Epigenetic Impacts on Neurodevelopment: Pathophysiological Mechanisms and Genetic Modes of Action

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ABSTRACT: Disruptions of genes that are involved in epigenetic functions are known to be causative for several mental retardation/intellectual disability (MR/ID) syndromes. Recent work has highlighted genes with epigenetic functions as being implicated in autism spectrum disorders (ASDs) and schizophrenia (SCZ). The gene-environment interaction is an important factor of pathogenicity for these complex disorders. Epigenetic modifications offer a mechanism by which we can explain how the environment interacts with, and is able to dynamically regulate, the genome. This review aims to provide an overview of the role of epigenetic deregulation in the etiopathology for neurodevelopment disease. (*Pediatr Res* 69: 92R–100R, 2011)

Over a decade following the availability of the human genome sequence (1), we are still far from understanding the genetic basis of many neurodevelopmental disorders (2,3). Epigenetics is growing in prominence as a significant contributor to the etiology of these diseases (4,5). Epigenetics is broadly defined as those heritable changes not dependant on the genomic sequence. Therefore, it is a method of controlling the genome without involving the alteration of the genomic sequence itself.

Epigenetics is especially attractive in the context of complex disease, as it is able to define a molecular mechanism that links environmental effects to gene function. That is, epigenetic modulation is able to act as an interface between the environment and the genome. This is especially relevant when discussing neurofunctional disorders as they often involve a large environmental component in their etiology. For this reason, there is an increasing attention on epigenetics in pathophysiological studies in schizophrenia (SCZ), autism spectrum disorder (ASD), and mental retardation/intellectual disability (MR/ID). We elaborate on these themes in this article.

The epigenetic machinery includes factors that can "write" (covalently attach), "read" (differentially bind), and "erase" (remove) chemical moieties to chromatin thereby moderating genomic expression. These modifications are often dynamic and may be amenable to control. Broadly, we can discuss epigenetic processes as DNA methylation, histone modifications, and chromatin remodeling. In this review, we will collectively refer to the effector proteins for these functions as epigenetic regulators.

In vertebrates, DNA methylation results in the covalent addition of methyl groups to the 5 position of cytosines and occurs predominantly at cytosines that are situated next to a guanine (written as CpG, with p reflecting the phosphodiester bond) in the DNA strand. CpG dinucleotides are found concentrated around gene promoter regions in what are termed "CpG islands" (6). Therefore, methylation of CpG islands serves as an "epigenetically modifiable" mark. Although most cytosines in CpG islands remain unmethylated (thus the gene is functional), methylation of CpG islands occurs in gene silencing events such as X-inactivation and silencing of imprinted genes (6,7). The majority of CpGs outside of islands are methylated, and while variation in such methylation may impact local chromatin structure, many current strategies (8) measuring genome-wide methylation have focused on gene promoter methylation (9).

Eukaryotic nuclear DNA is present as chromatin, which is made up of repeating units of nucleosomes. A nucleosome consists of a length of $\sim$147 bp of DNA wrapped around a core of histone proteins. How tightly the DNA is wrapped around the histones impacts the amenability of the DNA to transcription. Modification of the histone protein tails can significantly alter the binding properties of DNA to the histones and the compactness of the nucleosomes to each other. Therefore, such modifications serve as a key transcriptional regulatory mechanism. For example, acetylation of lysine residues is associated with transcriptional activation, whereas silencing is associated with certain lysine methylation signatures (*e.g.* K9me3 or K27me3), and other lysine methylation signatures are considered activating (*e.g.* K4me3) (10).

In addition, there are large multiunit chromatin remodeling complexes, which are necessary for the assembly or displacement of nucleosomes and also serve to insert variants of the histones, which alter chromatin compactness. The net outcome of these processes is to render chromatin as transcriptionally active or euchromatic, or conversely transcriptionally inactive or heterochromatic (11).

DNA methylation, histone modifications, and chromatin remodeling complexes work together, and there are significant interactions in their recruitment. This "cross-talk" is multidi-

Abbreviations: ASDs, autism spectrum disorders; **CNV,** copy number variant; **MR/ID,** mental retardation/intellectual disability; **SCZ,** schizophrenia

rectional and multimodal (12,13), for instance, a DNA methylase can recruit a histone modifier, which in turn can recruit chromatin remodeling complexes. Not only the effector molecules (*e.g.* DNA methyl transferase) but also the regulatory marks themselves (*e.g.* DNA methylation) can be involved in recruiting other regulators. Figure 1 illustrates the interplay between these factors. In summary, we see that epigenetic regulation is a complex and intricate process. It is a finely orchestrated system involving the synchronized working together of many diverse proteins, often in large multicomponent complexes that act on vast portions of the genome. Therefore, even small changes in the balance of factors comprising the machinery may be pathogenic.

Epigenetic Perturbation in Neurogenetic Disorders

A growing body of work is highlighting the extent of epigenetic involvement in neurological disease (2,4,5,14,15). Neurodevelopmental pathologies, such as MR/ID and ASDs, neurofunctional disorders such as SCZ and bipolar disorder (BD) and neurodegenerative disorders such as Alzheimer's disease, Parkinson disease, and Huntington's disease are now recognized to have epigenetic perturbation as a causative factor (4).

The cause of MR/ID (MR/ID— diagnosed by the presentation of an intelligent quotient (IQ) <70, age of onset <18 y, and deficiency in two or more areas of adaptive behavior) can be primarily categorized as genetic or nongenetic (*i.e.* caused by insults during development such as external prenatal or teratogenic, paranatal, and postnatal causes). However, in over half of the cases no etiology is determined (16).

A significant proportion of MR/ID syndromes are because of single gene perturbations, either resulting from dosage change or mutation (17). A few years ago, the number genes recognized to contribute to MR/ID was reported as ~300 (17,18). Since then, many more causative genes have been identified, as indicated by reported candidate genes from the plethora of microarray studies focused on elucidating novel genetic causes for MR/ID that have been published (19–21). However, these candidates have not been collated as far as we are aware. Dr. Hans Roper, in his recent overview of the

genetics of MR/ID, calculates a total number of genes implicated in autosomal MR/ID to be at least between 800 and 850, based on the evidence that the known 91 X-linked causative genes accounts for 10–12% of MR/ID in males (3). Genes pathogenic for MR/ID can be classified according to their molecular function into many categories, of which two are particularly overrepresented. These are as follows: 1) genes involved in synapse formation and function and 2) genes controlling epigenetic regulation and related transcriptional activity (18); the latter of which will be the focus of this review.

Several well-characterized MR/ID syndromes are caused by perturbation of genes involved in epigenetic regulation (18). For example, Rett syndrome, one of the most common causes of MR/ID in women (22), is caused by mutations in the *MECP2* gene (23). The protein encoded by this gene is a member of the methyl CpG-binding domain (MBP) protein family and is an epigenetic regulator of transcription (24). Rubinstein-Taybi syndrome is caused by mutations in the *CBP* gene (25). CBP is known to have intrinsic histone acetyltransferase activity and is also a transcriptional coactivator (26). Coffin-Lowry syndrome is caused by mutations of *RSK2* (27), which codes for a modulator of the CBP protein (28). Loss of function mutations of *DNMT3B* are causal for another MR/ID syndrome and immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome. DNMT3B is a DNA methyltransferase necessary for methylation of cytosine residues (29). ATRX (alpha thalassemia X-linked MR) is caused by mutations of the *ATRX* gene, which codes for a protein that is a chromatin remodeler (30). *CHD7*, which encodes an ATP-dependant chromatin remodeling enzyme, is the causative gene for CHARGE syndrome, characterized by a nonrandom pattern of congenital anomalies including heart, ear, and eye phenotypes in addition to MR/ID (31). In addition to these well-known pathologies, some of the candidate genes above are also being discovered to be causative of rarer phenotypes (Table 1).

The examples mentioned above are monogenic disorders that may be defined as those caused by a disruption of epigenetic regulation because of the dysfunction of genes
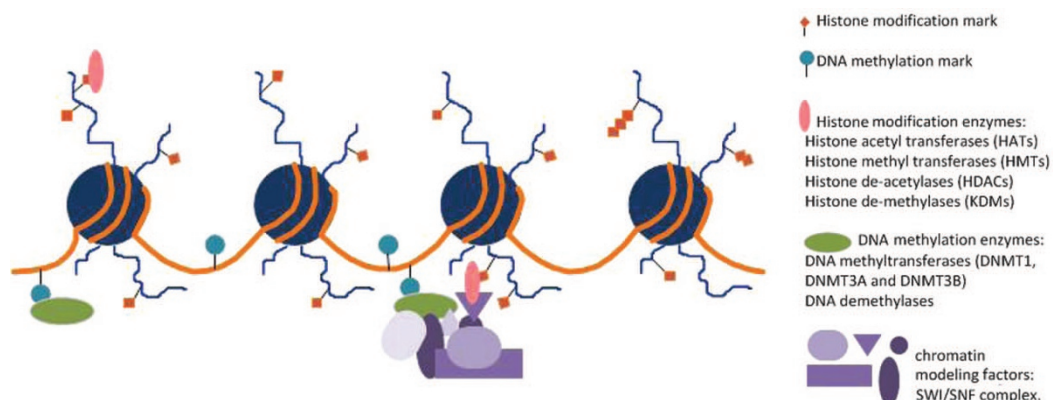

Figure 1. Interactions between DNA methylation, histone modification and chromatin remodeling. The DNA strand is wrapped around histone protein cores to form repeating nucleosomes that make up chromatin. Histone tail modifications are attached to histone tails, and DNA methylation marks are attached to the DNA strand. Epigenetic regulators that have DNA methylation, histone modification or chromatin remodeling interact with each other and display cross-recruitment.

Table 1. *Genes encoding epigenetic regulators that have been implicated in neurodevelopmental pathologies*

Gene	Protein	Epigenetic class	Pathogenicity	OMIM no.	Defect	Selected references*
DNMT3B	DNMT3B	DMT	Immunodeficiency, Centromeric instability and facial Dysmorphisms (ICF) syndrome	242860	Homozygous or compound heterozygous mutations	(1,2)
NSD1	NSD1	HMT	Sotos syndrome	117550	Heterozygous deletions and truncating mutations	(3)
EHMT1	EHMT1	HMT	9q Subtelomeric deletion syndrome	610253	Heterozygous deletions and truncating mutations	(4)
CREBBP	CBP	HAT	Rubenstein Taybi syndrome	180849	Heterozygous microdeletions and truncating mutations	(5)
CREBBP	CBP	HAT	Rubenstein Taybi syndrome	180849	Heterozygous deletions	(6,7)
CREBBP	CBP	HAT	Incomplete Rubenstein-Taybi syndrome	180849	Heterozygous missense mutation	(8)
CREBBP	CBP	HAT	16p13.3 duplication syndrome	613458	Heterozygous duplications	(9)
EP300	P300	HAT	Rubinstein-Taybi syndrome	180849	Heterozygous mutations	(10)
RPS6KA3 (X-linked)	RSK2	HP	Coffin-Lowry syndrome	303600	Heterozygous deletions, nonsense and missense muations	(11,12)
RPS6KA6 (X-linked)	RSK4	HP	Nonsyndromic MR	300303	Deletion	(13)
PHF8 (X-linked)	PHF8	HD	Siderius X-linked MR syndrome	300263	Deletions and mutations	(14)
PHF8 (X-linked)	PHF8	HD	ASD and ID	300263	Deletion encompassing other genes	(15)
HDAC4	HDAC4	HDAC	Brachydactyly-MR Syndrome	600430	Heterozygous deletions	(16)
HDAC4	HDAC4	HDAC	SCZ	300055	Associated	(17)
MECP2 (X-linked)	MeCP2	DMD-CR	Rett Syndrome	312750	Deletions and severe loss of function mutations (females)	(18,19)
MECP2 (X-linked)	MeCP2	DMD-CR	Severe neonatal encephalopathy	300673	Severe loss of function mutations (males)	(20,21)
MECP2 (X-linked)	MeCP2	DMD-CR	ASD	300496	severe loss of function mutations (females)	(22)
MECP2 (X-linked)	MeCP2	DMD-CR	X-linked MR	300055	Mild loss of function mutations (males)	(23)
MECP2 (X-linked)	MeCP2	DMD-CR	X-linked MR and MECP2 Duplication syndrome	300260	Duplications (males)	(24)
MECP2 (X-linked)	MeCP2	DMD-CR	ASD	300496	Over and under expression	(25,26)
MECP2 (X-linked)	MeCP2	DMD-CR	SCZ	300055	Nonsynonymous mutations	(27)
MECP2 (X-linked)	MeCP2	DMD-CR	Angelman syndrome	105830	Mutations	(28)
ATRX (X-linked)	ATRX	CR (interacts with MECP2)	Alpha-thalasemia X-linked MR	301040	Mutations and intragenic duplications leading to loss of function	(29,30)
ATRX (X-linked)	ATRX	CR (interacts with MECP2)	MR-hypotonic Facies syndrome, X-linked	309580	Mutations	(31–33)
CHD7	CHD7	CR	CHARGE syndrome	214800	Heterozygous deletions and truncating mutations	(34,35)
JARID1C (X-linked)	JARID1/SMCX	CR	X-linked MR	300534	Mutations (males)	(36,37)
PHF6 (X-linked)	PHF6	CR	Borjeson-Forssman-Lehmann syndrome	301900	Truncating and missense mutations (males and one report of female)	(38)
ZEB2	ZEB2	CR	Mowat Wilson syndrome	235730	Heterozygous deletions	(39)
ZEB2	ZEB2	CR	Hirschprung disease-MR syndrome (Mowat-Wilson syndrome variants)	235730	Heterozygous mutations (often truncating)	(40,41)
REST	REST	CR	Down syndrome	190685	Reduced expression	(42)
CDKL5 (X-linked)	CDKL5/STK9	CR	Atypical Rett syndrome, infantile spasms, and severe MR	300672	Mutation (female)	(43)

DMT, DNA methyltransferase; HMT, histone methyltransferase; HAT, histone acetyltransferase; HP, histone phosphorylation; HD, histone demethylase; HDAC, histone deacetylase; DMD-CR, DNA methylation-dependant chromatin remodeling; CR, chromatin remodeling protein.

* References noted in this table are available as supplemental material online http://links.lww.com/PDR/A68.

encoding epigenetic regulators. Not unexpectedly, genes that are under epigenetic regulation can also be candidates for causing MR/ID because of the disruption of the elements involved in the recruitment of the epigenetic mark. An important example of this effect is the deregulation of imprinted genes. Imprinting refers to when a gene, though present in two copies, is only expressed by one chromosome, dependant on parent-of-origin, *i.e.* a preferential transcription for either the

maternal or the paternal allele (32). Imprinting is currently known for a hand full of human genes (32). The parent-of-origin-dependant expression is regulated by which parental allele is differentially methylated, thus imprinting is an effect brought about by epigenetic control. Prader-Willi and Angelman syndrome both include MR/ID in their phenotypic spectrum and are caused by parent-of-origin-specific defects of 15q11q13 (33,34).

Intriguingly, copy number variation of the 15q11q13 region is also associated with ASD (35–37), and there is emerging evidence for ASD symptomatology presenting with the imprinting disorder Prader-Willi Syndrome (36). Other MR/ID syndromes are also now being understood to include ASD phenotypes (*e.g.* 16q11.2 microdeletion and microduplication Ref. 38; 22q13 microdeletion Ref. 39). Genes implicated in MR/ID syndromes are also being found to be pathogenic for ASD (*e.g.* the *MECP2* gene was thought to be lethal if deleted in males; however, there is now evidence of milder phenotypes including ASD behavioral phenotypes manifesting in males with deficient *MECP2* (Table 1) (40).

Epigenetic dysfunction in the pathogenesis of SCZ is gaining in prominence as evidenced by the many physiological, molecular, and epidemiological studies focused on the involvement of epigenetic disruption in SCZ (for review, see refs 14, 41, and 42). A recent study interrogated the incidence for disruptions of genes encoding histone deacetylators (HDACs) in SCZ causation. Kim *et al.* (43) investigated a select group of *HDAC* genes for causation in a large South Korean SCZ cohort and found *HDAC4* to be associated with the disease. Others have found elevated brain expression levels for HDAC1 in SCZ postmortem brain samples (44,45). In this context, it is worth mentioning the growing body of evidence pointing to SCZ being a neurodevelopment disorder (41,42). Given that epigenetic programming bears significant functional importance during neurodevelopment (especially *in utero*), it can be presumed there will be an increasing emphasis on epigenetic mechanisms concurrent with the growing understanding of the neurodevelopmental aspects of SCZ. *Ergo*, there is growing evidence supporting an overlap between MR/ID, ASD, and SCZ not only in terms of phenotypic presentation but also in terms of the underlying genetics and epigenetics. In this review, we hope to explore the common epigenetic mechanisms that may lead to neurodysfunction (manifesting in the above disorders) and discuss how changes in the finely orchestrated epigenetic machinery can be pathogenic.

Pleiotropy and Functional Complexity

As epigenetic modulators are often involved in multiprotein complexes (13) and given that epigenetic change is impacted by multiple chromatin modifying pathways (11), we suggest that mutations in epigenetic modifiers may be particularly prone to exhibiting pleiotropy. This certainly seems to be the case for *MeCP2* as mutations of the gene are known to cause a number of different phenotypes (Table 1).

Pleiotropy can arise when the dysfunctional gene's product affects a number of downstream targets (46). In the epigenetic context, the mutated gene could encode an epigenetic regulator, and the anomalous product (or absence/overexpression of the product) therefore would cause deregulated expression of a number of other genes. A good example of this is provided by MeCP2, which specifically binds to methylated cytosine residues of CpG islands and recruits other factors that contribute to establishing an inactive chromatin state (24). There have been thorough reviews of the phenotypic outcome of the large number of mutations found in *MeCP2* (24,47). Focusing on the hypothalamus in mice, Chahrour *et al.* (48) show that the mecp2 protein can act as both an activator and a repressor, and that it serves as a direct transcriptional regulator for the majority of genes that it affects. Notably, it is clear that the mecp2 activity is central to further epigenetic control of the genes targeted. Of the 2582 genes tested, they found that abnormally elevated or abnormally decreased mecp2 levels (engineered by using a gene construct with a hyperactive promoter and a null allele, respectively, in transgenic mice of two different strains) affected the expression patterns of a staggering ~85% of genes. A2bp1, Gamt, and Gprin1 are among the target genes. Interestingly, disruption of *A2BP1* in humans has been implicated in ASD susceptibility (49) as well as MR/ID and epilepsy (50), GAMT deficiency has been shown to cause severe MR/ID (51), and the human homolog of Gprin1, *GRIN* is well documented as a causative gene for SCZ (52–54). Therefore, pleiotropy in this example could be a manifestation of the multiplicity of binding targets for MeCP2.

Pleiotropy can also be brought about by mutations altering the protein functionality in a domain-specific manner. Thus, the phenotypic outcome could vary according to which functional domain of the protein was altered by the mutational event. MeCP2 also provides a good example of this, being a protein with multiple well-characterized functional domains. Three distinct domains are known for MeCP2: a methyl-binding domain (MBD) that binds to methylated cytosine residues in the DNA strand, a transcriptional repression domain (TRD) that binds to other chromatin remodeling factors as a protein-protein interaction domain, and a C-terminal domain that can bind naked DNA and RNA splicing factors (48). In this case, where one protein has many binding partners, it can be hypothesized that genetic changes that alter specific binding properties of the protein (24) can affect the phenotypic outcome in different ways.

Another source of phenotypic variability possibly due to dysfunction of epigenetic regulators depends on their extent of involvement in coincident pathways. This is illustrated by the case of DNMT3B. The enzyme does have a primary epigenetic programming function, being a DNA methyl transferase; however, it is one of three major DNA methyltransferases, the other two being DNMT3A and DNMT1 (55). Of these, DNMT1 is considered to be the maintenance methyltransferase, and DNMT3A and DNMT3B are termed *de novo* methyltransferases (56). DNMT1 is the most abundant methyltransferase in somatic cells (56). Aberrant expression of DNMT1 has been shown to result in extreme global DNA methylation defects and embryonic lethality in mammals (57–59). However, members of the DNMT3 family display more specific tissue expressivity (55,56). DNMT3B in particular

seems to have a smaller effect size. Rhee *et al.* (60) reported that disruption of DNMT3B only reduced global methylation by <3%; however, when both DNMT3B and DNMT1 were disrupted, the global methylation was changed by >95%. Functional interactions of the DNA methyltransferases are reviewed in Rottach *et al.* (55). The take-home message is that the overlap/redundancy with other family members can influence the pathogenicity for defects in epigenetic regulators.

In a similar vein, for epigenetic regulators that function in more than one multiunit complex, the alteration of its function can have a nuanced impact dependant on which multiunit complex is affected, and how. In this context, genetic background would play an important role. A mutation in a member of a multiunit chromatin remodeling complex may not be phenotypically evident in one individual; however, in another individual, who may have a variant in a different member of the same multiunit complex, or perhaps in a related or partially redundant complex, the combined effects of the mutated epigenetic regulators may manifest in a disease outcome. This would be analogous to the situation for copy number variant (CNV) pathogenicity, where it has been shown that a CNV which is benign in one individual could be pathogenic in another individual who carries a second benign CNV affecting different genes (61). In this case, the combined effect would be pathogenic, whereas each CNV on its own is nondisease-causing (62).

Epigenetic regulatory protein expression levels can also contribute to pleiotropy. *CBP* deletions are considered a common cause of Rubenstein-Taybi syndrome (25,63,64), and duplications are causative for the recently described characteristic 16p13.3 syndrome (65,66) (Table 1), indicating that the over- and underexpression of the gene product affects different molecular pathways or the same pathways differently. CBP is a histone acetyltransferase and functions as a transcriptional co-activator (67). The distinct phenotypes observed due to its under *versus* overexpression highlight the sensitivity to incorrect copy number or dosage imbalance of epigenetic regulators for correct neurodevelopment.

CNVs are frequent in the population and are thought to be causative for ~15% of MR/ID (3). In keeping with our understanding of neurogenetic pathogenicities caused by CNVs in general, we see that the loss of an epigenetically functional gene is more frequently implicated than the gain of the same gene (Table 1) (62). The indication is not that losses occur more frequently than gains, but that losses are less well tolerated than gains (62). It can be theorized that the overexpression of epigenetic regulators should not impact the overall functional outcome because having more product would not alter the normal sequestering of these factors. However, the lack of sufficient epigenetic regulators would result in an impairment of the sum functional outcome. But given the context that many epigenetic regulators, especially those involved in chromatin remodeling complexes, do act as part of large multiunit complexes, the situation may be much more complex.

Recent studies using a microarray with a resolution able to identify even single exon changes, targeted to all genes with epigenetic function (197 in total known at the time of microar-ray design in 2007), resulted in 9% of a cohort of 177 trios with idiopathic MR/ID being identified to carry *de novo* CNVs that included an epigenetic regulator (unpublished data). These potentially causative genes add to a rapidly growing list of epigenetic players implicated in disease and are noteworthy in several respects. First, the majority of candidate events are losses as opposed to gains. Second, the phenotypic spectrum of their patient cohort falls into the category of idiopathic or nonsyndromic MR/ID, indicating possibly more subtle functional outcomes for the CNVs. Third, the potentially pathogenic epigenetic regulator genes identified belong mostly to the chromatin remodeling class of epigenetic regulation. As discussed earlier, mutations to members of this class might be anticipated to have a milder or more variable outcome. Fourth, the 9% hit rate given the relatively small number of genes encoding epigenetic regulators included in the study underlines the necessity of correct epigenetic control for normal neurodevelopment.

Endophenotypes and Epigenetic Modes of Action in the Brain

The task of correctly correlating genotypes to phenotypes is particularly challenging for neurodevelopmental disorders. There is an overlap of features among different MR/ID syndromes (3). In addition, an overlap is also observed between the broader clinical neurodevelopmental disorder categories. For instance, ASD is often part of the presentation for MR/ID cases (3), and patients with SCZ can display behaviors, which are part of the spectra of other disease categories such as BD, attention deficit hyperactivity disorder (ADHD), MR/ID, or ASD (68). The finding of a phenotypic overlap and a common genotype (*e.g.* Table 1, *MeCP2* defects causing Rett syndrome, ASD, and SCZ) lends weight to the approach to study the genetic basis of these disorders by breaking them down in to endophenotypes (68,69) An endophenotype can be defined as a largely heritable quantitative trait that is part of the pathophysiology of a given disorder but not necessarily sufficient to manifest the disorder itself (70). For example, there has been focused study of specific brain morphologies as an endophenotype of ASD (71–74), MR/ID (58), and SCZ (75). The hope is that an endophenotype approach will help demystify the genotype to phenotype connection and articulate a more straightforward cause and effect model (69). This is especially relevant in the context of neurodevelopmental disorders, where the syndromic presentation and behavioral phenotypes are complex, and to say a given gene may directly control a given characteristic (*e.g.* IQ) is at best an oversimplification (76).

An endophenotype-based approach is also practical for the use of animal models to study complex neurodevelopmental disorders. Although it is virtually impossible to assess a model organism as having MR/ID or ASD or SCZ, it is possible to assess and quantify whether they manifest specific endophenotypes found in these disorders (68,69). A number of studies have been conducted investigating the role of epigenetic regulation in animal models using endophenotypes of neurodevelopmental disorders (77–81). Considering methylation de-

fects, a dose-dependant effect has been shown for DNMT1 in mice, where mice heterozygous for *Dnmt1* show reduced infarcts following ischemia (82), which can be considered an endophenotype of neuronal activity. In conjunction, it has been shown that for patients with SCZ, there is a reduced mortality following stroke (83). In another example, mice null for Mbd1 (a MBD containing protein; an epigenetic regulator that can bind methylated DNA) have been shown to display deficits in learning and social interaction (84), an endophenotype of ASD and MR/ID (85,86). In terms of histone modification defects, mice null for *Hdac2* (a histone deacetylase) were reported to have reduced body size (87), which can be considered a corollary of short stature and growth impairment; endophenotypes of syndromes included under both the MR/ID and ASD disorder spectra (3). These studies indicate that the co-occurrence of ASD, MR/ID, and SCZ phenotypes can be due to the perturbation of common epigenetic regulatory pathways in neuronal development and function.

Another important perspective for understanding the role of epigenetic regulation in neurodevelopment is looking at where and when epigenetic regulatory factors play a role in the developing CNS. MacDonald and Roskams (15), upon reviewing a number of studies researching the spatiotemporal expression patterns of epigenetic regulators in mouse brain, argue for the occurrence of "discrete epigenetic checkpoints" depending on the time and place of expression of Hdacs, Dnmts, and Mbd proteins. This opinion is interesting because it allows us to think in terms of not only gene targets for the pathogenicity of epigenetic deregulation but enables us to view epigenetic deregulation as affecting spatial and temporally bound aspects of neurodevelopment. The work by Chahrour *et al.* (48) lends support to this model as their groundbreaking findings came about due to approaching the investigation by looking not at the brain as a whole but at a specific brain region, in this case the hypothalamus.

Others have taken the spatiotemporal patterning a step further by looking at neuron subtype-specific expression of epigenetic regulators. For example, studies have shown that aberrant epigenetic events deregulate important targets in GABAergic neurons of SCZ postmortem brains (88,89). Costa *et al.* (90) detail the effects of DNMT expression levels in GABAergic neurons, showing a DNMT dosage-dependant activity of key target genes. These observations point to links between specific neuronal activity outcomes or endophenotypes and the way epigenetic factors play out in different brain regions and at different time points in cognitive development and function, although we are far from a thorough understanding of these complex processes.

Gene-Environment Interactions and Genetic Background

Epigenetic mechanisms provide a means to explain the molecular link between environment and gene function, which is particularly important when elucidating pathogenicity of complex disease such as ASD, MR/ID, and SCZ, as they are known to have significant gene-environment interaction (GxE) in their etiopathology (3,91–93). For example, findings detailing how diet can affect the methylation status of genes and thereby control their transcription (94) or how drugs can alter the expression levels of methyl transferases (95) demonstrate a clear link between environment and epigenetic control. Although many mechanisms for environment-dependent gene transcription control *via* an epigenetics model may exist, one that is easily perceptible, is based on the availability of the raw materials necessary for epigenetic regulators to function correctly, *e.g.* the availability of methyl donors (90). As has been shown by an environmental methionine-dependent control of target genes due to the impact of the substrate availability upon the intact methyltransferase enzyme's function (96,97).

Exploring the connection between environmentally supplied chemicals and their impact on epigenetic regulatory mechanisms is especially attractive as it offers a possible method of controlling gene expression *via* administrable therapeutics. Drugs with a mode of action involved in the epigenetic cascade are already known (*e.g.* Valproic acid (96)). There has been an increased focus on the ability to use these drugs and develop new drugs as effective therapeutics for neurodevelopmental disorders (90). The above interactions and other effects are substantially reviewed elsewhere (91,98) and serve to exemplify methods by which epigenetic involvement can explain GxE.

Genetic background offers another explanation for the variability possible due to epigenetic deregulation. For instance, in the case of CNVs, inherited variants are being shown to be benign and pathogenic in different individuals in an increasing number of MR/ID cases (62). Although we can explain the different effect of the same mutation in different individuals in terms of variable expressivity and penetrance purely situated on the genotypic background of the concerned individual (62), Van Winkel *et al.* point to the phenomenon that certain genotypes may be correlated with contradistinctive epigenetic signatures. They posit that the "genetic background" should be discussed in terms of the epigenetic landscape as there could be individual specific genotype-dependent differential DNA methylation states (91). This could potentially blur the boundary between GxE as traditionally understood and epigenetics (91), because it moves epigenetic regulation into the paradigm of the inherent individual's hereditary (or genomic and epigenomic) variability and not simply limiting epigenetic mechanisms to a mode of action. Therefore, although epigenetics is particularly attractive as a link between gene and environment, exactly how it functions in this context may not be straightforward.

Conclusion

The role of epigenetic regulation in neurodevelopment is multifaceted and complicated. Modeling the link between aberrant epigenetic control and neurocognitive disorders may be attempted from a number of angles. Figure 2 offers a schematic of possible pathophysiology in terms of epigenetic regulatory mechanisms, highlighting the relationships between molecular genetic functional pathways, the spatial and temporal aspects of regulation in the brain, and how the environment plays a part in the brain's function.
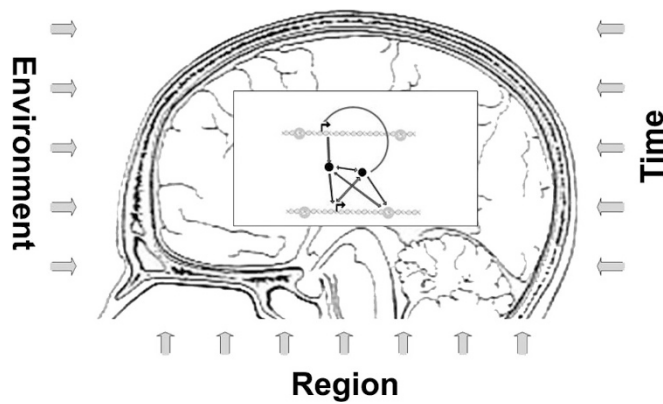
Figure 2. Showing the complex interplay possible between environment, spatiotemporal factors and epigenetic regulatory mechanisms in the brain. Epigenetic control of gene function is depicted in the inner box, where epigenetic regulator proteins are diagramed as black circles and the arrows show modes of action. An epigenetic regulator can directly affect the target gene by acting upon the DNA sequence (depicted by the lower DNA strand) *e.g.* by DNA methylation activity, or by acting upon the nucleosome (depicted by the gray shaded circle on the lower DNA strand), *e.g.* by histone modification activity or it may act in conjunction with other epigenetic regulators. In addition the gene encoding the epigenetic regulator itself (depicted by the upper DNA strand) may be amenable to epigenetic control.

The relatively smaller number of genes encoding epigenetic regulators *versus* the larger number of genes involved in neurodevelopment, which these regulators are able to control, emphasizes the extent of pleiotropy possible for defects involving epigenetic regulator encoding genes, depending on their binding targets. Functional domain-specific mutation ability within the epigenetic regulatory protein and the coincident or intergrative pathways that some epigenetic regulators act in, results in more layers of possible deregulatory genetic mechanisms, as phenotypic outcome may be domain specific or depend on whether related family members are also affected. Furthermore, that many epigenetic regulators operate as part of multiunit complexes allows for a higher sensitivity to dosage dependency for these factors, as the functional outcome may be fine-tuned to the overall stoichiometry for the complex, depending on what factors are bound and in what proportion. This is evidenced by the frequent occurrence of genes encoding epigenetic regulators as part of pathogenic CNV events.

Clinical boundaries between traditionally established disease states in neurofunction, viz, MR/ID, ASD, and SCZ, are blurring. Assisted by a new wave of diagnoses made using a genetics first approach (99), a growing number of cases are being reported of patients who carry the same gene defect, yet clinically belong to either MR/ID or ASD or SCZ or have more than one of these presentations. This trend emphasizes the utility of an endophenotype-based approach to research CNS pathologies because it allows us to address the study of genetics in neurocognitive free of clinical delimiters, thereby leading to a better understanding of how epigenetics can regulate specific behaviors and aspects of neurodevelopment.

The brain is a highly sophisticated organ, required to have an extreme level of plasticity, because it must continually react and adapt to diverse external stimuli (100). Given that

epigenetic regulation can be situated as an attractive and versatile "switching mechanism" able to finely tune its scope and extent of control, there is indication for a much greater degree of epigenetic regulatory involvement in CNS development and function than we currently understand. In the context of neurodevelopmental disease, delineating the epigenetic role is particularly attractive, due to the possibility for correcting the causative epigenetic perturbation by administration of therapeutics, consequently raising hope for effective treatment for these debilitating disorders.

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