalyzed the public available datasets Brainspan and GTEx, and designed and drew the figures. All the authors contributed to the final manuscript.

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