CHAPTER 7

Epigenetics and Genetics of Development

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ABBREVIATIONS

5-HTT	serotonin transporter gene
ADP	adenosine diphosphate
AHRR	aryl hydrocarbon receptor repressor
ARC	arcuate nucleus
AS	Angelman syndrome
ATP	adenosine triphosphate
BDNF	brain-derived neurotrophic factor
BWS	Beckwith–Wiedemann syndrome
CpG	cytosine-guanine dinucleotide
CpH	cytosine-adenosine/cytosine/thymine dinucleotide
CGI	cytosine-guanine dinucleotide island
COMT	catechol-*O*-methyltransferase
DNA	deoxyribonucleic acid
DNAhm	DNA hydroxymethylation
DNMT	DNA methyltransferase
DOHaD	developmental origins of health and disease
ESC	embryonic stem cell
F0/F1/F2/F3	initial, first, second, or third generation
FASD	fetal alcohol spectrum disorder
FGF	fibroblast growth factor
FKBP5	FK506 Binding Protein 5
G × E	gene by environment
GnRH	gonadotropin-releasing hormone
GR	glucocorticoid receptor
H3K4me	histone 3 lysine 4 methylation
H3K9me	histone 3 lysine 9 methylation
H3K27me	histone 3 lysine 27 methylation
HAR1A	highly accelerated region 1A
HAT	histone acetyltransferases
HDAC	histone deacetylase

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HDM	histone demethylases
HMT	histone methyltransferases
HTT	Huntington gene
HP1	heterochromatin protein 1
IAP	intracisternal A particles
ICM	inner cell mass
IGF2	insulin growth factor 2
IQ	intellectual quotient
Kiss1	kisspeptin gene
LEARn	latent early-life associated regulation
LINE-1	long interspersed nuclear element 1
MAF	minor allele frequency
MAOA	monoamine oxidase-A
MeCP2	methyl CpG binding protein 2
NFR	nucleosome-free regions
NPC	neural progenitor cell
NR3C1	nuclear receptor subfamily 3 group C (GR-encoding gene)
PCDH	protocadherin
PcG	polycomb group
PD	Parkinson's disorder
PGC	primordial germ cell
PTM	posttranslational modifications
PTSD	posttraumatic stress disorder
PWS	Prader Willi syndrome
QTL	quantitative trait locus
mQTL	methylation quantitative trait locus
RNA	ribonucleic acid
RNAi	RNA interference
dsRNA	double-stranded RNA
lncRNA	long noncoding RNA
mRNA	messenger RNA
miRNA	microRNA
ncRNA	noncoding RNA
piRNA	PIWI-interacting RNA
pri-miRNA	primary miRNA
siRNA	short interfering RNA
snoRNA	small nucleolar RNA
snRNA	small nuclear RNA
spliRNA	splice-site RNA
ssRNA	single-stranded RNA
tRNA	transfer RNA
tiRNA	transcription initiation RNA
RSS	Russell–Silver syndrome
SNCA	alpha-synuclein gene
SNP	single nucleotide polymorphism
SNV	single nucleotide variant
TE	trophectoderm
TET	ten–eleven-translocation

TDG	thymidine DNA glycosylase
TrxG	trithorax group
Xi	inactivated X chromosome
Xic	X-inactivation center
Xist	X-inactive specific transcript
XCI	X chromosome inactivation

7.1 FOREWORD

Brain development consists of a series of complex and dynamic events, integrating contributions from genetic, epigenetic, and environmental factors to mediate the establishment and maintenance of neural networks throughout the life course. As such, characterizing the molecular mechanisms underpinning trajectories of brain development across the lifespan constitutes a fundamental cornerstone of neurobiological research. Although genetic factors comprise the inherited basis of developmental patterning, epigenetic factors are thought to form the regulatory overlay of the genome, playing crucial roles in the global shaping and maintenance of these patterns. Importantly, the same epigenetic processes that maintain ontogenetic stability can also exhibit environmentally influenced dynamic variation. Such responsiveness is critical to neural development in the brain and may be particularly critical for brain plasticity during sensitive periods of development. Furthermore, the dysregulation of epigenetic mechanisms can often lead to pathological consequences, contributing to a spectrum of disease phenotypes and neurodevelopmental disorders. Accordingly, delineating the key functions of both genetic and epigenetic factors throughout different developmental periods is crucial to understanding the complex molecular processes that underlie brain development and plasticity. Here, we provide a general framework for such genetic and epigenetic variation, detailing their roles in the context of different developmental stages across the life course, as well as neurodevelopmental and psychiatric disorders (Figure 7.1).

7.2 INTRODUCTION TO GENETICS

The mechanisms underlying the inherited basis of human health and disease have been a longstanding scientific challenge, particularly in the context of developmental research. Our understanding of the factors driving such inheritance only truly blossomed in the late 19th century, when Gregor Mendel ushered in the new era of genetics through his groundbreaking experiments in pea plants. Now considered the father of modern genetics, Mendel identified the basic principles of hereditary transmission, illustrating the predictable action of discrete units to produce inherited traits known as phenotypes. Further research in the field later identified DNA as the main hereditary molecule of the cell and the inherited units as specific genomic sequences known as

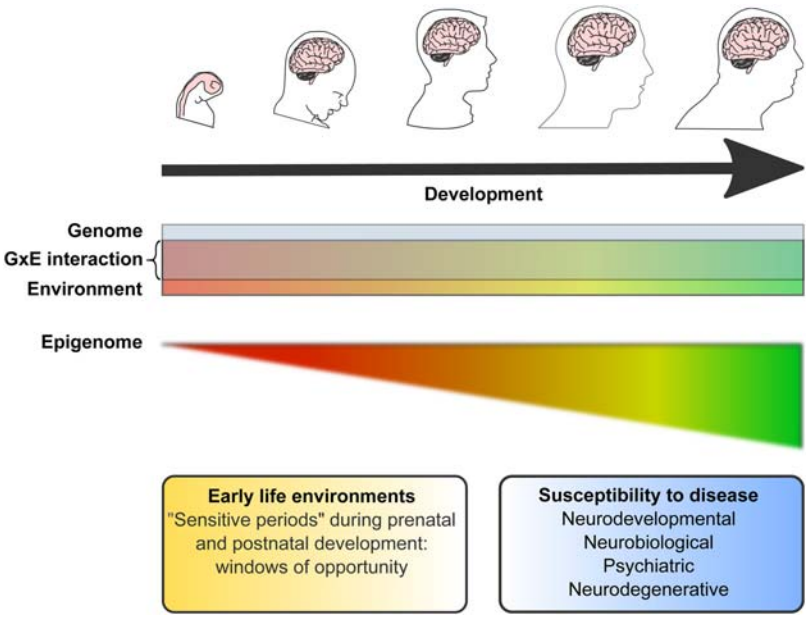

Figure 7.1 Biological variation and brain-related phenotypes are influenced by multiple sources throughout brain development. Genetic variation (blue bar) is inherited at birth and remains mostly stable throughout the lifetime. By contrast, the environment presents shifting conditions that can influence long-term health and behavior (rainbow bar). The intersection of these two influences represents gene by environment (G × E) interactions (overlap). Together, these factors are reflected in the epigenome, which is highly malleable in response to environmental conditions and strongly influenced by genetic variation. Epigenetic variability increases across the life course, with different developmental windows conferring differential sensitivity to G × E and environmental influences (widening triangle gradient). These windows of opportunity for developmental programing of epigenetic patterns and subsequent health are more vulnerable during early life, which ranges from preconception and prenatal life to postnatal environments. In turn, these effects can also influence vulnerability to disease, including neurodevelopmental disorders, neurobiological dysregulation, psychiatric disease, and neurodegeneration later in life. Taken together, the influences of both the genome and shifting environments are reflected in the epigenome, which can shape development and vulnerability to disease.

genes, which in turn encode different cellular products that interact to produce various phenotypes. Early research into the genetic underpinnings of disease focused mainly on monogenic, or Mendelian, diseases, which are caused by mutations in a single gene and show a defined inheritance pattern (dominant or recessive, and autosomal or sex-linked). For example, Huntington's disease is an autosomal dominant Mendelian disorder caused by trinucleotide repeat expansion mutations in the huntingtin gene (*HTT*) and results in age-related neurodegeneration, loss of motor control, and progressive cognitive decline. Although relatively few genes produce such drastic phenotypes, the study of Mendelian disorders has provided vital insight into the genes required for the

typical development of different physiological systems, especially in the context of the brain. While disruption of only a single gene's function is primarily involved in Mendelian disease pathogenesis, common complex diseases (e.g., type 2 diabetes, schizophrenia, and coronary heart disease), and quantitative biological traits (e.g., height, weight, and IQ) display multifactorial etiology involving variation from multiple genes and environmental conditions (Hirschhorn & Daly, 2005). The spectrum of genetic variation underlying such complex traits and common diseases ranges from single nucleotide variants (SNVs) to structural variants, such as insertions, deletions, duplications, inversions, and copy number differences (Frazer, Murray, Schork, & Topol, 2009). The former are further classified according to the frequency of the minor allele (i.e., less common allele in a given population). Specifically, single nucleotide polymorphisms (SNPs) refer to SNVs with a minor allele frequency (MAF) of at least 1% in the population, whereas low frequency and rare variants have a MAF of less than 1% or 0.05%, respectively (Frazer et al., 2009). Most common variants have relatively small effect sizes on a given phenotype when analyzed individually or in combination and can therefore only explain a small proportion of disease or trait heritability defined as the proportion of phenotypic variance attributed to additive genetic factors (Manolio et al., 2009). For example, while the human height shows an estimated heritability of 80%, its associated variants only account for 5% of the observed phenotypic variance (Visscher, 2008). This suggests that other undetected factors likely contribute to phenotypic variance and therefore constitute an appreciable proportion of the "missing heritability" in these complex diseases or traits (Manolio et al., 2009). Such unaccounted factors may arise from an inadequate ability to detect rare variants with large effect sizes, poor detection of structural variations using commercial SNP arrays, and low power to account for nonadditive (i.e., epistatic) effects or gene−gene interactions (Visscher, Hill, & Wray, 2008). Importantly, the contribution of environmental influences, particularly during dynamic periods of developmental susceptibility, and their interplay with allelic variation (known as gene × environment interactions) represent additional sources of heritable variability, which are thought to inflate estimates of total heritability (Boyce, 2016; Zannas, Provençal, & Binder, 2015; Zuk, Hechter, Sunyaev, & Lander, 2012). Accordingly, a functional characterization of the genetic architecture underlying complex phenotypes requires a thorough analysis of the diverse regulatory layers coordinating the precise and timely expression of the ∼25,000 genes in the human genome.

7.3 INTRODUCTION TO EPIGENETICS

7.3.1 What is epigenetics?

Although genetics may be considered the inscribed "blueprint" underlying the central dogma of molecular biology (i.e., DNA → RNA → protein), epigenetics can be

thought of as the regulatory overlay of genetic sequence that fine-tunes gene activity during development and in response to external signals (Boyce & Kobor, 2015). From a historical perspective, the term "epigenetics" was first introduced by Conrad Waddington in the early 1940s to describe "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" (Waddington, 1968). Waddington argued that epigenetics play a critical role in the development of multicellular organisms by creating "epigenetic landscapes" that drive cellular differentiation along a programmed trajectory toward a specific cell-type lineage (Waddington, 1968). Since the first introduction of this concept, the field of epigenetics has flourished into a highly active area of study aimed at characterizing the molecular mechanisms underlying gene regulation and biological programing. Today, epigenetics is operationally defined as modifications of DNA and its regulatory components, including chromatin and noncoding RNA, to potentially modulate gene transcription without changing the DNA sequence itself (Bird, 2007; Henikoff & Greally, 2016; Meaney, 2010). Notably, Waddington's initial hypothesis still holds true: The ontogeny of the ~200 different cell types in the human body is largely shaped by the unique epigenomic profiles and transcriptional activity of each cellular subtype (Domcke et al., 2015; Schuebeler, 2015). In addition, epigenetic regulation is now becoming increasingly recognized as a potential biological mediator of environmental influences, which can contribute to sculpting the epigenome (Feil & Fraga, 2012). Accordingly, epigenetic regulation involves both dynamic tissue- and cell-type-specific variation during development, as well as the preservation of the cellular memory required for developmental stability. The orchestration of such epigenetic control involves a number of distinct mechanisms, namely, (1) DNA modifications, (2) regulation of chromatin structure, and (3) noncoding RNA activity.

7.3.2 DNA modifications

Covalent modifications on DNA nucleotides, primarily cytosine, have long been an established form of epigenetic regulation. Specifically, DNA modifications are comprised of DNA methylation (which can occur in the context of cytosine-guanine (CpG) dinucleotides or at non-CpG positions) as well as oxidized derivatives of DNA methylation such as DNA hydroxymethylation (DNAhm). In this section, we review these variant forms of DNA modifications in the context of brain development.

7.3.2.1 DNA methylation

DNA methylation is arguably the most studied epigenetic mark and involves the covalent attachment of a methyl group to the 5′ position of cytosine, typically at CpG dinucleotide sites (Jones & Takai, 2001). These CpG dinucleotides occur relatively infrequently in the genome in order to minimize the potential for DNA methylation-induced

sequence mutability, as methylated cytosines can undergo spontaneous deamination to thymine (Gardiner-Garden & Frommer, 1987; Illingworth & Bird, 2009; Weber et al., 2007). Areas with comparatively high CpG content in the genome have been termed "CpG islands" (CGIs) and these CGIs are thought to exist as regions that were either never methylated or only transiently methylated in the germline while the rest of the genome experienced a loss of CpGs at methylated sequences (Gardiner-Garden & Frommer, 1987; Illingworth & Bird, 2009; Weber et al., 2007). Importantly, the DNA methylation status of the ~28 million CpG sites in the human genome is often dependent on genomic context (Jones, 2012; Ulahannan & Greally, 2015). For example, CGIs, which are associated with approximately 50%–70% of known promoters, tend to contain low levels of methylation in somatic cells, while nonisland CpGs exhibit generally higher methylation levels (Illingworth & Bird, 2009; Saxonov, Berg, & Brutlag, 2006; Weber et al., 2007). Moreover, DNA methylation is associated with the regulation of gene expression, although its effects on transcription are highly dependent on genomic context (Edgar, Tan, Portales-Casamar, & Pavlidis, 2014; Jones & Baylin, 2007; Lam et al., 2012). For example, DNA methylation at gene promoters is generally associated with gene expression silencing, although its role may be more variable within gene bodies (Jones & Baylin, 2007; Schuebeler, 2015). Conversely, in regions of lower CpG density which flank CGIs, known as "island shores," high DNA methylation levels are generally associated with highly expressed genes, especially if the associated CGI is lowly methylated (Baubec & Schuebeler, 2014; Edgar et al., 2014; Irizarry et al., 2008). While the exact mechanisms remain mostly unknown, transcriptional silencing by DNA methylation may potentially occur through the direct blocking of transcription factor binding or the recruitment of transcriptional repressors to promoter, enhancers, or insulator regions (Tate & Bird, 1993). Although DNA methylation patterns in promoter regions tend to negatively correlate with gene expression within an individual, emerging evidence shows that when comparing a single gene across a population, the association between DNA methylation and gene expression can be negative, positive, or nonexistent, highlighting the complex relationship between DNA methylation and transcription (Gutierrez-Arcelus et al., 2013; Jones, Fejes, & Kobor, 2013; Lam et al., 2012). Moreover, DNA methylation can be both active, by being a likely cause of gene expression variation, or passive, by being a consequence or an independent mark of gene expression levels (Gutierrez-Arcelus et al., 2013; Jones et al., 2013). In addition to its role in transcriptional control, DNA methylation within introns has been associated with altered messenger RNA (mRNA) splicing, and its presence within certain exons potentially regulates alternative transcriptional start sites (Maunakea et al., 2010; Maunakea, Chepelev, Cui, & Zhao, 2013; Shukla et al., 2011). Finally, DNA methylation in repetitive elements, which comprise more than half of the human genome including intergenic sequences, tends to occur at relatively high levels and is associated

with maintenance of chromosome structure and genomic integrity (Cordaux & Batzer, 2009; Donnelly, Hawkins, & Moss, 1999).

The establishment and maintenance of DNA methylation patterns are carried out by a highly conserved family of enzymes known as DNA methyltransferases (DNMTs). In mammals, three major DNMTs have been identified, DNMT1, DNMT3a, and DNMT3b, which are characterized by a conserved stretch of amino acids in the C-terminal catalytic domain that target the 5′ carbon of cytosine (Bestor, 2000). As the most abundant form in adult cells, DNMT1 maintains DNA methylation patterns during cell division by binding hemi-methylated CpG sites following DNA replication and methylating the cytosine on the newly synthesized daughter strand (Robertson et al., 1999). In contrast to DNMT1's role in DNA methylation maintenance, DNMT3a and DNMT3b establish de novo genome-wide DNA methylation patterns following embryo implantation (discussed in Section 7.5) (Okano, Xie, & Li, 1998). These enzymes show equal affinity for hemi-methylated or nonmethylated DNA, and are essential for early development, as deleting their encoding genes causes embryonic lethality in mice (Okano et al., 1998). DNMTs are vital components of epigenetic regulation, modulating the expression of different genes and suppressing repetitive elements throughout the genome to prevent transposition events and chromosomal instability, which could have severe consequences on the organism. For instance, missense mutations in DNMT3b can result in immunodeficiency-centromeric instability-facial anomalies syndrome, caused by chromatin dysregulation and increased genome instability due to recombination events between homologous repetitive elements (Ehrlich et al., 2009). Of note, the maintenance and de novo roles of these enzymes are not clear-cut, as DNMT1 can function as a *de novo* DNMT when overexpressed in cultured human fibroblasts (Vertino, Yen, Gao, & Baylin, 1996). Conversely, DNMT3a and DNMT3b can also play a role in DNA methylation maintenance, as loss of DNMT1 in human colorectal cancer cells results in a loss of DNA methylation at only 20% of CpG sites (Rhee et al., 2000). Finally, two additional DNMTs exist in vertebrates, DNMT3L and DNMT2. Although catalytically inactive, the former binds to DNMT3a/b to increase their enzymatic activity, a function required for reproduction, but not development (Gowher, Liebert, Hermann, Xu, & Jeltsch, 2005). Interestingly, the male germ cells of mice lacking this enzyme display increased activity of transposable elements, including LINE-1 (long interspersed nuclear element 1) and IAP (intracisternal A particles) classes, highlighting the role of DNMTs in suppressing transposition events (Bourc'his & Bestor, 2004; Webster et al., 2005). By contrast, DNMT2 has barely any detectable CpG methylation activity, but has been linked to transfer RNA (tRNA) methylation (Goll et al., 2006; Jeltsch, Nellen, & Lyko, 2006; Schaefer et al., 2010).

7.3.2.2 Non-CpG DNA methylation

While DNA methylation primarily occurs in the context of CpG dinucleotides, it can also occur at CpH (where H = A/C/T) sites. Indeed, both the maintenance DNMT1 and *de novo* DNMT3a/b enzymes have been shown to methylate non-CpG cytosines in vitro (Guo et al., 2014; Yokochi & Robertson, 2002). Previous studies have shown that methylated CH dinucleotides (mCH) occur in cultured embryonic stem cells (ESCs) and induced pluripotent stem cells (Laurent et al., 2010; Lister et al., 2009; Lister et al., 2012; Ramsahoye et al., 2000; Ziller et al., 2011). Moreover, analysis of adult human and mouse CNS neurons found that mCH is specifically enriched in neurons compared to other cell types, as non-CpG methylation is nearly absent in nonneuronal adult somatic cells, but can reach up to ~25% of all cytosines in neurons of the adult mouse dentate gyrus (Guo et al., 2014; Lister et al., 2013; Ziller et al., 2011). Levels of mCH increase rapidly during early postnatal brain development (mouse ~2–4 weeks; human 0–2 years), suggesting that mCH potentially plays an important role in the regulation of postnatal brain development. These changes are associated with a transient rise in DNMT3a levels, as knockdown of this enzyme results in significant loss of mCH, but not methylcytosine levels (Guo et al., 2014). Genome-wide profiling also showed that in neurons, mCH is present throughout the 5′ upstream, gene–body, and 3′ downstream regions of genes, where it is negatively correlated with gene expression (Guo et al., 2014; Lister et al., 2013). Furthermore, in vitro plasmid reporter gene analyses have shown that CH methylation is associated with transcriptional repression in mouse neurons (Guo et al., 2014). However, mCH is not associated with gene silencing in all cell types, as non-CpG methylation in ESCs positively correlates with gene expression (Lister et al., 2009). It is thought that the distinct distribution and role in gene expression of mCH in different cell types relates to differences in the relative abundance and activity of specific "readers" and "writers" of non-CpG methylation (Kinde, Gabel, Gilbert, Griffith, & Greenberg, 2015). Furthermore, in addition to CH methylation, very recent research has detected the presence of methylated adenosine nucleotides in vertebrates, suggesting that that DNA modification variants may be more diverse than previously thought (Dominissini et al., 2013; Koziol et al., 2015; Meyer & Jaffrey, 2016; Meyer et al., 2012).

7.3.2.3 DNA hydroxymethylation

Although the mechanisms underlying the establishment and maintenance of DNA methylation by DNMTs have been well characterized, the process of DNA demethylation remains unclear. Thought to involve both active and passive pathways, this phenomenon is vital for typical development and genetic regulation, particularly in the brain (Ooi & Bestor, 2008; Tognini, Napoli, & Pizzorusso, 2015; Wu & Zhang, 2014). For example, neuronal activity-induced DNA demethylation of specific

promoters and expression of corresponding genes such as brain-derived neurotrophic factor (*BDNF*) and fibroblast growth factors (*FGF*) occurs through the action of Gadd45b and represents an activity-dependent form of modulating neurogenesis in the adult brain (Ma et al., 2009). Passive DNA demethylation can occur due to a lack of DNMT1 activity, resulting in a gradual loss of DNA methylation over several rounds of replication (Bhutani, Burns, & Blau, 2011). By contrast, active DNA demethylation may potentially occur through the oxidation of 5-methylcytosine (5mC), catalyzed by the ten−eleven-translocation (TET) family of enzymes (Santiago, Antunes, Guedes, Sousa, & Marques, 2014; Tahiliani et al., 2009). This process generates a series of oxidized cytosine base variants, including hydroxymethylcytosine (hmC), formylcytosine (fC), and carboxycytosine (caC) (Ito et al., 2010; Tahiliani et al., 2009; Ulahannan & Greally, 2015). The oxidized site can then be removed by thymine DNA glycosylase to create an abasic site, which undergoes base excision repair to yield an unmodified cytosine (He et al., 2011). Alternatively, hmC can be converted to hydroxymethyluracil by activation-induced deaminase prior to base excision repair (Nabel et al., 2012). Although the exact details of active DNA demethylation remain unclear, the emerging evidence points to a process involving the coordinated activity of a number of key enzymatic players and intermediate modified cytosine species. In addition to their potential role in DNA demethylation, these cytosine variants may also play a role in modulating chromatin structure or recruiting various factors to key regions of the genome (Sadakierska-Chudy, Kostrzewa, Filip, & Comprehensive View, 2014). For instance, various members of the methyl-CpG-binding domain (MBD) protein family display different affinities for hmC, and given their role in recruiting different chromatin-modifying complexes, hmC could potentially alter chromatin landscapes throughout the genome (Pfeifer, Kadam, & Jin, 2013). Interestingly, DNAhm is present at high levels in pluripotent cells and the brain, where it has been implicated in neural stem cell functions, although its exact functional role remains to be uncovered (Ito et al., 2010; Kriaucionis & Heintz, 2009; Santiago et al., 2014). Genome-wide mapping of DNAhm in various brain regions, including the frontal cortex, hippocampus, and cerebellum, identified an enrichment of hmC in gene bodies, which was positively associated with gene transcription, particularly at developmentally activated genes (Lister et al., 2013; Wang et al., 2012). Finally, active DNA demethylation and TET activity is associated with memory formation and addiction in mice, further supporting its functional role in neural activity (Alaghband, Bredy, & Wood, 2016).

7.3.3 Regulation of chromatin structure

In eukaryotic genomes, DNA does not exist as a naked template but rather as a dynamic, nucleoprotein polymer. Known as chromatin, this structure is regulated by a

multitude of factors to modulate access to genetic material and allow for DNA compaction within the nucleus. The fundamental repeating unit of chromatin is the nucleosome, consisting of 147 base pairs of DNA wrapped around a protein octamer containing two molecules each of core histone proteins, H2A, H2B, H3, and H4 (Kornberg, 1974; Luger, Mäder, Richmond, & Sargent, 1997). Nucleosomes are interconnected by short sections of DNA associated with the linker histone H1 to form an 11-nm-wide "beads-on-a-string" structure (Kornberg, 1974; Olins & Olins, 1974). In turn, this structure is thought to coil into a 30-nm chromatin fiber, although the elucidation of this structure remains widely debated (Joti et al., 2014; Li & Reinberg, 2011). The chromatin fiber structure can subsequently undergo additional levels of condensation to ultimately form the typical chromosome structure seen during mitosis (Li & Reinberg, 2011; Robinson, Fairall, Huynh, & Rhodes, 2006). Transitions between higher order chromatin conformations are dependent on several factors, such as cell cycle phase, transcriptional activity, and cell type (Ma, Kanakousaki, & Buttitta, 2015). For example, the beads-on-a-string structure represents the active and largely unfolded configuration that occurs during interphase to permit access of transcriptional machinery to DNA, while condensed chromosomes occur during mitosis to permit segregation of replicated DNA during anaphase (Ma et al., 2015). Eukaryotic nuclei display two main types of chromatin structure, tightly packed regions known as heterochromatin, and relatively less condensed regions known as euchromatin (Allis & Jenuwein, 2016). In general, euchromatin assumes a relatively open and more accessible conformation that contains actively transcribed genes. By contrast, heterochromatin is highly condensed and tends to contain largely transcriptionally silenced element, such as repetitive sequences in pericentromeric and telomeric regions (Allis & Jenuwein, 2016; Grewal & Jia, 2007). Given that chromatin structure and transcriptional activity are tightly linked processes, their relationship requires a dynamic interplay between histone modifications, histone variants, and chromatin remodeling complexes (Deal & Henikoff, 2010).

7.3.3.1 Histone modifications

Histones are small and highly basic proteins possessing a flexible N-terminal tail that protrudes from the nucleosome core particle. This structure is the predominant target of posttranslational modifications (PTMs) in which chemical groups or short protein peptides are covalently attached to specific amino acid residues to confer an additional level of regulatory control on the chromatin structure. Different types of histone PTMs include acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and adenosine diphosphate-ribosylation (Table 7.1) (Bannister & Kouzarides, 2011; Bowman & Poirier, 2015; Kouzarides, 2007). These influence nucleosome stability and positioning by altering the chemical interactions within nucleosomes, between neighboring nucleosomes, or between histone-DNA contacts (Shogren-Knaak et al., 2006;

Table 7.1 Summary of histone posttranslational modifications[a]

Histone	Modified residue	Modification	Modifying enzymes	Proposed function
H1	Lys26	Methylation	EZH2	Transcriptional silencing
	Ser27	Phosphorylation	Unknown	Transcriptional activation, chromatin decondensation
H2A	Lys5	Acetylation	Tip60, p300/CBP	Transcriptional activation
	Ser1	Phosphorylation	Unknown, MSK1	Mitosis, chromatin assembly, transcriptional repression
	Ser139 (mammalian H2AX)	Phosphorylation	ATR, ATM, DNA-PK	DNA repair
	Lys119	Ubiquitylation	Ring2	Spermatogenesis
	Lys9	Biotinylation	Biotinidase	Unknown
	Lys13	Biotinylation	Biotinidase	Unknown
H2B	Lys5	Acetylation	p300, ATF2	Transcriptional activation
	Lys12	Acetylation	p300/CBP, ATF2	Transcriptional activation
	Lys15	Acetylation	p300/CBP, ATF2	Transcriptional activation
	Lys20	Acetylation	p300	Transcriptional activation
	Ser14	Phosphorylation	Mst1, unknown	Apoptosis, DNA repair
	Lys120	Ubiquitylation	UbcH6	Meiosis
H3	Lys9	Acetylation	Gcn5, SRC-1, unknown	Transcriptional activation, histone deposition
	Lys14	Acetylation	Unknown, Gcn5, PCAF, Esal, Tip60, SRC-1, Elp3, Hpa2, hTFIIIC90, TAF1, Sas2, Sas3, p300	Histone deposition, transcriptional activation, DNA repair, RNA polymerase II & III transcription, euchromatin
	Lys18	Acetylation	Gcn5, p300/CBP	Transcriptional activation, DNA repair and replication
	Lys23	Acetylation	Unknown, Gcn5, SAs3, p300/CBP	Histone deposition, transcriptional activation, DNA repair
	Lys27	Acetylation	Gcn5	Transcriptional activation
	Lys4	Methylation	Set7/9 (vertebrates), MLL, ALL-1	Permissive euchromatin (di-Me), transcriptional activation
	Arg8	Methylation	PRMT5	Transcriptional repression
	Lys9	Methylation	Suv39h,Clr4, G9a, SETDB1	Transcriptional silencing (tri-Me), transcriptional repression, genomic imprinting, DNA methylation (tri-Me), transcriptional activation

	Arg17	Methylation	CARM1	Transcriptional activation
	Lys27	Methylation	EZH2, G9a	Transcriptional silencing, X inactivation (tri Me)
	Lys36	Methylation	Set2	Transcriptional activation (elongation)
	Lys79	Methylation	Dot1	Eurchromatin, transcriptional activation (elongation), checkpoint response
	Thr3	Phosphorylation	Haspin/Gsg2	Mitosis
	Ser10	Phosphorylation	Aurora-B kinase, MSK1, MSK2, IKK-α, Snf1	Mitosis, meiosis, immediate-early gene activation, transcriptional activation
	Thr11	Phosphorylation	Dlk/Zip	Mitosis
	Ser28	Phosphorylation	Aurora-B kinase, MSK1, MSK2	Mitosis, immediate-early activation
	Lys4	Biotinylation	Biotinidase	Gene expression
	Lys9	Biotinylation	Biotinidase	Gene expression
	Lys18	Biotinylation	Biotinidase	Gene expression
H4	Lys5	Acetylation	Hat1, Esal, Tip60, ATF2, Hpa2, p300	Histone deposition, transcriptional activation, DNA repair
	Lys8	Acetylation	Gcn5, PCAF, Esal, Tip60, ATF2, Elp3, p300	Transcriptional activation, DNA repair
	Lys12	Acetylation	Hat1, Esal, Tip60, Hpa2, p300	Histone deposition, telomeric silencing, transcriptional activation, DNA repair
	Lys16	Acetylation	Gcn5, Esal, Tip60, ATF2, Sas2	Transcriptional activation, DNA repair, euchromatin
	Arg3	Methylation	PRMT1/PRMT5	Transcriptional activation
	Lys20	Methylation	PR-Set7, Suv4-20	Transcriptional silencing (mono-Me), heterochromatin (tri-Me), transcriptional activation, checkpoint response
	Lys59	Methylation	Unknown	Transcriptional silencing
	Ser1	Phosphorylation	Unknown, CK2	Mitosis, chromatin assembly, DNA repair
	Lys12	Biotinylation	Biotinidase	DNA damage response

[a]Note only listed histone modifications pertaining to vertebrates and mammal.

Tropberger et al., 2013; Williams, Truong, & Tyler, 2008). These changes modulate the accessibility of the local chromatin structure, resulting in either open or closed chromatin states (Berger, Kouzarides, Shiekhattar, & Shilatifard, 2009; Venkatesh & Workman, 2015). For example, acetylation of lysine neutralizes its positive charge, thereby weakening interactions with the negatively charged DNA and promoting a more accessible chromatin structure (Grunstein, 1997). Moreover, different PTMs may regulate transcription in their vicinity by serving as a docking platform to recruit various effector proteins, such as chromatin remodeling complexes, or by preventing various proteins from binding to chromatin (Venkatesh et al., 2013). For example, heterochromatin protein 1 (HP1) binds to the methylated lysine 9 of histone H3, subsequently leading to the formation of heterochromatin and transcriptional silencing (Talbert & Henikoff, 2006). In general, most histone PTM marks can be classified as activating or repressive in relation to transcriptional status (Smolle & Workman, 2013). Importantly, histone modifications, along with their corresponding "readers," play key roles in mediating crosstalk between transcriptional regulators and chromatin-modifying complexes to dynamically regulate chromatin structure and function (Bannister & Kouzarides, 2011).

Covalent modifications of histones are reversible, requiring the action of histone-modifying enzymes. Specifically, separate enzymes that add and remove histone PTMs are referred to as "writers" and "erasers," respectively. Distinct classes of "writers" and "erasers" exist in eukaryotes, each specialized to act on a specific histone to catalyze a different PTM. For example, acetylation of specific lysine residues is catalyzed by histone acetyltransferases, while methylation is catalyzed by histone methyltransferases, phosphorylation is performed by kinases, and ubiquitination is carried out by ubiquitinases (Table 7.1) (Marmorstein & Trievel, 2009). Reciprocally, "erasers" include histone deacetyltransferases (HDACs) for deacetylation, histone demethylases (HDMs) for demethylation, phosphatases for dephosphorylation, and deubiquitinases for deubiquitination (Table 7.1) (Marmorstein & Trievel, 2009). The targeted activity of these enzymes often occurs on the same histone in a manner that can influence the transcriptional potential of the chromatin region. For example, Trithorax Group (TrxG) and Polycomb Group (PcG) proteins catalyze the trimethylation of lysine 4 and lysine 27 of histone 3 (H3K4me3 and H3K27me3), respectively, and the colocalization of these marks occur in regions known as bivalent domains (Bernstein et al., 2006; Voigt, Tee, & Reinberg, 2013). These bivalent domains are often found in ESCs at the promoters of developmental genes and are believed to poise the expression of developmental genes, keeping them in a reversibly silenced state, which allows for rapid activation or stable silencing upon differentiation (Mikkelsen et al., 2007; Pan et al., 2007). Given the immense diversity and biological specificity associated with distinct patterns of histone PTMs, it has been proposed that a "histone code" exists in which the combination of histone modifications on a single nucleosome would result

in a unique downstream effect (Strahl & Allis, 2000). However, the idea of a "histone code" remains a debated topic, which requires more defined biochemical, epigenomic, and functional characterizations of its potential combinatorial complexity (Rando, 2012).

7.3.3.2 Histone variants

An additional feature in the regulatory landscape of chromatin is the presence of histone variants, which are nonallelic variants of the core histones encoded by unique genes (Weber & Henikoff, 2014). These variants are highly conserved across species and exist for all canonical histones, except for histone H4 (Weber & Henikoff, 2014). The H2A and H2B families of variants exhibit substantial sequence variations, while the H3 family of variants tends to be less diverse (Talbert & Henikoff, 2010). While most eukaryotes express the core histones during the S phase of the cell cycle to allow for replication-coupled deposition, histone variants are largely expressed in a replication-independent manner (Talbert & Henikoff, 2010). This allows for varying levels of deposition that is dependent on the degree of exchange with its corresponding canonical histone (Weber & Henikoff, 2014). For example, variant H3.3 comprises ~90% of the histone 3 in terminally differentiated neurons, but only ~20% in dividing cells (McKittrick, Gaften, Ahmad, & Henikoff, 2004; Piña & Suau, 1987; Szenker, Ray-Gallet, & Almouzni, 2011). Moreover, histone variants exhibit specific genomic localization and distribution patterns, creating distinct chromatin neighborhoods. For instance, studies in yeast have shown that the H2A.Z is localized in genomic areas flanking the nucleosome-free regions, which occur at many gene promoters (Albert et al., 2007; Ranjan et al., 2013; Yen, Vinayachandran, & Pugh, 2013). In relation to the brain, H2A.Z exchange in the hippocampus and prefrontal cortex of the adult brain has been shown to have a restrictive effect on memory formation (Schauer et al., 2013; Zovkic, Paulukaitis, Day, Etikala, & Sweatt, 2015). Accordingly, histone variants can have a profound effect on nucleosome structure, stability, dynamics, and ultimately, gene expression and cellular function.

7.3.3.3 Chromatin remodeling complexes

Chromatin remodeling complexes play a critical role in regulating the chromatin landscape, often using the energy from ATP hydrolysis to disrupt histone-DNA contacts to assemble nucleosomes, alter nucleosome composition, or modulate DNA accessibility (Cairns, 2007; Narlikar, Sundaramoorthy, & Owen-Hughes, 2013). The assembly class of chromatin remodeling complexes facilitates the formation and positioning of nucleosomes, often working in concert with histone chaperones, specialized proteins involved in histone storage, transport, and nucleosome assembly and disassembly (Venkatesh & Workman, 2015). The second class of chromatin remodelers edits the composition of nucleosomes, exchanging canonical histones with histone variants. For

example, the human SRCAP complex alters the composition of conventional nucleosomes by removing H2A/H2B dimers and incorporating histone variant H2A.Z/H2B dimers, forming unique chromatin neighborhoods characterized by H2A.Z occupancy (Ruhl et al., 2006; Wong, Cox, & Chrivia, 2007). The final class of chromatin remodeling complexes facilitates access to DNA by sliding or ejecting the histone octamer (Cairns, 2007). Notably, chromatin remodelers possess "reading" domains, allowing interactions with histone PTMs and other chromatin factors to target their functions. Accordingly, the collective function and crosstalk between histone modifications, histone variants, and chromatin remodeling complexes regulates the chromatin structure in a dynamic and responsive manner (Bannister & Kouzarides, 2011). Importantly, disruption in the expression and/or activity of these factors involved in chromatin regulation can lead to a number of neurobiological disorders (**see Section 7.8**).

7.3.4 Noncoding RNA

The final layer of epigenetic regulation is mediated through noncoding RNAs (ncRNAs), which are distinct from mRNA in that they are not translated into protein. This category includes several different species of RNA, which widely differ both in terms of length and cellular roles. These mediate a wide variety of regulatory functions, ranging from the regulation of mRNA and protein levels to the repression of repetitive and transposable elements. This additional level of epigenetic control appears to play an essential role in the central nervous system, as neural cells express very high levels of ncRNAs (Gustincich et al., 2006; Kapranov et al., 2010; Spadaro & Bredy, 2012). Furthermore, ncRNAs may have played a key role in the evolution of the human brain, given that noncoding regions encoding RNA transcripts involved in neural development display the quickest evolution rates in primate genomes (Pollard et al., 2006). By contrast, several ncRNAs are also found in evolutionarily constrained elements, displaying highly conserved spatiotemporal expression profiles across different species (Chodroff et al., 2010). Given that the majority of these are expressed from genomic regions associated with neurodevelopmental genes displaying correlated expression patterns, they likely play important roles in brain development. Here, we focus on several species of short ncRNAs, long noncoding RNAs (lncRNA), as well as other ncRNAs with functions related to neural development.

7.3.4.1 Short noncoding RNA

Some of the best characterized species of ncRNA are short, ranging from 20 to 200 base pairs. These include several different forms of ncRNA, which play crucial roles in the regulation of cellular functions. For instance, RNA interference (RNAi) pathways involve several different short ncRNA species, including microRNA (miRNA), PIWI-interacting RNA (piRNA), and short interfering (siRNA), and mainly inhibit

mRNA translation or suppress transposition events in the genome. These ncRNAs act through different, although similar mechanisms, and are typically generated from longer precursor transcripts, which are enzymatically processed to create several small ncRNAs. For instance, miRNA are typically expressed from primary miRNA or introns (mirtrons), which are then processed and exported from the nucleus as precursor miRNA. These are then processed by DICER1 into mature miRNA, composed of 20–23 base pairs of single-stranded RNA (ssRNA), and loaded into the RISC complex where they repress target mRNA through imperfect complementarity of the 5′ seed sequence to induce subsequent translational repression. Of note, a single miRNA can target multiple different mRNAs or ncRNAs and multiple miRNAs can repress the same RNA target, providing a wide range of target sensitivity and regulatory specificity. Furthermore, miRNA also appear to have considerable importance in alterations to neural gene expression patterns, as knockdown of DICER1 in mice produces a wide range of neurodevelopmental defects and several miRNA have been directly implicated in brain development to date (Fiore, Khudayberdiev, Saba, & Schratt, 2011). Moreover, different miRNA variants (isomiRs) display tissue-specific and developmental stage-dependent profiles, suggesting that miRNA are likely integrated into the complex transcriptional and epigenetic networks involved in brain development (Martí et al., 2010). In contrast to miRNA, endogenous siRNA (endo-siRNA) are expressed from cis- or trans-acting sense–antisense pairs, inverted repeats, and transposons. Although they play similar functional roles to miRNA, these are processed by DICER2 to produce double-stranded RNA 21–26 nucleotides in length (Okamura et al., 2008). Moreover, once incorporated into the RISC complex as single strands, they silence both mRNA and transposon-derived RNA through endonucleic cleavage of perfectly complementary sequences to the 5′ seed sequence. Finally, piRNAs are a distinct class of RNAi, 26–30 nucleotides in length. Generated from piRNA loci or transposons, they ultimately regulate mRNA expression levels and transposon activity, respectively, following a series of complex processing mechanisms known as the "ping-pong" cycle. While these ncRNAs were initially identified in germ cells, their expression has been recently discovered in neurons, suggesting a key role not only for genome maintenance and regulation, but also in brain function and development (Yan et al., 2011). Moreover, the ncRNAs involved in retrotransposons regulation, endo-siRNAs and piRNA, may potentially mediate the high frequency of transposition events in the human brain necessary for neural development and plasticity. Given their role in the regulation of transposable elements, these small ncRNA may control the establishment and maintenance of the brain's transcriptional architecture by increasing neuronal cellular diversity (Baillie et al., 2011; Coufal et al., 2009; Faunes et al., 2011; Muotri, Zhao, Marchetto, & Gage, 2009). Additional species of short ncRNA also play important roles in the posttranscriptional control of mRNA, although through distinct mechanisms than RNAi pathways. In particular, small

nuclear RNA and small nucleolar (snoRNA) are involved in RNA splicing and modification, mediating alternative splicing events and guiding RNA-modifying enzymes to promote posttranscriptional modifications of different RNA species. Given the wide variety of isoforms and protein variants in the brain, it is possible that these molecular pathways are involved in neurodevelopment and neural function through life. For instance, brain-specific snoRNAs expressed from the C/D box 115 locus promote alternative splicing of the serotonin receptor 2C, suggesting that these ncRNAs play an important role in regulating key isoforms within neural cells (Kishore & Stamm, 2006; Soeno et al., 2010). Furthermore, the majority of genomic regions containing snoRNA clusters can also express miRNA-like RNAs, which suggests a potential role for snoRNA loci in RNAi pathways (Ender et al., 2008; Taft et al., 2009).

7.3.4.2 Long noncoding RNA

Defined as any noncoding transcript longer than 200 nucleotides in length, lncRNA are critical regulators of the cell, providing an essential layer of epigenetic control for a number of different processes. Mainly transcribed from intergenetic regions, telomeres, antisense to protein-coding genes, or regulatory regions such as promoters and enhancers, lncRNA serve a wide variety of cellular functions (Guttman et al., 2009; Hung et al., 2011; Khalil et al., 2009; Mercer et al., 2011; Orom et al., 2010). Several of these regulate the genomic regions from which they are expressed, either through enhancer-like functions or the promotion of repressive epigenetic states (Orom et al., 2010; Rinn et al., 2007; Wutz, 2011). Others play key roles in transcriptional and epigenetic regulation of different genes, recruiting transcription factors or chromatin remodeling complexes to specific genetic loci. In addition, they can act as decoys for different chromatin modifiers and transcription factors, preventing their accumulation within certain regions of the genome. Furthermore, some lncRNAs contribute to the regulation of chromatin states across broad genomic regions and even an entire chromosome in the case of *XIST* (**see Section 7.5.2**). LncRNA also appear to play roles in alternative splicing, posttranscriptional RNA modifications, nuclear-cytoplasmic shuttling, and translational control (Wang & Chang, 2011). Indeed, they sometimes serve as precursors for other small ncRNAs, including snoRNA, and miRNA, suggesting an important role in RNAi pathways. Furthermore, they can act as buffers for miRNA, particularly in the case of lncRNA expressed antisense to protein-coding genes, modulating the levels of RNAi transcripts through complementary binding sites. Multiple lines of evidence also point to the crucial role of lncRNAs in brain function and development. In particular, the highly accelerated region 1 A (*HAR1A)* lncRNA evolved rapidly following the divergence of humans from apes, and its expression highly correlates with that of reelin, a crucial gene in forebrain organization, which suggests that it helps coordinate brain development (Pollard et al., 2006).

Furthermore, the lncRNA antisense to DLX6, *Evf2*, is expressed from an ultraconserved enhancer and plays an essential role in regulating the population of GABAergic interneurons in the hippocampus and dentate gyrus. Several hundreds of additional lncRNAs are also dynamically expressed during GABAergic neurogenesis and oligodendrocyte lineage specification, underscoring the importance of these ncRNA species in brain development (Mercer et al., 2010). Finally, aberrant expression of several different lncRNAs has been associated with different neurodevelopmental disorders, including autism, Fragile X syndrome, Rett syndrome, schizophrenia, and anxiety-like disorder (Barry et al., 2013; Millar et al., 2000; Pastori et al., 2014; Petazzi et al., 2013; Spadaro et al., 2015; Williams et al., 2009; Ziats & Rennert, 2013). Overall, lncRNA appear to play important roles in the integration of developmental, spatial, temporal, and stimulus-specific cues by regulating a wide variety of cellular processes, necessary for the complex epigenetic and transcriptional patterns required during brain development (Wang & Chang, 2011).

7.3.4.3 Additional noncoding RNA classes and RNA modifications

Perhaps the most important RNA species for basic cellular functions are tRNA and rRNA, as they are essential for mRNA translation into protein. However, they do not perform any regulatory functions *per se*, and as such might not be considered epigenetic regulators, but instead represent vital mediators of translation. Furthermore, additional subclasses of ncRNA are now emerging, including, among many others, antisense termini-associated short RNAs, splice-site RNA (spliRNA), transcription initiation RNAs (tiRNAs), termini-associated short RNAs, centromere-associated RNAs, telomere small RNAs, mitochondrial ncRNAs, and miRNA-offset RNAs (Cao et al., 2009; Carone et al., 2009; Kapranov et al., 2010; Landerer et al., 2011; Lung et al., 2006; Taft et al., 2009; Taft et al., 2010). Although some work has characterized the functions of these transcripts, such as research demonstrating a role for tiRNA in transcription factor binding, their regulatory roles remain poorly understood and their implication in cellular functions unclear (Taft, Hawkins, Mattick, & Morris, 2011). As such, these are important research avenues in which further investigation may identify important roles for these transcripts in mediating developmental and tissue-specific epigenetic variation. Finally, covalent modifications to mRNA and different ncRNA species also play important regulatory roles, including in modulating RNA expression, stability, and subsequent translation, interactions with different protein complexes, and cell-specific developmental programs. Although still a nascent field, several different chemical groups have been identified in RNA, including N^6-methyladenosine (m^6A), 5-methylcytidine, and 5-hydroxymethylcytidine (Shafik, Schumann, Evers, Sibbritt, & Preiss, 2016). In particular, levels of m^6A increase in the prefrontal cortex of mice following behavioral training, suggesting a potential role in key cognitive functions such experience-dependent learning (Widagdo et al., 2016).

In addition to their role in mRNA stability, these modifications can regulate the interaction profiles of lncRNA and miRNA, modulating their ability to bind other RNA molecules, DNA, or proteins (Liu et al., 2015). Although the functional implications of these modifications remain unclear, they are relatively abundant in the brain and evidence is emerging to support their vital importance in regulating RNA species in neural tissues.

7.4 GENE–ENVIRONMENT INTERACTIONS

Although epigenetic processes play a fundamental role in maintaining ontogenetic stability in cell differentiation during development, these same epigenetic mechanisms exhibit dynamic variation to allow for finely tuned gene regulation in response to environmental influences. Such a phenomenon represents an "epigenetic paradox," whereby both cellular stability and environmentally influenced plasticity is conferred by the same epigenetic processes (Boyce & Kobor, 2015). Related to its latter role, there is growing interest in epigenetics as a potential mediator of gene–environment (G × E) interactions, defined as genetic or environmental effects on phenotype or outcome that are dependent on each other. More specifically, certain genes can moderate an environment's influence on a particular individual, or environmental influences can only be revealed among individuals of a particular genotype (Rutter, 2010). Classic examples of G × E interaction include the effect of serotonin transporter gene (*5-HTT*) variants in moderating the influence of stressful life events on depression and common regulatory variants of the monoamine oxidase-A (*MAOA*) gene moderating the effects of childhood maltreatment on male antisocial behaviors (Caspi et al., 2003; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Haberstick et al., 2014; Kim-Cohen, Caspi, Taylor, & Williams, 2006; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014; Taylor & Kim-Cohen, 2007). A burgeoning body of work has implicated epigenetic processes as putative molecular mechanisms underlying G × E interactions in various contexts. For example, a link between childhood maltreatment and an allelic risk variant for posttraumatic stress disorder (PTSD) was established in the *FKBP5* gene, which encodes a chaperone of the glucocorticoid receptor (GR), a key mediator of the stress response (Klengel et al., 2012). This association is potentially mediated through a decrease in methylation of a CpG located in the intron of the *FKBP5* risk allele, leading to the suppression of GR function, dysregulation of stress responsivity, and increased risk for PTSD (Klengel et al., 2012). This work not only provided one of the first demonstrations of epigenetics as a molecular mediator in G × E interplay, but also pointed to the functional effects of a methylation quantitative trait locus (mQTL), defined as an allelic variant that correlates with CpG methylation levels in its vicinity (Jones et al., 2013). A number of studies have explored the occurrence of mQTLs in the context of the human brain, finding that mQTLs tend to occur as *cis*

associations in different brain regions and may underlie risk loci of various neuropsychiatric diseases, such as schizophrenia and bipolar disorder (Gamazon et al., 2013; Gibbs et al., 2010; Hannon et al., 2015; Jaffe et al., 2015; Zhang et al., 2010). Indeed, a recent study reported brain-specific differential susceptibility of G × E effects on the epigenome in which maternal anxiety × BDNF Val66Met polymorphism interact with DNA methylation as measured in neonatal cord tissue to predict differential volumes of the amygdala and the hippocampus, two brain structures that have been associated with the risk for psychopathology (Chen et al., 2015). Moreover, when modeling variability in human neonatal methylomes, the inclusion G × E interaction terms account for up to 75% of the variably methylated regions between individuals over models containing only G or E terms, suggesting that G × E interactions play an important role in mediating the genomic response to external stimuli and potentially shaping developmental trajectories in early life (Teh et al., 2014). Finally, more recent demonstration of epigenetic mediation of G × E interaction in the context of substance use intervention programs in youth has highlighted the potential positive impact of considering G × E effects in the design of intervention schemes and prevention strategies (Sharpley et al., 2014). Taken together, these observations provide a compelling framework for further investigating the role of epigenetics as a potential molecular mediator of G × E interactions. Future studies aimed at addressing if such epigenetic mediation occurs across many or select tissue types or what critical periods of development are particularly vulnerable to epigenetically mediated G × E interactions would help clarify the biological implications of gene−environment interplay.

7.5 MAJOR EPIGENETIC EVENTS DURING DEVELOPMENT

The epigenome undergoes a number of fundamental changes during development, which play crucial roles in preparing the genome for the activation and implementation of developmental programs. In particular, DNA methylation patterns in the genome undergo widespread changes throughout the course of gametogenesis, fertilization, and subsequent embryonic development (Smith & Meissner, 2013). Prior to gametogenesis, genome-wide DNA demethylation occurs in primordial germ cells (PGCs), erasing epigenetic marks throughout the vast majority of the genome. Epigenetic patterns are reestablished de novo during gametogenesis to restore developmental potency and establish imprinted loci. However, following fertilization of the oocyte, the genome undergoes a second wave of global DNA demethylation, though imprinted genes, repetitive elements, and transposons appear to be largely protected from this epigenetic remodeling. DNA methylation patterns are subsequently reestablished in the blastocyst during cellular differentiation (**see Section 7.6 for more details**). Finally, two additional processes play important roles in development and have laid the foundation for the study of developmental epigenetics—imprinting and

X-inactivation. Highly conserved among mammals, imprinting and X-inactivation events provide substantial insight into the molecular mechanisms underlying epigenetic regulation, both in general and in the context of developmental programing. Furthermore, given that imprinting and X-inactivation both play important roles in brain development, alterations to the typical unfolding of these processes may potentially beget the emergence of certain neurodevelopmental disorders.

7.5.1 Imprinting

The vast majority of genes in diploid cells are expressed from both the maternally and paternally contributed chromosomes. However, a small but very important subset of genes, known as imprinted genes, display monoallelic expression from either the maternal or paternal chromosome, where epigenetic mechanisms repress the other parental allele. In general, paternally expressed imprinted genes function as growth promoters, while maternally derived monoallelic genes act as growth repressors (Barlow & Bartolomei, 2014). Though the evolutionary aspects of this phenomenon remain unclear, the leading theory for the presence of imprinted genes proposes that they arose in response to a "parental conflict," stemming from opposing goals of the parental genomes (Moore & Haig, 1991). Here, paternal genes would seek to maximize fitness and growth in their offspring, while maternal genes would strive to maximize the female's own reproductive fitness and allocate equal resources to each offspring, which may have originated from different fathers.

Nearly 100 imprinted genes have been confirmed in humans, with nearly double that number predicted as potential genes with monoallelic expression. In the mouse genome, which shows considerable overlap with human imprinting, 150 imprinted genes have been identified, with more than 80% mapping to one of 16 genomic clusters containing two or more genes (Wan & Bartolomei, 2008). Furthermore, the mechanisms regulating imprinting are relatively well conserved between species, and animal models provide a useful framework to assess their molecular underpinnings and functional implications. Thus far, it appears that several different epigenetic mechanisms determine which allele becomes inactivated, with DNA methylation and lncRNA playing integral parts in the suppression of gene expression from one parental allele (for a complete review of the mechanisms underlying imprinting, please see the review by Massah, Beischlag, & Prefontaine, 2015). While the majority of imprinted genes are conserved between rodents and humans, some genes display species-specific imprinting, where some imprinted genes in mice display biallelic expression in human tissues. Furthermore, expression appears to be dependent on both the stage of development and tissue, as certain genes that are imprinted in one tissue display biallelic expression in another (Davies, 1994). Others are imprinted in a tissue-specific manner, such as *UBE3A*, which is maternally expressed in the brain and likely plays a key role

in neurodevelopment. Interestingly, in mice, the maternal genome appears to contribute considerably to embryonic brain development, particularly within the forebrain, while the paternal genome is more important in adult limbic structures, such as the cortex and hypothalamus (Gregg et al., 2010).

As imprinted genes are essential for proper mammalian growth and development, their disruption can often lead to severe consequences. Indeed, several disorders are associated with alterations of imprinted loci, with mutations or deletions within the same region presenting different phenotypes depending on whether the maternal or paternal chromosome was affected (Cattanach & Kirk, 1985). For instance, classic examples of imprinting disorders are Russell–Silver (RSS) and Beckwith–Wiedemann (BWS) syndromes, which are caused by epigenetic or genetic abnormalities of 11p15.5 on the paternal and maternal chromosomes, respectively. These syndromes display opposite phenotypes, where individuals with RSS show undergrowth and dwarfism, whereas patients with BWS display abnormal overgrowth. Furthermore, Prader Willi Syndrome (PWS) and Angelman Syndrome (AS), caused by deletions within the paternal or maternal 15q11–13 chromosomal region, respectively, also present with distinct symptoms. Individuals with PWS (paternal deletion) display hypotonia and intellectual disability, while those with AS (maternal deletion) present with speech impediments and developmental impairments (Kernohan & Bérubé, 2010). Of note, transcription of the maternal lncRNA from the PWS region rescues the growth retardation phenotype associated with this disorder in mice, highlighting the vital importance of ncRNA in the regulation of imprinted genes (Rozhdestvensky et al., 2016). Furthermore, mouse models with various alterations to imprinted genes often display deficits in higher brain functions, such as social behavior, learning, and memory (Agis-Balboa et al., 2011; Champagne, Curley, Swaney, Hasen, & Keverne, 2009; Chen et al., 2011; Drake, Devito, Cleland, & Soloway, 2011; Lefebvre et al., 1998; Li et al., 1999). Deviations from typical imprinted gene expression may also be linked to psychosis and autistic spectrum disorders (Badcock, 2011; Crespi, 2008). Given that many imprinting-related disorders cause varying degrees of mental retardation, imprinted genes likely play a critical part in the central nervous system.

7.5.2 X-inactivation

Early in development, the second X chromosome of females is inactivated through epigenetic mechanisms in a process known as dosage compensation or X chromosome inactivation (XCI) (Lyon, 1961; Lyon, 1962). This ensures equal levels of X-linked gene expression between males (XY) and females (XX), and perhaps not surprisingly, its failure results in embryonic lethality in females (Takagi & Abe, 1990). From the 2-cell stage and up to the morula stage, the paternal X chromosome of the

preimplantation embryo is gradually inactivated through paternal imprinting XCI (Okamoto, Otte, Allis, Reinberg, & Heard, 2004). However, upon implantation of the early blastocyst into the uterus, this phenomenon is reversed, with both chromosomes becoming active once again (Mak et al., 2004). At this stage, several epigenetic mechanisms within each cell come into play to randomly inactivate one copy of the X chromosome, an irreversible process resulting in mosaicism that is passed on to subsequent daughter cells. Nevertheless, some exceptions to this rule have been observed. In the mouse placenta, the paternal X chromosome is always inactivated, and XCI is reversed in oocytes of the female germline prior to meiosis, given that oocytes are haploid and must contain an active X chromosome (Ohhata & Wutz, 2013; Takagi & Sasaki, 1975).

Several epigenetic mechanisms act in concert to regulate XCI, which is triggered through a unique locus, the X-inactivation center (Xic), expressing several genes involved in XCI (Massah et al., 2015; Rastan, 1983). In particular, the X-inactive specific transcript (Xist), a 17-kilobase lncRNA expressed from the inactivated X (Xi), plays an essential role in this process by coating the chromosome from which it is expressed and recruiting epigenetic remodelers to catalyze XCI (Borsani et al., 1991; Brown et al., 1991; Penny, Kay, Sheardown, Rastan, & Brockdorff, 1996). Following the initiation of XCI, Xist RNA spreads over the X chromosome, recruiting chromatin remodeling factors such as PRC2 to increase the proportion of repressive histone modifications, while decreasing activating marks (Peters et al., 2002; Boggs et al., 2002; Boggs, Connors, Sobel, Chinault, & Allis, 1996; Heard et al., 2001; Jeppesen & Turner, 1993; Plath et al., 2003; Silva et al., 2003). Furthermore, different macroH2A isoforms such as macroH2A1.1, macroH2A1.2, and macroH2A2 are incorporated into chromatin to create a tightly compacted chromatin structure, which condenses into a structure known as the Barr body (Chadwick & Willard, 2001; Csankovszki, Panning, Bates, Pehrson, & Jaenisch, 1999). In combination with alterations to the chromatin landscape, the association of DNMT1 with the Xi catalyzes the accumulation of DNA methylation, which preserves the inactive state of the X chromosome and potentially acts as the final "lock" on the Xi (Lock, Takagi, & Martin, 1987; Sado et al., 2000). A number of additional genes also come into play during X inactivation, such as *Tsix*, a lncRNA maintaining the activation of Xa and a number of additional proteins and ncRNA species mediating the finely tuned recruitment of epigenetic regulators to the X chromosome. For a complete review of the factors involved in XCI, please refer to the following reviews (Gendrel & Heard, 2014; Massah et al., 2015).

Although most genes on the Xi are fully inactive, nearly 15% remain somewhat expressed. Known as escape genes, many of these play important roles in brain development, regulating a number of key neuronal processes, such as cellular differentiation, dendritic outgrowth, and cell survival (reviewed in Berletch, Yang, Xu, Carrel,

& Disteche, 2011). Moreover, a number of escape genes have also been associated with intellectual disability syndromes, further supporting their crucial role in typical brain development (Ropers, 2010). These genes display different chromatin structure than their inactivated counterparts, showing a depletion of repressive histone marks, loss of macroH2A, and generally feature of open and active chromatin. Furthermore, unlike CpGs within the promoters of inactivated genes on the X chromosome, which are heavily methylated, those in XCI-escaping genes are generally hypomethylated (Weber et al., 2005; Cotton et al., 2015). From a genetic standpoint, escape genes appear to contain intrinsic genomic elements allowing them to escape XCI, including Alu elements, short ACG/CGT motifs, and the L1 subclass of LINEs (Carrel & Willard, 2005; Cotton et al., 2014; Tannan et al., 2014). Nevertheless, the exact mechanisms underlying the escape of these genes from X inactivation remains mostly unknown, though a considerable amount of research is currently being devoted to uncovering the molecular mechanisms and evolutionary advantages conferred by this process. For a more complete review of genes that escape XCI, please see the following review (Peeters, Cotton, & Brown, 2014).

7.6 PRECONCEPTION EPIGENETICS

Characterized by the unique transcriptional and epigenetic landscapes of gametes, the preconception period has the power to shape developmental trajectories in offspring. As such, environmental conditions, nutritional factors, and stress during this time could influence the maturation of gametes and reprogram subsequent epigenetic patterns, potentially leading to altered brain development or disease susceptibility in subsequent generations. Nevertheless, epigenetic programing in gametes is crucial to prime developmental potency and pass on genetic and potentially epigenetic information to the offspring.

7.6.1 Spermatozoa

The development of the male gamete lasts approximately four months, during which time immature sperm cells are generated from PCGs and differentiate into fertile spermatozoa. Throughout this period, the epigenome undergoes widespread epigenetic alterations, crucial for the highly specialized cellular functions of sperm cells and the subsequent programming of zygotic development. Environmental factors present during this time, such as nutrition, exposure to toxins, or stress, can alter these dynamic epigenetic patterns, potentially resulting in long-term changes to developmental trajectories in the offspring. For instance, in mice, paternal exposure to a high-fat diet leads to deficits in glucose tolerance and insulin sensitivity in offspring, as well as alterations to epigenetic and transcriptomic profiles (Ng et al., 2010; Wei et al., 2014). Similarly, human studies have shown that paternal obesity results in altered DNA

methylation patterns of imprinted genes, including the *IGF2* locus (Soubry et al., 2013; Soubry et al., 2013). As such, epigenetic inheritance through the father may represent a vital aspect of long-term health outcomes in children, adults, and potentially subsequent generations as well (reviewed in Soubry, Hoyo, Jirtle, & Murphy, 2014).

To facilitate nuclear compaction of the spermatozoa, the vast majority (90%–95%) of histones within chromatin are replaced with highly basic proteins known as protamines (Corzett, Mazrimas, & Balhorn, 2002; Oliva, 2006). These may play an important role in genome protection from oxidative damage caused by the female reproductive tract, as elevated DNA damage in sperm appears to directly correlate with increased histone retention (Aoki et al., 2005; Garcia-Peiro et al., 2011; Torregrosa et al., 2006). Once inserted into chromatin, several PTMs to protamines are required for higher order chromatin condensation, including phosphorylation at a number of sites (Aoki & Carrell, 2003). Furthermore, decreased fertility has been linked to abnormal protamine levels and ratios, including decreased sperm counts and function, as well as diminished embryo quality during in vitro fertilization, suggesting that protamines are essential for fertilization and subsequent development (Carrell, Emery, & Hammoud, 2007; de Mateo et al., 2009; Simon, Castillo, Oliva, & Lewis, 2011; Torregrosa et al., 2006). In addition to their role in DNA compaction and protection, these proteins also effectively inhibit transcription, leading to repression of most genes within the sperm genome. However, while the majority of the sperm genome is repressed within protamine-induced compaction, some regions retain histones, which are typically located in the promoters of genes involved in development, miRNA, and imprinted genes (Arpanahi et al., 2009; Hammoud et al., 2009). Furthermore, histones in developmental genes are generally marked with transcription-activating H3K4me2 or H3K4me3 and repressive H3K27me3, creating a poised bivalent state similar to ESCs. By contrast, H3K4me3-specific regions are mostly located within genes involved in spermatogenesis, HOX gene clusters, noncoding RNAs, and paternally expressed imprinted loci (Hammoud et al., 2009). Taken together, these findings suggest that histone modifications play a critical role in poising developmental programs within the spermatozoal genome to ensure proper development following fertilization. In addition to canonical nucleosomal subunits, spermatozoal chromatin also contains a unique histone variant, testes-specific histone H2B, which is abundant in mature sperm cells (Churikov et al., 2004; Gatewood, Cook, Balhorn, Schmid, & Bradbury, 1990). This variant shows enrichment in the promoters of ion channel and spermatogenesis genes, which may reflect a remnant/history of the conditions found during sperm maturation (Hammoud et al., 2009). Additional histone variants are also involved in the regulation of the sperm genomes, including H2A.Z, which plays a role in poising essential developmental genes (Rangasamy, Berven, Ridgway, & Tremethick, 2003). As a whole, histones within

spermatozoal chromatin appear to potentially play a role in the retention of a historical record of sperm maturation and preparation for later developmental programs (Carrell & Hammoud, 2009). In addition to the contribution of 50% of genetic material and some specialized epigenetic patterns to the zygote, the paternal gamete also appears to transmit a number of ncRNA species to the zygote, including piRNA, lncNRA, miRNA, and tRNA, which may also influence subsequent development (Hamatani, 2012; Jodar, Selvaraju, Sendler, Diamond, & Krawetz, 2013; Liebers, Rassoulzadegan, & Lyko, 2014).

7.6.2 Oocytes

In contrast to male germ cells, which are mitotically arrested until spermatogenesis begins during puberty, female germ cells remain in the diplotene stage of the first meiotic division from birth until ovulation. As no new oocytes are produced in mammals following birth, the growth and release of each cell is tightly regulated. During the growth stage of oocytes, lasting approximately 4 months, the cell accumulates a large supply of mRNA and organelles to regulate and direct embryogenesis (Ma et al., 2013; Oktem & Oktay, 2008; Sánchez & Smitz, 2012). However, in the late stages of growth, transcriptional activity within the oocyte decreases drastically, with little to no transcription occurring once it reaches full size. At this time, the chromatin structure of the oocyte partially condenses around the nucleolus, coinciding with the arrest of gene expression (Andreu-Vieyra et al., 2010; Bouniol-Baly et al., 1999; De La Fuente et al., 2004; Tan et al., 2009; Wickramasinghe, Ebert, & Albertini, 1991; Zuccotti, Garagna, Merico, Monti, & Redi, 2005). Once fully grown, luteinizing hormone, secreted by the hypothalamus, stimulates oocyte maturation and reentry into the cell cycle. Here, maturing oocytes complete meiosis I and advance to the metaphase of meiosis II, where they arrest again until fertilization (Kang & Han, 2011). While no active gene expression is present in the maturing oocyte, the large stockpile of mRNA generated during the growth phase regulates this process to produce a fertile oocyte, highlighting the importance of the pre- and periconceptional periods in developmental programing.

Female gametes contain a highly specialized and dynamic epigenome, which exerts tight regulatory control of their unique physiological status and development, not to mention the potential biological embedding of environmental factors. At birth, oocytes contain almost no DNA methylation, having been reset as PGCs to erase and then reestablish the marks necessary for later development. However, retrotransposons from the IAP family, repetitive elements, and a number of additional CpG islands within the genome retain DNA methylation patterns in the oocyte (Guibert & Weber, 2013; Popp et al., 2010; Seisenberger et al., 2012). This state persists until the growth phases of the oocytes, when DNA methylation begins to accumulate in the

genome, resulting in approximately 15% of CpG and 15% CH sites becoming fully methylated by the end of growth, making oocytes one of the few cell types with appreciable levels of non-CpG methylation (Kobayashi et al., 2012; Shirane et al., 2013; Smallwood et al., 2011; Tomizawa et al., 2011). Although the absolute levels of DNA methylation in oocytes are only half those found in spermatozoa, sperm cells do not contain any CH methylation (Kobayashi et al., 2012). DNA methylation also accumulates in imprinted loci, although the various loci acquire epigenetic marks during different stages of oocyte development, which may reflect transcriptional activity within or near those regions or sensitive period of oocyte development and programming (Chotalia et al., 2009; Obata & Kono, 2002). During the growth phase, oocytes also show increasing methylation levels of histone H3 on K4 (me2/me3) and K9 (me2), as well as high levels of acetylation on histones H3 and H4 (Clarke & Vieux, 2015; Kageyama et al., 2007). As such, the chromatin state of growing oocyte is quite permissive to transcription, consistent with the very high levels of mRNA accumulation. Furthermore, oocyte chromatin includes the specific histone H1 variant H1FOO, an essential variant for oocyte maturation that maintains the expression of pluripotent genes during early development (Hayakawa, Ohgane, Tanaka, Yagi, & Shiota, 2012). Finally, endo-siRNAs appear to play a crucial role in postnatal oocyte development. While their exact roles remain to be determined, they likely act to repress transposition events and modulate mRNA translation during oocyte growth and maturation (Clarke & Vieux, 2015).

Given the protracted nature of oocyte development (oocytes may be arrested for decades in humans), environmental factors, potentially throughout the lifetime, could affect the growth and maturation of the female gamete. While robust DNA damage repair mechanisms prevent the majority of potential genetic mutations, which could decrease offspring fitness, epigenetic marks within the genome are more responsive to environmental factors and may mediate their long-term effects (Bock, 2009; Carroll & Marangos, 2013). As such, stressors or environmental conditions affecting the mother may have the power to shape the developmental trajectories of the offspring through epigenetic mechanisms, potentially altering cognitive and behavioral functions later in life, or predisposing the infant to disease throughout life. For a thorough review of epigenetic dynamics in the oocyte, please refer to the following reviews (Clarke & Vieux, 2015; Dean, 2013).

7.6.3 Trans and intergenerational inheritance

Putative evidence is now emerging to support the possibility that environmentally induced phenotypic variation persists over multiple generations, which potentially occurs through epigenetic alterations retained during germ-cell development and passed on to following generations. Although this is an intriguing avenue of research,

it remains a young field requiring moderated interpretation and further consideration before it is taken at face value (van Otterdijk & Michels, 2016). This is especially true considering the limitations imposed by biological processes during gamete development and fertilization outlined in the previous and following sections. To date, two different, though similar, types of transmission have been proposed, intergenerational and transgenerational effects. The former manifest themselves in any organisms directly exposed to the factors influencing these changes, while the latter are defined by alterations persisting in generations that have not been directly exposed to the condition. For example, environmental conditions affecting a pregnant mother (F0) could affect the PGCs of her direct offspring (F1), which in turn give rise to a second generation (F2) manifesting intergenerational effects, as the gametes of F1 were directly exposed to the altering factor. However, if the third generation (F3) were to display the same environmentally induced phenotype, these effects would be considered a transgenerational effect, given that no cells were directly exposed to the conditions. By contrast, transgenerational inheritance through males or the maternal prior to gestation only requires transmission to F2, as the reproductive cells of F1 will not be directly affected. While the evidence for transgenerational effects in mammals remains elusive, some early examples are emerging, notably in rodent models. For example, odor fear conditioning in male mice induces behavioral sensitivity in the F1 and F2 generations, as well as CpG hypomethylation in the *Olfr151* gene of F0 and F1 sperm (Dias & Ressler, 2014). In addition to paternal transmission, prenatal maternal stress during the first week of pregnancy alters the transcriptional profiles of male rats, and more specifically, miRNA expression patterns in the brain, with the progeny of these animals displaying similar alterations (Morgan & Bale, 2011). Although few examples of intergenerational epigenetic inheritance in humans exist to date, some lines of evidence are beginning to emerge. For instance, children conceived during the Dutch Hunger Winter of 1944–45 displayed lower DNA methylation levels in the imprinted gene *IGF2* compared to unexposed siblings, even 60 years after the exposure (Heijmans et al., 2008). Nevertheless, transgenerational inheritance in humans may difficult to confirm for a number of reasons. In contrast to the controlled environments of animal models, environmental conditions differ between individuals, introducing additional stochastic variation. Moreover, the heterogeneity of human populations and influence of genetic background on epigenetics limit our ability to distinguish effects caused by genetics or epigenetic transmission. Finally, longitudinal studies combining several generations are required to prove that epigenetic patterns are transmitted, and a cohort of this type is not yet available (van Otterdijk & Michels, 2016).

Although the exact mechanisms underlying these effects remain unclear, several different hypotheses have been put forth to explain their persistence over time, and most require an incomplete erasure of epigenetic patterns during gametogenesis and early development. Thus far, DNA methylation has been an attractive candidate for

inter/transgenerational inheritance, given its potential role in the regulation of gene expression, relative stability over time, and response to environmental cues (Bock, 2009). While the majority of the DNA methylome is wiped clean in PGCs, certain regions of the genome appear to resist the initial wave of demethylation, particularly those containing repetitive elements (Sakashita et al., 2014). A number of studies using the Agouti mouse model have demonstrated that environmental conditions can alter the DNA methylation status of an IAP element upstream of the agouti gene to produce variable phenotypes persisting across multiple generations (Lane et al., 2003; Morgan, Sutherland, Martin, & Whitelaw, 1999; Wolff, Kodell, Moore, & Cooney, 1998). Imprinted loci may also play a role in transgenerational inheritance, as they resist the second wave of DNA demethylation following fertilization and the gametes of mice treated with streptozocin display altered DNA methylation of the Peg3 imprinted gene (Ge et al., 2013; Stouder & Paoloni-Giacobino, 2010). However, in all likelihood, several epigenetic mechanisms probably act in concert to pass on epigenetic programing to the subsequent generation. For instance, some histone modifications originating from the paternal gametes are stable until the blastocyst stage of development, suggesting that histone modifications may also play a role in intergenerational epigenetic inheritance (Sarmento et al., 2004). Furthermore, ncRNA are also likely to play a role in inter/transgenerational inheritance, with potentially great importance for male transmission, given their abundance in spermatozoa. In particular, injection of certain miRNA into fertilized eggs can cause effects across at least three generations, indiscriminate of the parent of origin (Wagner et al., 2008). Furthermore, the exposure of male mice to chronic stress prior to breeding alters the miRNA profile of their spermatozoa, leading to a blunted stress response in offspring and altered gene expression programs within the hypothalamus (Rodgers, Morgan, Leu, & Bale, 2015). Although the authenticity of epigenetically induced inheritance has not yet been fully established, this remains a fascinating opportunity to explain the missing heritability of different factors or lasting programing effects of environmental conditions. For balanced reviews of the current literature on transgenerational epigenetic inheritance, please refer to Bohacek, Gapp, Saab, and Mansuy (2012) and van Otterdijk and Michels (2016).

7.7 PRENATAL DEVELOPMENT

Prenatal development begins upon fertilization of the oocyte by a sperm cell, where the two haploid parental genomes combine to produce a diploid zygote. This event initiates a number of widespread genetic and epigenetic events to effectively sculpt the new organism's development. The epigenome of the zygote must be reprogrammed to achieve a totipotent state capable of generating the wide variety of cellular subtypes found in a fully developed organism.

7.7.1 Periconceptional development

The preimplantation period leads to the creation of two distinct cell lineages, the inner cell mass (ICM) and trophectoderm, which result in the fetus and placenta, respectively, as well as several distinct tissues, including the umbilical cord, chorion, and amnion. During the first step of this process, known as the maternal-to-zygotic transition, oocyte-specific transcripts are degraded and replaced with zygotic transcripts, facilitating epigenetic reprogramming of the early embryo (Latham, Solter, & Schultz, 1991). In parallel, chromatin takes on a transcriptionally repressive state throughout the majority of the genome, though the promoters of key totipotency genes become active to establish gene expression patterns required for early development (Li, Lu, & Dean, 2013).

Given that both the sperm and oocytes contain highly specific and diverse DNA methylation patterns, necessary for their specialized functions, these must be reset following fertilization to create the totipotent state required for cell lineage generation. Sperm DNA is heavily methylated (80%–90% of all CpGs) relative to maternal haploid DNA, which contains half the levels of sperm DNA methylation (Kobayashi et al., 2012). As such, both parental pronuclei must undergo radical global DNA demethylation before the zygote can reach a totipotent state, though they occur through different mechanisms (Marcho, Cui, Mager, 2015; Smith & Meissner, 2013). By the morula stage of development, DNA methylation within the genome is nearly absent (Lane et al., 2003; Santos, Hendrich, Reik, & Dean, 2002).

The paternal genome is quickly and completely demethylated through active DNA demethylation during the first several hours postfertilization, independent of replication. This process begins in the paternal pronucleus immediately following fertilization and prior to the first cell division through the action of TET3, which mediates the conversion of 5-methylcytosine (5mC) to 5-hydromethylcytosine (5hmC) (Gu et al., 2011; Wossidlo et al., 2011). This oxidized version of cytosine is subsequently removed through thymidine DNA glycosylase (TDG)-mediated base excision repair (Kohli & Zhang, 2013). However, the TDG repair machinery is not required for loss of DNA methylation in the paternal genome, suggesting that additional mechanisms come into play (Guo et al., 2014). Indeed, as the maintenance DNMT, DNMT1, has low affinity for 5hmC and is absent from the preimplantation nucleus, replication-dependent dilution of 5hmC also appears to plays a vital role in this process (Hashimoto et al., 2012; Howell et al., 2001).

In contrast to the paternal genome, the maternal genome mostly undergoes passive demethylation through the progressive dilution of DNA methylation levels over the course of cell divisions throughout the preimplantation period. This process is facilitated by its relatively low initial DNA methylation levels (Guo et al., 2014). Furthermore, while the maternal pronucleus contains TET3, the maternal genome is

protected from active DNA demethylation by the protein STELLA, which is expressed in oocytes and gonads, as well as during germ-cell specification (Saitou, Barton, & Surani, 2002; Sato et al., 2002). Through its binding to H3K9me2, a feature enriched in the maternal genome and protamine-free regions of the paternal genome, STELLA alters the chromatin structure to prevent TET3 binding and activity (Nakamura et al., 2012). The protection of imprinted genes from the wave of global DNA demethylation is thought to partially occur through STELLA-dependent mechanisms as well (Nakamura et al., 2007).

Considerable alterations to chromatin structure also begin immediately following fertilization, with several epigenetic modifications taking place in both haploid genomes. In the paternal genome, protamines are replaced by maternal histones in a replication-independent fashion, decondensing the highly compacted chromatin and causing the sperm nucleus to mature into the paternal pronucleus (Marcho et al., 2015). More specifically, protamines are replaced with nucleosomes containing the H3 variant H3.3, which is included in place of H3 when nucleosome assembly occurs outside transcription (Torres-Padilla, Bannister, Hurd, Kouzarides, & Zernicka-Goetz, 2006). While this variant is typically associated with transcriptionally active chromatin states, the zygotic genome is not transcriptionally active immediately upon fertilization. As such, H3.3 inclusion likely poises the paternal genome for subsequent activation of developmental programs (Lin, Conti, & Ramalho-Santos, 2013). Histone modification patterns also undergo widespread changes following fertilization, displaying asymmetric patterns between the maternal and paternal haploid genomes. While the exact functions and genomic localization of such marks remain mostly unknown, they highlight the complexity of the distinct programming required for proper embryonic gene activation or repression (Marcho et al., 2015). Most importantly, they likely serve to establish the totipotency programs required for early zygote development, while also providing a framework for the later divergence of epigenomic landscapes and generation of the wide variety of cellular subtypes.

7.7.2 Embryonic development and neurogenesis

Following implantation of the zygote at the blastocyst stage, DNA methylation patterns become reestablished in the ICM of the blastocyst, rising rapidly in the primitive ectoderm, which eventually matures into the entire embryo (Borgel et al., 2010; Santos et al., 2002; Smith et al., 2012). These changes correlate with the resumption of DNMT expression in the embryo, which establish lineage-specific DNA methylation patterns to guide cells along their specified developmental trajectories. These eventually culminate into the wide diversity of cellular subtypes arising from the different germ layers of the blastocyst (Santos et al., 2002). Given that the cells present in the blastocyst are precursors to all cells in the body, disruption of epigenetic programs

by different teratogens during this fundamental stage of development can result in widespread defects in the organism. Cells arising from the same lineage display more similar epigenetic patterns than those from other lineages. However, as cells differentiate, their epigenetic profiles become increasingly adapted to their particular functions. As such, differences in cell type remain the major drivers of epigenetic modifications (Smith & Meissner, 2013).

Of particular importance to the present chapter, several different layers of epigenetic regulation modulate the differentiation of neural cells, regulating neurogenesis in the developing brain. Epigenetic processes at this stage ensure adequate proportions of neurons, glia, astrocytes, and their specialized subtypes, as well as the proper encoding of the gene expression programs controlling brain patterning and maturation (Imamura, Uesaka, & Nakashima, 2014; Lilja, Heldring, & Hermanson, 2012; Shen, Ji, & Jiao, 2015). These act in concert to drive neurogenesis in the embryo, mediating the differentiation of neural progenitor cells (NPC) and patterning of the developing brain (LaSalle, Powell, & Yasui, 2013). In NPCs, chromatin remodeling complexes interact with repressive transcription factors to inhibit the expression of neuronal-specific genes, thus preventing differentiation. Upon cell division, repression of these genes is released and the daughter cells enter into the neuronal lineage, which is characterized by widespread alterations to epigenetic patterns throughout the cell and the activation of neuronal-specific transcription programs.

A complex interplay between different epigenetic factors is necessary during neural development, as each factor plays a fundamental role in regulating neuronal differentiation and brain patterning. For one, DNA methylation is vital for neuronal differentiation, as NPCs lacking DNMT1 give rise to dysfunctional neurons (Fan et al., 2001; LaSalle et al., 2013). By contrast, DNAhm is associated with neuronal differentiation, accumulating in intragenic regions during neurogenesis, concomitant with decreases in H3K27me3 and increased gene expression (Hahn et al., 2013). Several ncRNA species are also involved in neuronal differentiation and patterning, with miRNA and lncRNA playing key roles in NPC proliferation, lineage commitment, and spatiotemporal regulation of brain development (Fatica & Bozzoni, 2014; Lv, Jiang, Liu, Lei, & Jiao, 2014; Mercer et al., 2010; Pollard et al., 2006; Wang & Chang, 2011; Zhao, Sun, Li, & Shi, 2009). Finally, monoallelic gene expression, which shows similar mechanisms to imprinting, may also play a key role in generating neuronal cell surface diversity through the stochastic expression of different protocadherin (*PCDH*) genes, which encode cell-surface adhesion molecules (Massah et al., 2015). As such, various neuronal subpopulations might express vastly different subsets of these genes from a single allele, likely resulting in their wide variety of functions and localizations (Esumi et al., 2005; Frank et al., 2005).

Furthermore, several disorders associated with mutations in epigenetic mediators and regulators are apparent even at a young age, supporting a vital role for epigenetic

mechanisms in typical early brain development and function (Kramer & van Bokhoven, 2009; Vissers, Gilissen, & Veltman, 2015). For instance, a number of severe diseases marked by defects in brain development and function result from mutations in epigenetic regulators, including Fragile X, Rett, Rubinstein-Taybi, Sotos, and Weaver syndromes, as well as several additional types of X-linked mental retardation. Interestingly, the disruption of distinct epigenetic mechanisms, which likely regulate different gene sets, gives rise to various forms of mental retardation with similar phenotypes, suggesting that global epigenetic patterns are crucial for normal brain function and that most epigenetic marks are closely interconnected (Kramer & van Bokhoven, 2009; Vissers et al., 2015). In particular, X-linked intellectual disability is associated with various mutations on the X chromosome, with the majority falling within key epigenetic factors such as MeCP2, the histone kinase RSK2, and the H3K4-specific HDM JARID1C. Furthermore, minor alterations to MeCP2 or other methyl-binding protein expression and genome-wide changes to DNA methylation patterns have been associated with cases of autism spectrum disorder, further supporting the crucial role of epigenetic regulators in brain organization and development (Berko et al., 2014; Cukier et al., 2010; Gonzales & LaSalle, 2010). While the majority of severe disorders resulting from mutations in epigenetic regulators manifest during childhood, more complex disorders such as schizophrenia, depression, or Alzheimer's disease often manifest later in life, potentially requiring additional environmental factor or brain maturation to fully emerge (Boyce & Kobor, 2015). Nevertheless, epigenetic mechanisms likely play a vital role in shaping brain development and subsequent biological trajectories during early life and can potentially influence health outcomes throughout the lifetime.

7.8 DEVELOPMENTAL VULNERABILITY THROUGHOUT THE LIFETIME

From a biological standpoint, development is an ongoing, lifelong process involving the intersection of genetic programming and environmental cues (Boyce & Kobor, 2015). For instance, prenatal environments may shape the vulnerability to disease, leading to long-term effects on health and behavior. Childhood is a highly sensitive period of life, given the high neuronal plasticity of the neonatal and child brain and the high rates of neurogenesis and synapse formation. Adolescence represents an important window of vulnerability for brain development, with critical neuronal changes occurring parallel to the physical changes of puberty. Given the heightened plasticity of the brain during these periods, neurobiological development may be particularly sensitive to environmental factors, leading to long-term effects of these exposures on cognitive abilities, behavioral patterns, emotional functioning, and susceptibility to mental illnesses.

7.8.1 Prenatal environments

The developmental origins of health and disease (DOHaD) hypothesis suggest that environmental factors during early life development can influence future health outcomes (Barker, 1990; Barker, 1995). Specifically, signals received during development, such as nutritional and hormonal status, may preemptively lead the organism toward a phenotype best adapted for the anticipated external environment (Hanson, Low, & Gluckman, 2011). This early-life programming is a manifestation of developmental plasticity, where a single genotype can lead to multiple phenotypic outcomes due to differing environmental conditions (Barker, 2007). However, in the event of a mismatch between early and later life environments, this adaptive response may no longer confer a fitness advantage, but instead, lead to deleterious phenotypes (Godfrey, Lillycrop, Burdge, Gluckman, & Hanson, 2007). As such, adverse early-life conditions, including maternal undernutrition, obesity, stress, or exposure to teratogens, such as lead, ethanol, and nicotine, have the potential to permanently imprint physiological and behavioral systems during development, leading to long-term consequences in offspring (Godfrey & Robinson, 1998; Hanson & Gluckman, 2008). Given the relationship of epigenetic factors, biological programs, and environmental responsivity, epigenetics may represent a potential mechanism for the biological embedding of prenatal exposure. Thus, a considerably body of research has investigated the relationship between the alterations to epigenetic patterns and prenatal exposures.

Fetal alcohol spectrum disorder (FASD) is a prime example of the programming of physiological systems by early-life teratogens. Caused by gestational exposure to alcohol, this disorder manifests through both immediate and long-term alterations to cognition, behavior, immune function, and vulnerability to mental health disorders (Hellemans, Sliwowska, Verma, & Weinberg, 2010). In turn, these have been associated with changes in epigenetic patterns in the brain, including alterations to ncRNA, histone modifications, and DNA methylation (Lussier et al., 2017). Importantly, several findings from animal models were replicated through a study of DNA methylation patterns in the buccal epithelial cells of children with FASD, suggesting that alcohol may leave a lasting signature on the epigenome (Portales-Casamar et al., 2016). Several other studies have also investigated DNA methylation patterns following prenatal exposures in human populations. For instance, maternal undernutrition during pregnancy can also cause changes in the DNA methylation status of *IGF2*, which may influence growth and vulnerability to disease later in life (Heijmans et al., 2008). Finally, perhaps the best replicated association in human populations, prenatal exposure to cigarette smoke is associated with persistent alterations to DNA methylation of the *AHRR* gene (Joubert et al., 2012).

Although these findings suggest robust effects of prenatal exposures on the epigenome, and potentially long-term health and behavioral outcomes, they remain

correlative and cannot yet be interpreted as causative alterations. By virtue of fundamental biological properties, alterations to the epigenetic patterns of central tissues are not easily measurable in humans, given the difficulty of obtaining brain samples. Thus, the vast majority of epigenome-wide association studies are performed in peripheral tissues such as blood and buccal epithelial cells in the hope that they might reflect epigenomic variation in the brain. As epigenetic patterns are highly dependent on cell types that may respond differently in the face of the same exposures, these surrogate tissues may not fully portray the true changes driving disease. As such, the establishment of common epigenetic profiles between central and peripheral tissues is an ongoing and essential topic of research.

7.8.2 Childhood

The brain is particularly vulnerable during childhood, given its plasticity in response to the different stimuli shaping its development. Given the plasticity of the brain during early childhood, environmental factors during this critical developmental period have the potential to shape the trajectories of cognitive and behavioral functioning. Indeed, associations between later life disease and numerous environmental conditions have been identified throughout these windows of vulnerability, including, but not limited to socio-economic status, parental stress, abuse, and exposure to toxins such as alcohol and tobacco (Godfrey & Robinson, 1998; Hanson & Gluckman, 2008). In line with the DOHaD hypothesis, these factors may potentially become biologically embedded into the epigenome, underlying lifelong vulnerability to stressors and chronic disorders (Kubota, Miyake, Hariya, & Mochizuki, 2015). As epigenetic mechanisms play an integral role in mediating experience-dependent processes and brain plasticity to regulate the establishment, refinement, and maintenance of neural circuits at this stage, it is possible that they could mediate the biological integration of external cues during this sensitive period of development, when these mechanisms are the most responsive to stimuli (Tognini et al., 2015).

An emerging number of epigenome-wide association studies are beginning to uncover potentially lasting relationships between adverse childhood environments and altered DNA methylation patterns later in life (Borghol et al., 2012; Essex et al., 2013; Lam et al., 2012; Powell et al., 2013). In turn, these changes have been associated with altered neurobehavioral profiles, supporting a potential link between the epigenome and long-term health outcomes. For example, hippocampal cells of suicide victims abused as children display increased DNA methylation levels in the *NR3C1* gene promoter (McGowan et al., 2009). Given that physically abused children also manifest these altered DNA methylation patterns in blood, it is possible that adverse childhood experiences integrate biological circuitry during childhood and potentially lead to long-term consequences (Romens, Mcdonald, Svaren, & Pollak, 2015).

7.8.3 Puberty

Puberty is characterized by the activation of the gonadal hormone systems, rapid growth, sexual maturation, and widespread changes in brain function. Several brain regions undergo extensive maturation and reorganization during this period, including sexually dimorphic alterations to the prefrontal cortex, hippocampus, and amygdala, among many others. Given that these sex-specific differences last throughout the lifetime, as well as the complex systems and timing involved, epigenetic mechanisms likely play a key role in pubertal maturation. Indeed, similar to early development, the epigenome is poised during puberty to modulate brain development and potentially influence disease risk (Morrison, Rodgers, Morgan, & Bale, 2014).

Brain maturation upon the onset of puberty is driven by the surge of gonadal hormones to which the brain had not previously been exposed. Given that steroid hormones readily cross the lipid bilayer and that their receptors also act as transcription factors, the long-lasting alterations to brain function are potentially mediated through epigenetic mechanisms. Studies in females have uncovered that the onset of puberty is associated with increased kisspeptin (*kiss1*) expression in the arcuate nucleus (ARC) of the medial basal hypothalamus (Oakley, Clifton, & Steiner, 2009). This derepression is linked to increased DNA methylation in the promoters of key epigenetic regulators, which decreases their expression and leads to a more transcriptionally permissive chromatin state of *kiss1*. Neurons expressing this neuropeptide then directly stimulate gonadotropin-releasing hormone (GnRH) neurons to initiate estrous cyclicity and pubertal onset. Furthermore, DNA methylation patterns and histone modifications within the promoter of GnRH modulate its expression levels in the Rhesus monkey brain, suggesting that this key regulator of puberty is also under epigenetic control (Kurian & Terasawa, 2013).

Several studies have investigated the role of global genetic and epigenetic factors during pubertal onset, identifying key roles for epigenetic mechanisms in the regulation of both pubertal onset and pubertal brain plasticity. For instance, disruption of global DNA methylation patterns delays the beginning of puberty in female rats, while exposure to high levels of methyl donors results in earlier puberty, highlighting a potential role for DNA methylation in pubertal onset (Almstrup et al., 2016; Morrison et al., 2014). Although little genome-wide data of epigenetic alteration during puberty have been collected, a genome-wide analysis of DNA methylation in the rat hypothalamus identified an increase in DNA methylation within the promoters of chromatin modifiers, such as the Polycomb group genes and their interaction partners (Lomniczi et al., 2013). These alterations could potentially underlie the plasticity of the pubescent brain, and mediate vulnerability to the programming effects of different environmental stressors, which may lead to deleterious long-term effects on mental and physical health.

While these findings certainly present an attractive mechanism for the biological embedding of early life experiences in the genome and their manifestation in cognitive and behavioral profiles, the vast majority of epigenetic studies in humans are performed on peripheral tissues, such as buccal epithelial cells and blood, rather than central tissues. As environmental stimuli may not be associated with the same alterations in the brain, these results may not represent causal mechanisms and must be interpreted with caution. However, a number of studies have begun to investigate the concordance between peripheral and central tissues, assessing the relevance of different biological samples to neurobiological deficits and their potential use in biomarker discovery for neurological disorders (Farré et al., 2015; Marzi et al., 2016; Walton et al., 2015; Yu et al., 2016, Edgar et al., 2017). Furthermore, epigenetic studies have also begun to incorporate potential confounding factors, such as allelic variation, ethnicity, age, socio-economic status, and cellular heterogeneity, providing a solid framework for the study of epigenetic mechanisms in neurobiological disorders (Farré et al., 2015; Lister et al., 2013).

7.8.4 Later life manifestation of early life environments

In contrast to genetically linked neurodevelopmental disorders, which generally present early in life, alterations to the epigenome occurring during development may be more likely to manifest during later life. The concept of allostatic load suggests that the "wear and tear" caused by chronic stressors throughout the life course can contribute to the dysregulation of physiological systems and subsequent risk of maladaptive outcomes (McEwen & Wingfield, 2003). In the context of neurobiological diseases, it has been proposed by the "latent early-life associated regulation" (LEARn) model that the accumulation of epigenetic alterations across the life course, particularly beginning at early developmental stages, can lead to pathological outcomes that manifest much later in life (Delgado-Morales & Esteller, 2017; Lahiri, Maloney, & Zawia, 2009). More specifically, the phenotypes or symptoms caused by adverse early-life conditions often require additional factors to fully emerge, such as environmental stressors/insults or incubation period, in contrast to epigenetic changes which accumulate and interact with external factors to gradually disrupt homeostasis over the life course.

Several mental disorders, such as anxiety, schizophrenia, and bipolar disorder, emerge during adolescence, with symptoms materializing following the onset of puberty and its associated changes in brain plasticity and function. The emergence of certain mental health disorders later in life suggests a complex interplay between genetic and environment factors to produce long-term symptoms. While genetics certainly play a role in the predisposition to these mental illnesses, epigenetic mechanisms likely mediate gene by environment interactions in these instances. This is supported by the fact that monozygotic twins often display discordant prevalence of mental

disorders (Dempster et al., 2011; van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012). Given that the epigenome of twins becomes increasingly divergent with age, epigenetic mechanisms could play a key role in the etiology or emergence of their symptoms (Kaminsky et al., 2009; Kuratomi et al., 2008).

Although the etiology of these disorders remains mostly unknown and likely include multifactorial contributions from genetic variation and environmental influences, they have also been linked to alterations in epigenetic patterns and regulators. To date, multiple studies have linked both epigenetic factors and environmental factors to numerous disorders, including Alzheimer's disease, autism, fetal alcohol spectrum disorder, schizophrenia, Huntington's, bipolar disorder, and depression (Berko et al., 2014; De Souza et al., 2016; Guintivano, Aryee, & Kaminsky, 2013; Hannon et al., 2015; Horvath et al., 2016; Jaffe et al., 2015; Portales-Casamar et al., 2016). For instance, the promoter region of the *COMT* gene, which catalyzes dopamine breakdown in the brain, displays decreased DNA methylation levels in the frontal cortex of individuals with schizophrenia and bipolar disorder (Abdolmaleky et al., 2006). Furthermore, a polymorphism in the *COMT* produces a more active protein variant and has been directly linked to schizophrenia and bipolar disorder in adults, supporting a role for both epigenetic and genetic factors in the emergence of these disorders (Glatt, Faraone, & Tsuang, 2003; Shifman et al., 2004). In addition, altered DNA methylation patterns of the *Reelin* gene, crucial for neuronal migration and early brain organization, have also been identified in the postmortem brain of schizophrenics, further supporting a role for epigenetic dysregulation in the manifestation of mental disorders and abnormal brain development (Grayson et al., 2005). Finally, Parkinson's disorder (PD) is another classic example of a heritable disorder that emerges later in life in only some individuals. Previous studies demonstrating that intronic DNA methylation results in reduced expression of alpha-synuclein (*SNCA*), a major risk gene for PD, along with reports of miRNA deregulation in human PD brain samples (Jowaed, Schmitt, Kaut, & Wüllner, 2010; Miñones-Moyano et al., 2011; Mullin & Schapira, 2015). Taken together, these studies provide compelling evidence for the contribution of epigenetic variation to the development of neurobiological disorders, and suggest a potential role for epigenetic mechanisms in the design of future therapeutic strategies and/or diagnostic tools.

7.8.5 Aging

The epigenome does not remain stable over time, as nearly one-third of DNA methylation patterns are associated with the aging process (reviewed in Jones, Goodman, & Kobor, 2015). Indeed, DNA methylation levels within certain regions of the genome gradually decrease, particularly in regions of low CpG density and gene bodies (Heyn et al., 2012). Repetitive elements, which contain high

CpG densities and typically display high levels of DNA methylation, also lose DNA methylation with age. By contrast, DNA methylation levels within CpG islands and other high CpG density regions tend to increase with age (Christensen et al., 2009; Johansson, Enroth, & Gyllensten, 2013). Given that the majority of CpG sites within the genome are fully methylated, these changes ultimately lead to a global decrease in DNA methylation levels over time. Furthermore, the epigenome undergoes gradual drift over time, with interindividual epigenetic patterns becoming increasingly divergent over time. For instance, the concordance of epigenetic patterns in monozygotic twins, born with very similar epigenomes, decreases with age, which is likely due to both stochastic events and differing environmental conditions (Fraga et al., 2005; Jones et al., 2015; Teschendorff, West, & Beck, 2013). Although the increase of epigenetic variability over time may potentially contribute to certain mental health illnesses, such as depression, the contribution of epigenetic aging to altered health outcomes in adulthood or later life remains relatively unknown (Córdova-Palomera et al., 2015). However, given the importance of epigenetic patterns in modulating neural functions and maintaining brain homeostasis, it is likely that epigenetic aging contributes to the gradual development and ultimate decline of the brain in adult life (Farré et al., 2015).

7.9 CONCLUSION

The convergence of genetic and epigenetic variation forms a powerful and dynamic regulatory framework that works to sculpt developmental trajectories across a lifespan, particularly in the context of shifting environmental cues. Over the past few decades, scientific discoveries positioned at the nexus of these fields have considerably illuminated our understanding of developmental regulation. It is now understood that genetic variation, comprised of structural sequence variants or single base polymorphisms, represent the heritable factors that drive developmental course. By contrast, the epigenome represents a structural overlay of the genome, comprised of DNA modifications, chromatin compaction and noncoding RNA activity, which allow for enduring ontogenetic programming and modulating environmentally influenced reorganization. Importantly, epigenetic processes are now thought to serve as potential mediators of gene–environment interplay, permitting brain-specific plasticity during key developmental windows. Despite these important research advances, a number of key issues remain: how these factors cooperatively function during different developmental periods of susceptibility; if these marks may be used as biomarkers to indicate disease risk; and finally, the potential reversibility of epigenetic marks in developmental diseases.

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