

Epigenomics and Proteomics of Brain Disorders

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Received July 25, 2017; Accepted July 30, 2017; Published November 30, 2017

ABSTRACT

Epigenomic mechanisms (DNA methylation, chromatin remodeling/histone modifications, miRNA regulation) are involved in the transcriptional and post-translational regulation of genes in physiological and pathological conditions leading to potentially reversible phenotypes. Mutations in the genes encoding elements of the epigenetic machinery cause epigenetic Mendelian disorders. Epigenetic aberrations contribute to the pathogenesis of neurodevelopmental, imprinting, neuropsychiatric, and age-related neurodegenerative disorders. Some brain disorders exhibit proteoepigenomic changes resulting from primary genomic traits and/or secondary epigenetic events which induce pathogenic (structural, functional, conformational) changes in key proteins. Proteomic biomarkers and epigenomic signatures may help in the prediction, early diagnosis, and prognosis of CNS disorders. Epigenetic drug discovery, application of pharmacoepigenomic procedures for personalized therapeutics, novel approaches to decode and resolve drug resistance, and targeting miRNAs in prevention and treatment of brain disorders are promising areas of future development.

Keywords: Keywords: Alzheimer's disease, Epigenomics, Epigenetic Mendelian disorders, Neurodegenerative disorders, Neurodevelopmental disorders, Neurological disorders, Parkinson's disease, Pharmacoepigenomics, Proteomics, Psychiatric disorders.

INTRODUCTION

Epigenomic regulation is a universal phenomenon of gene expression control during development, maturation and aging in physiological conditions. When this mechanism of control is altered by endogenous and/or exogenous factors, probably acting as an interface between the genome and the environment (nature vs nurture) [1,2], then epigenomic changes become pathogenic due to the abnormal expression of genes under epigenetic control. Harris et al. [3] define these metastable epialleles as mammalian genomic loci where epigenetic patterning occurs before gastrulation in a stochastic fashion, leading to systematic interindividual variation within one species. This gene expression abnormally leads to a potential reversible pathological phenotype which, in some cases, can be transferred to future generations, assuming that epigenetics refers to phenotypic changes with no apparent alterations in structural DNA. Preconceptional

parental exposure to environmental stimuli may determine the offspring's phenotype via meiotically and mitotically heritable epigenetic mechanisms [1], and exposure to diverse external elements (nutrition, pollutants, drugs, toxins) may condition several categories of human diseases. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and regulation by microRNAs (miRNAs), are

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Citation: Cacabelos R, Meyyazhagan A, Carril J C & Tejjido O. (2017) Epigenomics and Proteomics of Brain Disorders. J Genomic Med Pharmacogenomics, 2(1): 267-330.

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among the major regulatory elements that control metabolic pathways at the molecular level. DNA methylation/demethylation and chromatin remodeling/histone modifications regulate gene expression transcriptionally, and miRNAs suppress gene expression post-transcriptionally [4]. Mutations in the genes encoding elements of the epigenetic machinery can lead to an epigenetic Mendelian disorder [5]. Epigenetic marks contribute to natural human variation [6] and configure the emerging field of neuroepigenetics [2]. Not only nuclear DNA, but also mitochondrial DNA may be subjected to epigenetic modifications related to disease development, environmental exposure, drug treatment and aging [7]. Some epigenetic modifications are conceptually

reversible and can potentially be targeted by pharmacological and dietary interventions [8-10].

Age-related neuropsychiatric disorders (from neuro-development to aging) are complex diseases in which genomic defects, together with environmental factors and epigenetic alterations, may be involved [11]. Most of these disorders exhibit proteoepigenomic changes resulting from primary genomic traits and/or secondary epigenetic events which induce pathogenic (structural, functional, conformational) changes in key proteins [12]. Consequently, neuroepigenetic perturbations in genes involved in brain development, maturation and aging, may alter gene expression and

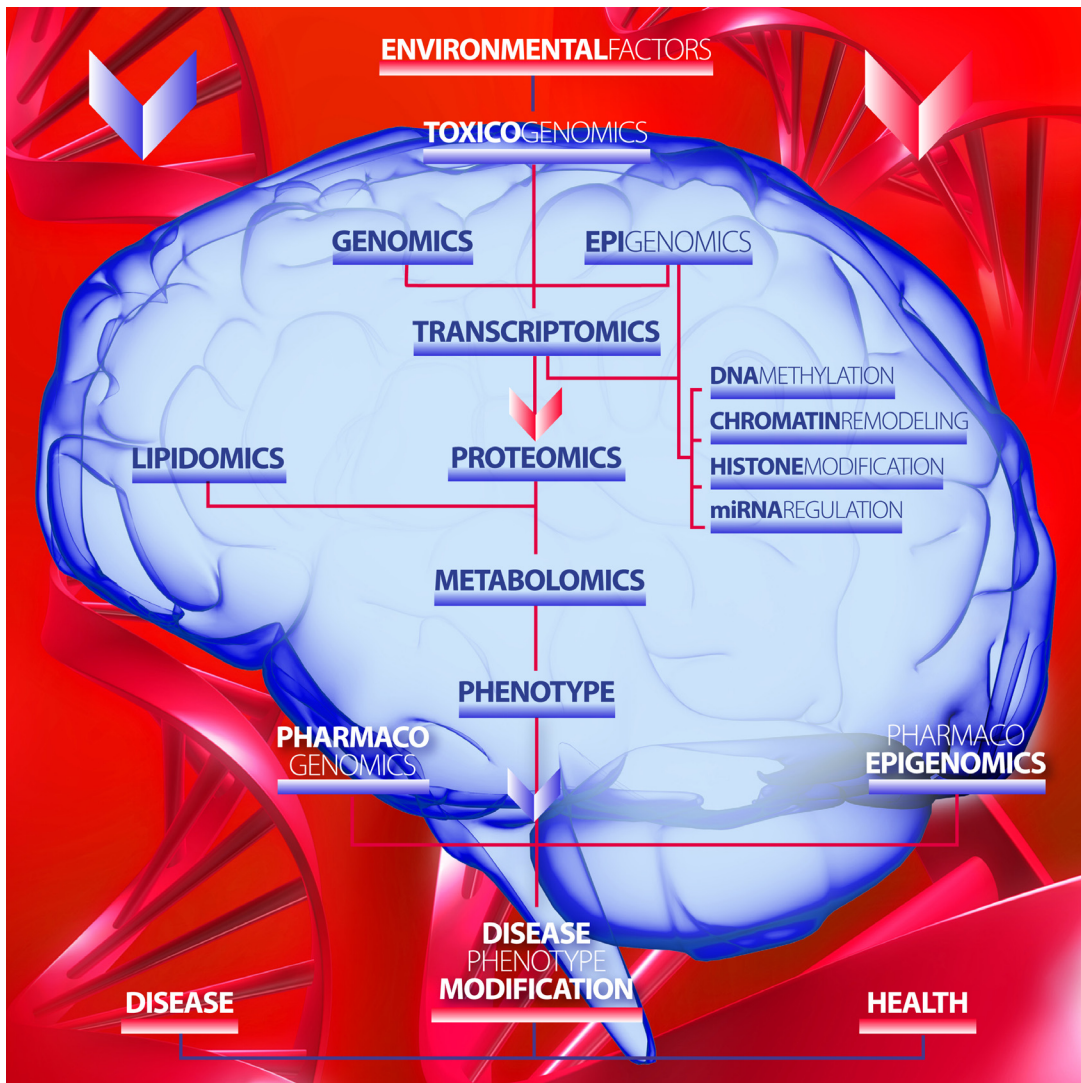


Figure 1. Potential pathogenic players in CNS disorders and -OMICS intervention.

(From Cacabelos et al., J Genom Med Pharmacogenomics 2016; 1(2): 151-209)

protein synthesis (and conformational protein configuration) leading to neurodevelopmental, neuropsychiatric, and neurodegenerative disorders [13] (Table 1). Epigenetic changes in genes involved in pharmacogenomics (pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes) can also influence drug efficacy and safety and drug resistance in brain disorders and cancer [14].

EPIGENETIC MECHANISMS

DNA methylation

DNA methylation is a process by which methyl groups are incorporated into cytosine molecules by DNA methyltransferases (DNMTs), forming 5-methylcytosine and contributing to the suppression of transcription. The human genome may contain approximately ~29 million CpG dinucleotides, and the number of potential methylation patterns per haploid genome might be around $10^{8,700,000}$, this contributing to increase the information content of the genome and endowing mammalian genomes with the ability to subjugate specific sequences to irreversible transcriptional silencing [15]. Methylation varies spatially across the genome, with a majority of the methylated sites mapping to intragenic regions [16]. Approximately 70% of CpG dinucleotides within the human genome are methylated. CpG islands in promoter regions of genes are defined as 200 bp regions of DNA where the GC content is greater than 60%. DNA methylation inhibits transcription by interfering with the binding of transcription factors to recognition sites on promoters or by recruiting and binding transcriptional repressors, methyl-CpG-binding proteins (MBDs), and altering chromatin structure into an active state. 5-Methylcytosines (5mC) can also be oxidized to form 5-hydroxymethylcytosine (5hmC) to reduce the interaction of DNA with DNA-binding proteins [17]. CpG methylation may also cause a dual effect on transcription, repressing transcription when CpG methylation occurs at the promoter level or promoting transcription when CpG methylation affects the gene sequence [18]. A family of DNMTs catalyzes the transfer of methyl groups from S-adenosyl-methionine (SAM) to cytosine in CpGs. In mammals there are 2 *de novo* DNMTs (DNMT3A, DNMT3B) and a maintenance DNMT (DNMT1) that is expressed in neurons. DNMT2 methylates aspartic acid tRNA, and does not methylate DNA [19,20]. DNA demethylation can be produced by at least 3 enzyme families: (i) the ten-eleven translocation (TET) family, mediating the conversion of 5mC into 5hmC; (ii) the AID/APOBEC family, acting as mediators of 5mC or 5hmC deamination; and (iii) the BER (base excision repair)

glycosylase family involved in DNA repair [17]. Lysine-Specific Demethylase 1 (LSD1) (also known as KDM1A and AOF2) is a histone modifier involved in transcriptional repression, forming a stable core complex with the corepressor of REST (CoREST) and histone deacetylases (HDAC1/2) [9,10].

Non-CG methylation (mCH) is abundant and nonrandomly distributed in the genomes of pluripotent cells and brain cells, and is present at lower levels in many other human cells and tissues. mCH in pluripotent cells is distinct from that in brain cells in terms of sequence specificity and association with transcription, indicating the existence of different mCH pathways. In brain cells, mCH accumulates during the establishment of neural circuits and is associated with Rett syndrome [21].

Histone modifications

Histone modifications (HMs) (histone acetylation, methylation, phosphorylation, sumoylation, ubiquitylation, glycosylation, ADP ribosylation, biotinylation) are essential epigenetic features, with fundamental roles in biological processes such as transcription, DNA repair and DNA replication. [17,22]. Histone acetylation is achieved by the action of histone acetyltransferase (HAT), which adds an acetyl group to a lysine residue, resulting in chromatin/transcriptional activation; histone deacetylation is produced by histone deacetylases (HDACs) which remove the acetyl groups, and is related to chromatin inactivation and transcriptional repression [22,23].

Chromatin remodeling. Stable heterochromatin is necessary to silence transposable elements (TEs) and maintain genome integrity. Chromatin regulators (CRs) mediate HMs to adjust chromatin structures and functions. ATP-dependent chromatin remodeling complexes (ACRCs) use ATP hydrolysis to move, destabilize, eject or restructure nucleosomes, allowing the accessibility of transcription factors to DNA. There are at least 4 families of ACRCs: (i) the SWI/SNF (switching defective/sucrose nonfermenting) family; (ii) the ISWI (imitation SWI) family; (iii) the CHD (chromodomain, helicase, DNA binding) family; and (iv) the INO (inositol requiring 80 family) [24]. Their transcriptional effects (activation or repression) depend upon the recruitment of coactivators or corepressors [17].

Post-translational histone modifications. Post-translational histone changes include acetylation, ubiquitylation, or sumoylation at K (lysine) residues, methylation at K, R (arginine) or H (histidine) residues, and phosphorylation at S

Table 1. Selected Genomic, Epigenomic, and Proteomic markers in Neurodevelopmental Disorders.

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/ Histone modifications	Non-coding RNAs	
Neurodevelopmental disorders									
Angelman syndrome	UBE3A <i>Ubiquitin protein ligase E3A</i>	15q11.2	1020	1999	UBE3A Ubiquitin protein ligase E3A	PWS-IC hypomethylation promotes UBE3A expression in paternal allele PW-S-IC hypermethylation inhibits UBE3A expression in maternal allele	H4 histone acetylation H3 histone methylation	snoRNA cluster at 15q11-q13 imprinted locus	
						Hypermethylated	Histone modifying genes <i>p300, MYST4, HDAC1, MeCP2</i> Histone acetylation	Decreased expression (miR-18a-5p, miR-22-3p, miR-24-3p, miR-106b-5p, miR-107) Increased expression (miR-155a-5p, let-7d)	
Attention deficit-hyperactivity disorder (ADHD)	DRD4 <i>Dopamine receptor D4</i>	11p15.5	993	637	DRD4 D(4) dopamine receptor	Hypermethylated			
						DRD5 D(1B) dopamine receptor			
Autism spectrum diseases (ASDs)	CHD8 <i>Chromodomain helicase DNA binding protein 8</i>	14q11.2	926	493	CHD8 Chromodomain helicase DNA binding protein 8				
						CNTNAP2 <i>Contactin associated protein-like 2</i>			
						EN2 <i>Engrailed homeobox 2</i>			
						MECP2 <i>Methyl CpG binding protein 2</i>	Hypermethylated	Histone methylation (H3K4) Low <i>MCEP2</i> activity HDAC1 inhibition Reduced capacity of condensing chromatin Overactive mRNA transcription	miR-34b, miR-103a-3p, miR-181b, miR-486
						MET <i>MET proto-oncogene, receptor tyrosine kinase</i>			
						OXYR <i>Oxytocin receptor</i>	Hypermethylated		
						RELN <i>Reelin</i>	Hypermethylated		
						SHANK2 <i>SH3 and multiple ankyrin repeat domains 2</i>	Hypermethylated		
						DMD <i>Dystrophin</i>			
						DMD <i>Dystrophin</i>			
Duchenne/Becker muscular dystrophy	DMD <i>Dystrophin</i>	Xp21.2-p21.1	1058	2757	DMD Dystrophin		Dysregulated HDACs	miR-1, miR-133, and miR-206	
Fragile X syndrome (FRAXA)	FMR1 <i>Fragile X mental retardation 1</i>	Xq27.3	1042	2391	FMR1 Fragile X mental retardation protein 1	Hypermethylated	Recruitment of histone deacetylases Histone H3K9 H3K27, H4K20 methylation Heterochromatin condensation	FMR1 knockout mice (miR-34b, miR-148a, miR-340) FMR1 human (miR-23a, miR-32, miR-124, miR-335-5p, miR-350)	

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/ Histone modifications	Non-coding RNAs
Neurodevelopmental disorders								
Prader Willi syndrome	<i>NDN</i> <i>Necdin, melanoma antigen (MAGE) family member</i>	15q11.2	951	998	NECD Necdin	Hypermethylation silencing paternal allele	H4 histone acetylation H3 histone methylation	snoRNA cluster at 15q11-q13 imprinted locus
	<i>SNRPN</i> <i>Small nuclear ribonucleoprotein polypeptide N</i>	15q11.2	955	481	RSMN Small nuclear ribonucleoprotein-associated protein N	Hypermethylation silencing paternal allele		
Rett syndrome	<i>UBE3A</i> <i>Ubiquitin protein ligase E3A</i>	15q11.2	1020	1999	UBE3A Ubiquitin protein ligase E3A			
	<i>CDKL5</i> <i>Cyclin-dependent kinase-like 5</i>	Xp22.13	901		CDKL5 Cyclin-dependent kinase-like 5		H4 hyperacetylation (H4K16) Decreased H3 acetylation (AcH3K14) Decreased H3 methylation (MeH3K4/MeH3K9)	miR-29, miR-146a, miR-146b, miR-382
Rett syndrome	<i>FOXG1</i> <i>Forkhead box G1</i>	14q12	918	1077	FOXG1 Forkhead box protein G1			
	<i>MECP2</i> <i>Methyl CpG binding protein 2</i>	Xq28	1060		MECP2 Methyl CpG-binding protein 2	Defective		

(serine), T (threonine) or Y (tyrosine) residues, which affect transcription, DNA replication, and DNA repair [17].

Histone acetylation is catalyzed by 5 families of histone lysine acetyltransferases (KATs) (KAT2A/GCN5, KAT2B/PCAF, KAT6-8, CREBBP/CBP, EP300) [25]. Histone acetylation is associated with transcriptional activation and open chromatin conformation. In contrast, histone deacetylation is involved in transcriptional repression and closed chromatin structure. 18 HDACs, present in mammals, are organized into 4 classes (class I, II, III, IV): (i) Class I HDACs (HDAC1, 2, 3, and 8), nuclear proteins; HDAC1 and HDAC2 are often found in transcriptional corepressor complexes (*SIN3A*, *NuRD*, *CoREST*), and HDAC3 is found in other complexes (SMRT/N-CoR); (ii) class II HDACs are subdivided into class IIa (HDAC4, 5, 7, and 9), and IIb (HDAC6 and 10), which are located in the nucleus-cytoplasm interface and in the cytoplasm, respectively; (iii) class III HDACs belong to the sirtuin (SIRT) family, with nuclear (SIRT1, 2, 6, 7), mitochondrial (SIRT3, 4, 5), or cytoplasmic (SIRT1, 2) localization; and (iv) class IV HDAC (HDAC11), a nuclear protein. HDACs regulate gene expression by inducing conformational changes in chromatin [9,10,17,22,26,27]. H3 (K9, K14, K18, K56), H4 (K5, K8, K12, K16), and H2B (K6, K7, K16, K17) acetylation, H3 (K4me2, K4me3, K36me3, K79me2) methylation, and H3 (S10) phosphorylation activate transcription, and H3 (K9me3, K27me3) and H4 (K20me3) methylation represses transcription [28].

Non-coding RNAs

Over 95% of the eukaryotic genome is transcribed into non-coding RNAs (ncRNAs) and less than 5% is translated [29,30]. Long non-coding (lnc) RNAs are non-protein-coding RNAs, distinct from housekeeping RNAs (tRNAs, rRNAs, and snRNAs) and independent from small RNAs with specific molecular processing machinery (micro- or piwi-RNAs) [31]. Long RNA (lncRNA)-mediated epigenetic regulation depends mainly on lncRNA interactions with proteins or genomic DNA via RNA secondary structures. ncRNAs are classified by size into 2 categories: (i) small RNAs (<200 nucleotides): (a) structural RNAs: ribosomal (rRNA), transfer (tRNA), small nuclear RNAs (snRNA); (b) regulatory RNAs: microRNAs (miRNA), small interfering RNAs (siRNA), small nuclear RNAs (snRNA), piwi-interacting RNAs (piRNA), splice junction-associated RNAs; and (ii) long RNAs (lncRNAs) (>200 nucleotides), present in >8000 loci in the human genome: large intergenic non-coding RNAs (lincRNA), natural antisense transcripts (NATs), non-coding RNA expansion repeats, promoter-associated RNAs (PARs), enhancer RNAs (eRNAs), small

activating RNAs (saRNAs, RNAa) [17,32,33]. Small non-coding RNAs(ncRNAs) -miRNAs, siRNAs, piRNAs-show mature forms of 20-30 nucleotides (nt) that associate with members of the Argonaute (AGO) superfamily of proteins, the central effectors of RNA interference (RNAi) pathways. miRNAs and siRNAs are post-transcriptional gene silencers, guiding AGO complexes to complementary mRNAs in the cytoplasm, inducing transcript degradation and blocking translation [32]. miRNAs repress translation with RISC (RNA-induced silencing complex) and induce mRNA degradation by binding to the 3' untranslated region (3'UTR). Other miRNAs may enhance mRNA translation and induce gene expression by binding to the promoter of the target gene. ncRNAs are essential in the regulation of epigenetic mechanisms (silencing of transposable elements, gene expression control, X-chromosome inactivation, DNA imprinting, DNA methylation, histone modifications). piRNAs are essential for fertility, associating with the PIWI clade of Argonautes to silence transposons in the germline [32]. RNA activation (RNAa) is currently accompanied by changes in histone modifications around the target promoter, and DNA methylation does not appear to be affected by RNAa [32], although RNA-directed DNA methylation (RdDM) and RNA-induced transcriptional silencing (RITS) phenomena have been reported [34]. Endogenous small RNA-mediated epigenetic gene regulation involves miRNA-induced RNAa and miRNA-induced transcriptional gene silencing [34].

NATs are lncRNAs arising from the opposite strand of protein-coding or non-protein-coding genes that regulate mRNA expression at the level of transcription via competition for regulatory factors, or through physically hindering the progress of transcription. NATs edit or activate cellular siRNA-related pathways that lead to degradation of homologous transcripts, ultimately eliciting gene silencing and can regulate RNA processing including translation, polyadenylation, splicing, transport or degradation. NATs can also bind to epigenetic enzymes and act as a scaffold to form active or repressive chromatin modifying complexes [35]. NATs have been associated with neurodegenerative, neurodevelopmental and psychiatric disorders (schizophrenia, bipolar disorder, autism, and fragile X mental retardation gene (*FMRI*) [36].

The lncRNA Xist initiates X chromosome inactivation (Xi) in female somatic cells, silencing a number of genes on the inactive X chromosome, necessary for a normal brain development [37]. lncRNAs also regulate gene expression through genomic imprinting [38]. lncRNAs can also regulate gene expression through interaction with paraspeckles, membraneless subnuclear bodies that participate in nuclear organization, regulating gene

expression post-transcriptionally. The formation and maintenance of paraspeckles requires *NEAT1*, a lncRNA that localizes exclusively to paraspeckles. *NEAT1* is upregulated in Huntington's disease [39] and in amyotrophic lateral sclerosis (ALS) [40].

BRAIN DEVELOPMENT

Dynamic epigenetic changes are fundamental for normal brain development. All components of the epigenetic machinery participate in the normal process of brain development. Mendelian mutations in different epigenetic factors cause irreversible neurodevelopmental and imprinting disorders. DNA methylation is a mechanism of epigenetic control in mammals at different stages of the lifespan. During embryonic development, DNA methylation restricts differentiation and prevents regression into an undifferentiated state, compensates sex chromosome dosage, represses retrotransposons that threaten genome integrity, maintains genome stability, and coordinates the expression of imprinted genes [41]. Vertebrate genomes undergo epigenetic reprogramming during development and disease. Stable transmission of DNA methylation, transcriptomes and phenotypes from parent to clonal offspring are demonstrated in various asexual species, and clonal genotypes from natural populations show habitat-specific DNA methylation [42]. Prenatal exposure to deleterious factors may induce aberrations in DNA methylation and other epigenetic mechanisms, leading to the abnormal expression of genes with negative effects on neurodevelopment, experience-dependent plasticity, brain sex differentiation and brain maturation later in life [13,43]. There is evidence that adverse effects of early-life stress are pervasive, with well-established mental and physical health consequences for exposed individuals. The impact of early adverse experiences is also highly persistent, with documented increases in risk for mental illness across the lifespan. Stress phenotypes may persist even beyond the lifespan of the individual, with consequences for their offspring and grand-offspring. Phenotypic characteristics may be transmitted to future generations via either the matriline or the patriline, a phenomenon that has been demonstrated in both human and animal studies [44].

Regulation of specialized genes might also be a form of epigenetic predestination with effects on brain evolution, development and maturation. Sushi-ichi-related retrotransposon homolog 11/Zinc finger CCHC domain-containing 16 (*Sirh11/Zcchc16*) encodes a CCHC type of zinc-finger protein that exhibits high homology to an LTR retrotransposon Gag protein. *Sirh11/Zcchc16* is involved

in cognitive function and gene targeting of mouse *Sirh11/Zcchc16* causes abnormal behaviors (cognition deficits: attention, impulsivity and working memory). This gene is highly conserved in the eutherians (euarchontoglires, laurasiatheria and afrotheria) and is heavily mutated in xenarthran species such as the sloth and armadillo, suggesting that it has contributed to brain evolution in the three major eutherian lineages, including humans and mice. According to data reported by Irie et al. [45], *Sirh11/Zcchc16* is the first SIRH gene to be involved in brain function, instead of the placenta, as seen in the case of *Peg10*, *Peg11/Rtl1* and *Sirh7/Ldoc1*.

The regulation of methylation/demethylation pathways in the central nervous system (CNS) is highly controlled, depending on brain region and age [46]. 5-Hydroxymethylcytosine (5hmC) is an oxidative product of 5-methylcytosine (5mC), catalyzed by the TET family of enzymes. These enzymes are thought to play a role in mammalian development and differentiation. TET enzymes are mutated in several types of cancer, affecting their activity and likely altering genomic 5hmC and 5mC patterns. Oxidation of 5mC appears to be a step in several active DNA demethylation pathways, which may be important for normal processes, as well as global hypomethylation during cancer development and progression [47]. 5hmC is also involved in Rett syndrome [48].

Epigenetic modifications of histone proteins and DNA seem to be a leading molecular mechanism to modulate the transcriptional changes underlying the fine-tuning of synaptic connections and circuitry rewiring during activity-dependent plasticity [13]. Many lncRNAs are expressed in the CNS where they participate in essential processes for normal brain development [33,49].

AGE-RELATED EPIGENETICS

Altered DNA methylation patterns may account for phenotypic changes associated with human aging. Brain region-specific expression of genes can be epigenetically regulated by DNA methylation [50] and brain aging might be influenced by epigenetic changes in the neuronal microenvironment [51,52].

DNA Methylation

Age- and tissue-dependent DNA hypo- and hypermethylation has been reported [17]. It appears that global loss of DNA methylation predominates in aged cells. DNMT1, which maintains DNA methylation of CpGs, decreases with age [53]. In contrast, some loci have been found hypermethylated

with age (e.g. estrogen receptor, interferon γ , insulin-like growth factor II, promoters of tumor-suppressor genes such as lysyl oxidase (*LOX*), *p16INK4a*, runt-related transcription factor 3 (*RUNX3*), and TPA-inducible gene 1 (*TIG1*)) [17]. Xu and Taylor [54] analyzed 1,006 blood DNA samples of women aged 35 to 76 from the Sister Study, and found that 7,694 (28%) of the 27,578 CpGs assayed were associated with age, confirming the existence of at least 749 "high-confidence" age-related CpG (arCpGs) sites in normal blood. These age-related changes are largely concordant in a broad variety of normal tissues, and a significantly higher (71-91%) than expected proportion of increasingly-methylated arCpGs (IM-arCpGs) were over-methylated in a wide variety of tumor types. IM-arCpGs sites occurred almost exclusively at CpG islands and were disproportionately marked with the repressive H3K27me3 histone modification. These findings suggest that as cells acquire methylation at age-related sites they have a lower threshold for malignant transformation that may explain in part the increase in cancer incidence with age.

McClay et al. [55] performed a methylome-wide association study of aging in whole blood DNA from 718 individuals, aged 25-92 years. They sequenced the methyl-CpG-enriched genomic DNA fraction, averaging 67.3 million reads per subject, to obtain methylation measurements for the ~27 million autosomal CpGs in the human genome, and adaptively combined methylation measures for neighboring, highly-correlated CpGs into 4,344,016 CpG blocks for association testing. Eleven age-associated differentially methylated regions (DMRs) passed Bonferroni correction. 42 of 70 selected DMRs showed hypomethylation and 28 showed hypermethylation with age. Hypermethylated DMRs were more likely to overlap with CpG islands and shores. Hypomethylated DMRs were more likely to be in regions associated with polycomb/regulatory proteins (EZH2) or histone modifications H3K27ac, H3K4m1, H3K4m2, H3K4m3 and H3K9ac. Among genes implicated by the top DMRs were protocadherins, homeobox genes, mitogen-activated protein kinases (MAPKs), ryanodine receptors, and genes with potential relevance for age-related disease.

The absolute levels of 5-hydroxymethylcytosine (hmC), 5-formylcytosine (fC) and 5-methylcytosine (mC) vary in human brain tissues at various ages. For hmC, an initial steady increase is observed, which levels off with age to a final steady-state value of 1.2%. This level is nearly twice as high as in mouse cerebral cortex. fC declines rapidly with age during early developmental stages. While hmC is a stable epigenetic mark, fC is more likely an intermediate of active DNA demethylation during early brain development.

The trends in global cytosine modification dynamics during the lifespan are conserved between humans and mice and show similar patterns in different organs [56].

Histone modifications

Histone modifications are also observed with aging. Histone acetylation decreases and phosphorylation increases with age [57]. H4K20me and H3K36me₃ decrease in the brain of old senescence-accelerated prone mice (SAMP8) and H3K27m₃, H3K79me, and H3K79me₂ increase in these aged mice brains [58]. The silent information regulator 2 (Sir2) in yeast and its mammalian orthologs, sirtuin 1-7 (SIRT1-7), are histone-modifying enzymes which tend to be downregulated in aging, especially SIRT1. Activation of sirtuins may extend lifespan, modulating calorie restriction mechanisms [59] and promoting a healthy aging, which delays the onset of neurodegenerative processes [60]. In the epidermis, aging is associated with a limited destabilization of the epigenome at gene regulatory elements [61]. Wound treatment with Sirtuin activators and class I HDAC inhibitors induce keratinocyte proliferation and enhances healing via a nitric oxide (NO)-dependent mechanism. Acetylation of α -tubulin and histone H3 Lysine 9 may activate cell function and gene expression to foster tissue repair. The direct activation of P300/CBP-associated factor (PCAF) by the histone acetylase activator pentadecylidenemalonate 1b (SPV-106) induces lysine acetylation in the wound area. An impairment of PCAF and/or other GCN5 family acetylases may delay skin repair in physiopathological conditions [62].

Non-coding DNAs

There is a correlation between changes in miRNA expression and aging. miRNA lin-4 regulates lifespan in *C. elegans*; several miRNAs (miRNAs-34, -669c, -709, -93, -214) were found to be upregulated with age, while others (miRNAs-103, -107, -128, -130a, -155, -24, -221, -496, -1538, -17, -19b, -20a, -106a) appeared downregulated in peripheral tissues [63,64]. 70 miRNAs were found to be upregulated in the aging brain; 27 of these miRNAs may target genes of mitochondrial complexes III, IV, and F₀F₁-ATPase involved in oxidative phosphorylation and reduced expression in aging [65].

NEURODEVELOPMENTAL DISORDERS

Epigenetic mechanisms are determinant in brain development and maturation, puberty-related changes [66], mental disorders [67-70], addictive behaviors [71,72], and neurodegeneration [14,17,73,74]. There is a number of

neurodevelopmental disorders (**Table 1**) in which epigenetic dysregulation plays an important role (autism spectrum disorders, Rett syndrome, fragile X syndrome, Prader-Willi syndrome, Angelman syndrome, and Kabuki syndrome) [75,76] (**Table 1**).

Methylation of histone H3 lysine 4 (H3K4me) is a regulated post-translational modification, which is broadly associated with enhancers and promoters of actively transcribed genomic loci. Four H3K4me methyltransferases (KMT2A, KMT2C, KMT2D, KMT2F), four demethylases (KDM1A, KDM5A, KDM5B, KDM5C), and two reader proteins (PHF21A, PHF8) are mutated in neurodevelopmental disorders [77].

Rett syndrome is an X-linked neurodevelopmental disease caused by *MECP2* mutations. The MeCP2 protein acts as a transcription repressor by binding to methylated CpG dinucleotides, and also as a transcription activator. MeCP2 is expressed in neurons and in glial cells. Reintroduction of MeCP2 into behaviorally affected *Mecp2*-null mice after birth rescues neurological symptoms, indicating that epigenetic failures in Rett syndrome are reversible [78]. Mutations in JMJD1C (jumonji domain containing 1C) contribute to the development of Rett syndrome and intellectual disability (ID). Mutant JMJD1C in Rett syndrome has abnormal subcellular localization, diminished activity to demethylate the DNA damage-response protein MDC1, and reduced binding to MECP2 [79].

A body of novel arguments postulates the involvement of epigenetic mechanisms in the pathogenesis of autism [80-82]. Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders which are comorbid with attention deficit hyperactivity disorder (ADHD), epilepsy, Rett syndrome, and Fragile X syndrome [83,84]. There are several epigenome-wide association studies of ASD suggesting a potential role for epigenetics in ASD pathogenesis [82].

Mbadiwe and Millis [80] reviewed mechanisms for altering DNA-histone interactions of cell chromatin to upregulate or downregulate gene expression that could serve as epigenetic targets for therapeutic interventions. The proposed rationale includes the following sequence: (i) DNA methyltransferases (DNMTs) phosphorylate histone H3 at T6; (ii) the DNMT lysine-specific demethylase-1 prevents demethylation of H3 at K4; (iii) during androgen-receptor (AR)-dependent gene activation, this sequence may produce AR-dependent gene overactivation which may partly explain the male predominance of autism; (iv) AR-dependent gene overactivation in conjunction with a DNMT mechanism for methylating oxytocin receptors could produce high arousal

inputs to the amygdala resulting in aberrant socialization, a prime characteristic of autism; (v) dysregulation of histone methyltransferases and histone deacetylases (HDACs) associated with low activity of methyl CpG binding protein-2 at cytosine-guanine sites in genes may reduce the capacity for condensing chromatin and silencing genes in frontal cortex, a site characterized by decreased cortical interconnectivity in autistic subjects; and (vi) HDAC1 inhibition can overactivate mRNA transcription, a putative mechanism for the increased number of cerebral cortical columns and local frontal cortex hyperactivity in autistic individuals [80,85].

Sullivan et al. [86] identified the bromodomain and extraterminal domain-containing proteins (BETs) as epigenetic regulators of genes involved in ASD-like behaviors in mice. The pharmacological suppression of BET proteins in the brain of young mice, by the novel, brain-permeable inhibitor I-BET858 leads to selective suppression of neuronal gene expression followed by the development of an autism-like syndrome. Many of the I-BET858-affected genes have been linked to ASD in humans, suggesting the key role of the BET-controlled gene network in the disorder.

A genome-wide differential expression of long noncoding RNAs (lncRNAs) was identified in blood specimens of ASD. A total of 3929 lncRNAs were found to be differentially expressed in ASD peripheral leukocytes, including 2,407 that were upregulated and 1,522 that were downregulated. Simultaneously, 2,591 messenger RNAs (mRNAs), including 1,789 upregulated and 821 downregulated, were also identified in ASD leukocytes. Functional pathway analysis of these lncRNAs revealed neurological pathways of the synaptic vesicle cycling, long-term depression and long-term potentiation to be primarily involved. Thirteen synaptic lncRNAs, including 9 upregulated and 4 downregulated, and 19 synaptic mRNAs, including 12 upregulated and 7 downregulated, were identified as being differentially expressed in ASD. Discovery of the lncRNAs *SHANK2-AS* and *BDNF-AS*, the natural antisense of genes *SHANK2* and *BDNF*, respectively, indicates that in addition to gene mutations, deregulation lncRNAs on ASD-causing gene loci presents a new approach for exploring possible epigenetic mechanisms underlying ASD [87].

Fragile X syndrome (FXS) is the most common monogenic form of developmental cognitive impairment. FXS represents a prototype of the so-called repeat expansion disorders due to “dynamic” mutations of a CGG repeat in the 5'UTR of the *FMRI* gene. This genetic anomaly is accompanied by epigenetic modifications (mainly DNA methylation and histone deacetylation), resulting in the inactivation of the

FMRI gene. The presence of an intact *FMRI* coding sequence allowed pharmacological reactivation of gene transcription, particularly through the use of the DNA-demethylating agent 5'-aza-2'-deoxycytidine and/or inhibitors of histone deacetylases. These treatments suggested that DNA methylation is dominant over histone acetylation in silencing the *FMRI* gene. The importance of DNA methylation in repressing *FMRI* transcription is confirmed by the existence of rare unaffected males carrying unmethylated full mutations [88].

The 22q11.2 deletion syndrome (22qDS), with a hemizygous deletion of 1.5-3 Mb on 22q11.2, is the most common microdeletion disorder (prevalence: 1/4000) and the second risk factor for schizophrenia. At least 9 (*COMT*, *UFDIL*, *DGCR8*, *MRPL40*, *PRODH*, *SLC25A1*, *TXNRD2*, *T10*, *ZDHHC8*) of 30 genes involved in 22qDS have the potential of disrupting mitochondrial metabolism. Deficits in bioenergetics during early postnatal brain development may set the basis for a disrupted neuronal metabolism or synaptic signaling. Altered metabolism in 22qDS reflects a critical role for the haploinsufficiency of the mitochondrial citrate transporter *SLC25A1*, further enhanced by *HIF-1 α* , *MYC*, and metabolite controls [89].

Imprinting disorders

Epigenetic regulation of imprinted genes during embryonic development is influenced by the prenatal environment [90]. Genomic imprinting refers to an epigenetic mark that distinguishes parental alleles and results in a monoallelic, parental-specific expression pattern in mammals. The alleles of imprinted genes are marked epigenetically at discrete elements termed ‘imprinting control regions’ (ICRs) with their parental origin in gametes through the use of DNA methylation. Imprinted gene expression is subsequently maintained using noncoding RNAs, histone modifications, insulators, and higher-order chromatin structure. Avoidance is manifest when imprinted genes evade the genome-wide reprogramming that occurs after fertilization and remain marked with their parental origin [91].

DNA methylation is a hallmark of genomic imprinting and differentially methylated regions (DMRs) are found near and in imprinted genes. Imprinted genes are expressed only from the maternal or paternal allele and their normal balance can be disrupted by uniparental disomy (UPD), i.e., the inheritance of both chromosomes of a chromosome pair exclusively from only either the mother or the father. A growing number of congenital disorders have been linked to

genomic imprinting. Each of these is caused by perturbed gene expression at one principal imprinted domain. Some imprinting disorders, including the Prader-Willi and Angelman syndromes, are caused almost exclusively by genetic mutations, although hypermethylation at the ICRs may also contribute to the maternal or paternal allele silencing. In other cases, including the Beckwith-Wiedemann and Silver-Russell growth syndromes, and transient neonatal diabetes mellitus, imprinted expression is perturbed mostly by epigenetic alterations at ICRs and at other specific regulatory sequences. In a minority of these patients, DNA methylation is altered at multiple imprinted loci, suggesting that common trans-acting factors are affected [92].

Maternal UPD for chromosome 7 (matUPD7) results in Silver-Russell syndrome (SRS) with typical features and growth retardation, but no gene has been conclusively implicated in SRS. Genome-scale analysis of eight matUPD7 patients, a segmental *matUPD7q31-qter*, a rare patUPD7 case, and ten controls on the Infinium HumanMethylation450K BeadChip with 30,017 CpG methylation probes for chromosome 7 showed highly significant clustering of DMRs only on chromosome 7, including the known imprinted loci *GRB10*, *SGCE/PEG10*, and *PEG/MEST*. Ten novel DMRs on chromosome 7, two DMRs for the predicted imprinted genes *HOXA4* and *GLI3*, and one for the disputed imprinted gene *PONI*, and differential expression for three genes with novel DMRs, *HOXA4*, *GLI3*, and *SVOP*, were also demonstrated. Allele-specific expression analysis confirmed maternal only expression of *SVOP* and imprinting of *HOXA4* was supported by monoallelic expression. These results reported by Hannula-Jouppi et al. [93] represent the first comprehensive map of parent-of-origin-specific DMRs on human chromosome 7, suggesting many new imprinted sites.

Kagami-Ogata syndrome (KOS14) is another imprinting disorder caused by an epimutation (hypermethylation) of two DMRs functioning as imprinting control regions, namely, *IG-DMR* and *MEG3-DMR* [94].

PSYCHIATRIC DISORDERS

Gene-specific and genome-wide studies of postmortem brain and blood cells indicate that aberrant DNA methylation, histone modifications and dysregulation of miRNAs are linked to the pathogenesis of mental diseases [95] (Table 2). Human exome sequencing and genome-wide association studies have linked several neurobiological disorders to genes whose products actively regulate DNA methylation and histone acetylation. Nucleosome remodeling has

been implicated in human developmental and intellectual disability disorders. Nucleosome remodeling is driven primarily through nucleosome remodeling complexes with specialized ATP-dependent enzymes. These enzymes directly interact with DNA or chromatin structure, as well as histone subunits, to restructure the shape and organization of nucleosome positioning and ultimately regulate gene expression. Mutations in genes of the the neuron-specific *Brg1/hBrm* Associated Factor (*nBAF*) complex subunit have been linked to Coffin-Siris syndrome (CSS), Nicolaides-Baraitser syndrome (NBS), schizophrenia (SCZ), and Autism Spectrum Disorder (ASD) [96].

Quality of maternal care experienced during infancy is a key factor that can confer vulnerability or resilience to psychiatric disorders later in life. Experiences within an adverse caregiving environment produce aberrant DNA methylation patterns at various gene loci in the medial prefrontal cortex of developing and adult experimental animals [97]. These particular conditions may alter the network of genes involved in mental activity whose region- and neurochemical pathway-specific dysregulation might lead to the future onset of mental disorders.

Schizophrenia

Schizophrenia (SCZ) is a neurodevelopmental heritable disorder (80–85%), in which hundreds of dysfunctional genomic regions are involved, with a high rate of monozygotic concordance [69,73,98,99]. Disruption of epigenetic processes may play an important role in the development of SCZ [100,101]; however, SCZ DNA methylation biomarkers in blood did not yield any conclusive result [102]. The application of padlock probe-based ultra-deep bisulfite sequencing for fine mapping of modified cytosines of the HLA complex group 9 gene in the postmortem brains of individuals affected with SCZ or bipolar disorder and unaffected controls detected significant differences between patients and controls in both CpG and CpH modifications, with epigenetic age effects [103]. Methylation of DNA repetitive sequences (*LINE-1* and *BAGE*) in peripheral blood leukocytes from first-episode schizophrenia (FES) patients vs healthy controls (HCs) indicate that FES⁺ patients have significantly lower *LINE-1* methylation in comparison with FES⁻ patients or HC⁻ subjects. Emotional abuse and total trauma score predicted lower *LINE-1* methylation in FES patients, while general trauma score was associated with lower *BAGE* methylation in HCs [104]. In genome-wide DNA methylation analysis in post-mortem human brain tissue, 4,641 probes corresponding to 2,929 unique genes were found to be differentially methylated. Of those

genes, 1,291 were located in a CpG island and 817 were in a promoter region. These include *NOS1*, *AKT1*, *DTNBPI*, *DNMT1*, *PPP3CC* and *SOX10*. More than 100 of these genes overlap with a previous DNA methylation study of peripheral blood from SCZ patients in which 27,000 CpG sites were analyzed [105].

Molecular dysregulation in SCZ affects disruption of the dopamine, N-methyl-D-aspartate (NMDA), and GABA signaling pathways under control of the epigenetic machinery [106]. The integration of methylome-wide association study results with GWAS findings replicated the top three methylation findings near genes *SDCCAG8*, *CREB1* and *ATXN7* in an independent sample using targeted pyrosequencing [107]. Hypomethylation at the *LRRTM1* promoter, particularly of the paternally inherited allele, may be an additional risk factor for the development of SCZ in a set of siblings affected with familial SCZ [108]. Histone deacetylases (HDACs) are key enzymes of histone acetylation, and abnormalities in histone modifications and in the level of HDAC proteins have been reported in SCZ. The most significant marker associated with SCZ is rs14251 (*HDAC3*); however, rs17265596 (*HDAC9*), rs7290710 (*HDAC10*) and rs7634112 (*HDAC11*) might also be involved to a lesser extent [109].

Men have a higher incidence of SCZ than women, with increases in negative and cognitive symptoms, and an overall poorer disease course. SCZ is conceptualized as a disorder of aberrant gene transcription and regulation. Peripheral histone methyltransferase (HMT) mRNA levels have been shown to be significantly increased in patients with SCZ and correlate with symptomology. Men with SCZ express the highest levels of *G9a*, *SETDB1* mRNA and H3K9me2 protein levels. Higher levels of symptom presentation and an overall poorer quality of life correlate with higher *HMT* mRNA and H3K9me2 protein levels in a sex-dependent pattern. These data support the hypothesis of a sex-dependent restrictive epigenome contributing towards the etiology of SCZ [110].

Downregulation of glutamic acid decarboxylase 67 (*GAD1*), reelin (*RELN*), and *BDNF* expression in SCZ and bipolar disorder is associated with overexpression of DNA methyltransferase 1 (DNMT1) and ten-eleven translocase methylcytosine dioxygenase 1 (TET1). Altered promoter methylation may be one mechanism underlying the downregulation of GABAergic and glutamatergic gene expression. Both DNMT1 and TET1 directly bind to unmethylated CpG-rich promoters through their respective Zinc Finger (ZF-CXXC) domains. The binding of DNMT1 to GABAergic (*GAD1*, *RELN*) and glutamatergic (*BDNF-IX*) promoters is increased in SCZ and bipolar disorder and this increase

does not necessarily correlate with enrichment in promoter methylation. Increased binding of DNMT1 positively correlates with increased expression of DNMT1 and with increased binding of MBD2. In contrast, the binding of TET1 to *RELN*, *GAD1* and *BDNF-IX* promoters failed to change [111]. Expression of *GAD1* GABA synthesis enzyme is highly regulated by neuronal activity and reaches mature levels in the prefrontal cortex not before adolescence. Patients with SCZ show deficits in *GAD1* RNA and protein levels in multiple areas of adult cerebral cortex, possibly reflecting molecular or cellular defects in subtypes of GABAergic interneurons essential for network synchronization and cognition. Deficits in cortical *GAD1* RNA are associated with changes in the epigenetic architecture of the promoter, affecting DNA methylation patterns and nucleosomal histone modifications. These localized chromatin defects at the 5' end of *GAD1* are superimposed by disordered locus-specific chromosomal conformations, including weakening of long-range promoter-enhancer loopings and physical disconnection of *GAD1* core promoter sequences from cis-regulatory elements positioned 50 kilobases further upstream [112]. *Gadd45b* siRNA transfection in neurons abolishes the NMDA-induced increase in *Bdnf IXa* mRNA and reductions in 5MC and 5HMC at the *Bdnf IXa* promoter in post-mitotic neurons [113]. Prenatal methylazoxymethanol (MAM) administration impairs histone acetylation in the prefrontal cortex, which might be involved in the development of some of the neurobehavioral deficits associated with SCZ; and blockade of HDAC2 with valproic acid might prevent the disruption of sensorimotor gating in adulthood [114].

Klinefelter syndrome (KS) is the most common sex-chromosome aneuploidy in humans. Most affected individuals carry one extra X-chromosome (47, XXY karyotype) and the condition presents with a heterogeneous mix of reproductive, physical and psychiatric phenotypes. Genomic, methylomic and transcriptomic variations in matched prefrontal cortex and cerebellum samples were identified in a patient with a 47, XXY karyotype who was comorbid for SCZ and had a notably reduced cerebellum mass compared with other individuals. Global DNA methylation, assessed via the interrogation of *LINE-1* and *Alu* repetitive elements, was significantly altered in the 47, XXY patient in a tissue-specific manner with extreme hypomethylation detected in the prefrontal cortex and extreme hypermethylation in the cerebellum [115].

Fisher et al. [116] explored whether differences in DNA methylation at age 10 were associated with monozygotic twin discordance for psychotic symptoms at age 12. The Environmental Risk (E-Risk) Longitudinal Twin Study cohort of 2,232 children (1,116 twin pairs) was assessed

Table 2. Selected Genomic, Epigenomic, and Proteomic markers in Psychiatric Disorders.

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/ Histone modifications	Non-coding RNAs	
Bipolar affective disorder	<i>ANKK3</i> <i>Ankyrin 3, node of Ranvier (ankyrin G)</i>	10q21.2	963	1599	ANKK3 Ankyrin-3		H3 phosphorylation H3 acetylation	miR-15b, miR-132, miR-134, miR-206, miR-652	
	<i>BDNF</i> <i>Brain-derived neurotrophic factor</i>	11p14.1	1022	3213	BDNF Brain-derived neurotrophic factor	Hypermethylated			
	<i>CACNA1C</i> <i>Calcium channel, voltage-dependent, L type, alpha 1C subunit</i>	12p13.33	1091		CAC1C Voltage-dependent L-type calcium channel subunit alpha-1C	Variable methylation			
	<i>BDNF</i> <i>Brain-derived neurotrophic factor</i>	11p14.1	1022	3213	BDNF Brain-derived neurotrophic factor	Hypomethylated			
Major depressive disorder (MDD)	<i>FKBP5</i> <i>FK506 binding protein 5</i>	6p21.31	1068	2356	FKBP5 Peptidyl-prolyl cis-trans isomerase FKBP5	Hypomethylated			
	<i>GRIN2A</i> <i>Glutamate receptor, ionotropic, N-methyl D-aspartate 2A</i>	16p13.2	1069	1775	NMDE1 Glutamate receptor ionotropic, NMDA 2A	Hypermethylated			
	<i>HTR2A</i> <i>5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled</i>	13q14.2	976	1599	5HT2A 5-hydroxytryptamine receptor 2A	Hypermethylated (polymorphism-dependent)	Histone methylation (H3K9) Increased HDAC2, 4, 5 and SIRT1, 2, 6	Up-regulated (miR-34a-5p, miR-221-3p, let-7d-3p) Down-regulated (miR-451a)	
	<i>IGF2</i> <i>Insulin-like growth factor 2</i>	1p15.5	1057		IGF2 Insulin-like growth factor II	Variable methylation			
	<i>MAPK11</i> <i>Mitogen-activated protein kinase</i>	22q13.33	1051	1341	MK11 Mitogen-activated protein kinase 11	Variable methylation			
	<i>NR3C1</i> <i>Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)</i>	5q31.3	1088	4162	GCR Glucocorticoid receptor	Hypermethylated			
	<i>TPH2</i> <i>Tryptophan hydroxylase 2</i>	12q21.1	1044	947	TPH2 Tryptophan 5-hydroxylase 2	Hypermethylated			
	<i>WDR26</i> <i>WD repeat domain 26</i>	1q42.13	829	4397	WDR26 WD repeat-containing protein 26	Differential methylation			

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/ Histone modifications	Non-coding RNAs
Psychiatric disorders	<i>ADCYAP1</i> Adenylate cyclase activating polypeptide 1 (pituitary)	8p11.32	964	2595	PACA Pituitary adenylate cyclase-activating polypeptide		H3 acetylation (H3K27ac)	miR-29a,c, miR-125a, miR-130a, miR-132, miR-181a, miR-337, miR-672
	<i>ADCYAP1R1</i> Adenylate cyclase activating polypeptide 1 (pituitary) receptor type 1	7p14.3	1086		PACR Pituitary adenylate cyclase-activating polypeptide type 1 receptor	Hypermethylated		
Schizophrenia (SCZ)	<i>AKT1</i> v-akt murine thymoma viral oncogene homolog 1	14q32.33	1099	1106	AKT1 RAC-alpha serine/threonine-protein kinase	Hypomethylated		
	<i>COMT</i> Catechol-O-methyltransferase	22q11.21	1710	372	COMT Catechol-O-methyltransferase	Hypomethylated		
	<i>DTNBP1</i> Dystrobrevin binding protein 1	6p22.3	1201	978	DTNBP1 Dysbindin	Hypomethylated		
	<i>HTR2A</i> 5-hydroxytryptamine receptor 2A, G protein-coupled	13q14.2	998		5HT2A 5-hydroxytryptamine receptor 2A	Hypermethylated		
	<i>L1RE1</i> <i>LINE1</i> retrotransposable element 1	22q11-q12			LORF1 <i>LINE-1</i> retrotransposable element ORF1 protein	Hypomethylated	HDAC1 upregulation H3 methylation H3 acetylation and demethylation at the <i>BDNF</i> promoters	miR-20, miR-30a-d, miR-128, miR-132, miR-134, miR-195, miR-202, miR-346
	<i>NOS1</i> Nitric oxide synthase 1 (neuronal)	12q24.22	1028	2191	NOS1 Nitric oxide synthase, brain	Hypomethylated		
	<i>PPP3CC</i> Protein phosphatase 3, catalytic subunit, gamma isozyme	8p21.3	1010	374	PP2BC Serine/threonine-protein phosphatase 2B catalytic subunit gamma isoform	Hypomethylated		
	<i>RELN</i> Reelin	7q22.1	1065	1156	RELN Reelin	Hypermethylated		
	<i>SOX10</i> <i>SRY</i> (sex determining region Y)-box 10	22q13.1	1044	1343	SOX10 Transcription factor SOX-10	Hypomethylated		
	<i>TAAR6</i> Trace amine associated receptor 6	6q23.2	1026		TAAR6 Trace amine-associated receptor	Hypomethylated		

for age-12 psychotic symptoms and 24 monozygotic twin pairs discordant for symptoms were identified for methylomic comparison. Site-specific DNA methylation differences were observed at age 10 between monozygotic twins discordant for age-12 psychotic symptoms. Similar DMPs were not found at age 5. The top-ranked psychosis-associated DMP (*cg23933044*), located in the promoter of the *C5ORF42* gene, was also hypomethylated in post-mortem prefrontal cortex brain tissue from SCZ patients compared to unaffected controls. Epigenetic variation in peripheral tissue is associated with childhood psychotic symptoms and may indicate susceptibility to SCZ and other mental health problems.

Epidemiological studies have identified prenatal exposure to famine as a risk factor for SCZ. Analysis of gene expression and epigenetic modifications in the brain of the offspring of the RLP50 rat, a recently developed animal model of prenatal famine malnutrition exposure, indicate that offspring of RLP50 exhibit differences in neurotransmitters and olfactory-associated gene expression. In the hippocampus, the differentially-expressed genes are related to synaptic function and transcription regulation. DNA methylome profiling of the hippocampus also shows widespread but systematic epigenetic changes; in most cases (87%) this involves hypermethylation. Genes encoded for the plasma membrane are significantly enriched for changes in both gene expression and DNA methylome profiling screens. *Mecp2* and *Slc2a1*, two genes associated with cognitive impairment, show significant down-regulation, and *Slc2a1* is hypermethylated in the hippocampus. Prenatal exposure to malnutrition leads to the reprogramming of postnatal brain gene expression and epigenetic modifications contribute to the reprogramming [117].

In the CNS, regulatory RNA networks and epigenetic mechanisms have broad relevance to gene transcription changes involved in long-term memory formation and cognition [118]. miR-137 is associated with SCZ and intellectual disability. miR-137 acts as a potent player in regulating glutamatergic synaptic transmission in the hippocampus by controlling the translation of functionally critical genes at spatially opposite ends of the synapse, contributing to the pathogenesis of cognitive impairments as seen in neurodevelopmental disorders [119]. *DISC-2*, *Gomafu*, *EVF-2* and *BDNF-AS* are lncRNAs associated with SCZ. These lncRNAs are responsible for specific proteomic changes in SCZ [38].

Proteomic analysis indicates that SCZ and affective psychosis are linked to a hypoglutamatergic state and hypofunction of energy metabolism, while bipolar disorder and major

depressive disorder (MDD) are linked to a hyperglutamatergic state and hyperfunction of energy metabolism [120]. Proteins with evidence for altered expression in SCZ are enriched for glutamate signaling pathway proteins (GRIA4, GRIA3, ATP1A3, and GNAQ). Synaptic protein co-expression is decreased in SCZ with the exception of a small group of postsynaptic density proteins, whose co-expression increases and inversely correlates with spine density in SCZ. Reduced ATP1A3 expression is supported by strong genetic evidence indicating that it may contribute to psychosis and cognitive impairment phenotypes [121].

Synapses are fundamental components of brain circuits and are disrupted in over 100 neurological and psychiatric diseases. The synapse proteome is physically organized into multiprotein complexes and polygenic mutations converge on postsynaptic complexes in SCZ, autism and intellectual disability [122]. The postsynaptic density (PSD) contains a complex set of proteins of known relevance to neuropsychiatric disorders, and SCZ specifically. Quantitative investigation of the PSD revealed more than 700 protein identifications and 143 differentially expressed proteins. Prominent among these were altered expression of proteins involved in clathrin-mediated endocytosis (CME) (Dynamin-1, adaptor protein 2) and NMDA-interacting proteins such as CYFIP2, SYNPO, SHANK3, ESYT and MAPK3. Pathway analysis of the differentially expressed proteins implicated the cellular processes of endocytosis, long-term potentiation and calcium signaling. Both single-gene and gene-set enrichment analyses in genome-wide association data from the largest SCZ sample to date of 13,689 cases and 18,226 controls show significant association of HIST1H1E and MAPK3, and enrichment of this PSD proteome [123].

Methamphetamine produces a progressive increase in locomotor activity (behavioral sensitization) in rodents that is believed to represent the underlying neurochemical changes driving psychoses. Alterations to the prefrontal cortex (PFC) are suggested to mediate the etiology and maintenance of these behavioral changes. Proteomic analysis revealed 96 proteins that were differentially expressed in the PFC of methamphetamine-treated rats, with 20% of these being previously implicated in the neurobiology of SCZ in the PFC. Proteins associated with synaptic regulation, protein phosphatase signaling, mitochondrial function, and GABAergic network are disrupted in the PFC of SCZ [124].

In serum proteomics of SCZ, over 140 proteins were found to be different from other groups. Two protein peaks at the mass-to-charge ratio of 1,207.41 and 1,466.78 were markedly different, with the lowest expression in specimens from SCZ patients. These proteins were identified as the

N-terminal fragments of fibrinogen [125]. Several markers (2-piperidinecarboxylic acid, 6-deoxy-mannofuranose, galactoseoxime and a serum peptide of *m/z* 3177) have an attractive discriminating value in serum proteomics of SCZ [126]. The analysis of whole saliva in SCZ revealed a 10-fold mean increase of α -defensins 1-4, S100A12, cystatin A and S-derivatives of cystatin B levels, suggesting a dysregulation of immune pathways in peripheral white blood cells [127].

The corpus callosum (CC), which is the largest portion of white matter in the human brain and responsible for inter-hemispheric communication, is altered in SCZ. CC proteomes were quantified by label-free spectral counting and 5,678 unique peptides, corresponding to 1,636 proteins belonging to 1,512 protein families, were identified. Of those proteins, 65 differed significantly in expression: 28 were upregulated and 37 downregulated. Among the differentially expressed proteins are those associated with cell growth and maintenance (neurofilaments and tubulins), cell communication and signaling (14-3-3 proteins), and oligodendrocyte function (myelin basic protein, myelin-oligodendrocyte glycoprotein) [128].

In a chronic phencyclidine (PCP) rat model in which glutamatergic hypofunction is induced through noncompetitive NMDAR-receptor antagonism, alterations in the levels of several cytokines (IL-5, IL-2, and IL-1 β) and fibroblast growth factor-2 were identified. Extensive proteomic and metabolomic brain tissue profiling revealed a more prominent effect of chronic PCP treatment on both the hippocampal proteome and metabolome compared to the effect on the frontal cortex. Bioinformatic pathway analysis confirmed prominent abnormalities in NMDA-receptor-associated pathways in both brain regions, as well as alterations in other neurotransmitter systems such as kainate, AMPA, and GABAergic signaling in the hippocampus and in proteins associated with neurodegeneration [129].

Comparing disease and control cases, 58 unique differentially expressed proteins were identified in SCZ, and 70 differentially expressed proteins in bipolar disorder. Both disorders were characterized by alterations of proteins involved in the oxidative stress response, mitochondrial function, and protein-endocytosis, -trafficking, -degradation, and -ubiquitination focused on GABAergic interneuron pathology in the hippocampus [130]. Human olfactory neurosphere-derived (ONS) cells have been used to study the cellular pathology of SCZ. Discovery-based proteomics and targeted functional analyses revealed reductions in 17 ribosomal proteins, with an 18% decrease in the total ribosomal signal intensity in SCZ-patient-derived ONS cells. Pathway analysis of dysregulated proteomic and

transcriptomic data sets from these ONS cells converged to highlight perturbation of the eIF2 α , eIF4 and mammalian target of rapamycin (mTOR) translational control pathways, and these pathways were also implicated in an independent induced pluripotent stem cell-derived neural stem model, and cohort, of SCZ patients. Analysis in SCZ-genome-wide association data from the Psychiatric Genetics Consortium specifically implicated eIF2 α regulatory kinase EIF2AK2, and confirmed the importance of the eIF2 α , eIF4 and mTOR translational control pathways at the level of the genome [131].

Depressive disorders

Recent evidence provides insights to epigenetic processes in depression; however, replication is lacking and care must be taken in the interpretation of current findings. Most studies have focused on DNA methylation in various CNS or peripheral tissues, with almost universally small sample sizes. Several epigenome-wide association studies have been reported and the majority of studies have used a candidate-gene approach. Three genes (*SLC6A4*, *BDNF*, *NR3C1*) have been investigated in more than one study [132]. Aberrant DNA methylation in the blood of patients with major depressive disorder (MDD) has been reported in several studies. Genome-wide DNA methylation profiling of peripheral leukocytes detected diagnostic differences in DNA methylation at 363 CpG sites. All of these loci showed greater DNA hypomethylation in patients with MDD than in controls, and most of them (85.7%) were located in the CGIs in the gene promoter regions [133]. A pilot study including an epigenome-wide methylation analysis on the hippocampus and prefrontal cortex of depressive patients revealed differential methylation profiles of 11 genes in hippocampus and 20 genes in prefrontal cortex, 5 of which were selected for replication of the methylation status using pyrosequencing. Among these replicated targets, *GRIN2A* was found to be hypermethylated in both prefrontal cortex and hippocampus. *GRIN2A* encodes the glutamatergic N-methyl-D-aspartate receptor subunit epsilon-1 (NR2A) which is known to be involved in synaptic plasticity-related regulatory processes probably disturbed in MDD [134]. Stress-induced maladaptive transcriptional regulation in limbic neural circuits contributes to the development of MDD, possibly through epigenetic factors that regulate chromatin structure. Sun et al. [135] established that persistent upregulation of the ACF (ATP-utilizing chromatin assembly and remodeling factor) ATP-dependent chromatin-remodeling complex, occurring in the nucleus accumbens of stress-susceptible mice and depressed humans, is necessary for stress-induced depressive-like behaviors. Altered ACF binding after chronic

stress correlates with altered nucleosome positioning, particularly around the transcription start sites of affected genes. These alterations in ACF binding and nucleosome positioning are associated with repressed expression of genes implicated in susceptibility to stress. The ACF chromatin-remodeling complex might be a critical component in the development of susceptibility to depression and in regulating stress-related behaviors.

The epigenetic regulation of BDNF may be involved in the pathophysiology of MDD. As compared to healthy controls, MDD patients exhibit reduced fractional anisotropy (FA) in the bilateral anterior and posterior corona radiata (ACR and PCR), genu of the corpus callosum, and the bilateral posterior thalamic radiations, and there is an inverse correlation between the DNA methylation of the *BDNF* promoter region and the FA of the right ACR in MDD patients. *BDNF* DNA methylation may contribute to structural white matter changes in MDD patients [136]. Prenatal maternal psychological distress increases risk for adverse infant outcomes. Prenatal depressive symptoms significantly predict increased *NR3C1* *IF* DNA methylation in male infants and decreased *BDNF* *IV* DNA methylation in both male and female infants [137]. Buccal DNA hypermethylation at the two most widely studied *BDNF* promoters, I and IV, was associated with chronic late-life depression. Three single-nucleotide polymorphisms (*rs6265*, *rs7103411* and *rs908867*) were also found to modify the association between depression and promoter I methylation [138]. Intrapair DNA methylation differences in an intron of *DEPDC7* (chr11:33040743) were associated with intrapair differences in current depressive symptoms and in co-twin studies [139]. Genome-wide methylome studies on depression suggest that, along with differential DNA methylation, affected co-twins of monozygotic pairs have increased DNA methylation variability, probably in line with theories of epigenetic stochasticity. One differentially methylated probe (*cg01122889*) was located in the *WDR26* gene, the DNA sequence of which has been implicated in MDD. Expression of *WDR26* has also been proposed as a biomarker of depression in human blood. Other genes (*CACNA1C*, *IGF2* and the p38 MAP kinase *MAPK11*) showed differential variability [140].

Some neonates are affected by prenatal exposure to serotonin reuptake inhibitor antidepressants (SRI) and maternal mood disturbances. Prenatal SRI exposure was first associated with increased DNA methylation status primarily at *CYP2E1*. Higher DNA methylation status across 16 CpG sites and at each specific CpG site was associated with exposure to lower 3rd trimester maternal depressed mood symptoms only in the SRI-exposed neonates, indicating a maternal mood x SRI exposure interaction. Higher DNA methylation levels at

CpG2, CpG9 and CpG10, in the interrogated *CYP2E1* region, were associated with increased birth weight, independently of prenatal maternal mood, SRI drug exposure, or gestational age at birth [141].

Greater DNA methylation in specific CpG sites at the serotonin transporter promoter in peripheral cells is associated with childhood trauma, depression, and smaller hippocampal volume [142]. There is an association of fMRI blood oxygen level-dependent reactivity with the level of epigenetic methylation of *SLC6A4* in blood DNA in patients with MDD. Activation in the anterior insula elicited by negative emotional content was significantly positively associated with the degree of *SLC6A4* methylation. Significantly negative associations were observed between activation in the posterior insula and the degree of *SLC6A4* methylation when judging the geometry of pictures after seeing negative, in contrast to positive, emotional stimuli [143]. Imipramine, a major antidepressant, is known to inhibit reuptake of serotonin and norepinephrine, which contributes to recovery from MDD. Acute imipramine treatment inhibits NMDA receptor activity. Acute imipramine treatment decreases Ca^{2+} influx through NMDA receptors, whereas long-term treatment increases Ca^{2+} influx via the same receptors. Long-term treatment increases NMDA receptor 2B (*NR2B*) subunit expression via epigenetic changes, including increased acetylation of histones H3K9 and H3K27 in the *NR2B* promoter and decreased activity of histone deacetylase 3 (HDAC3) and HDAC4 [144]. Treatment with venlafaxine decreases expression of prolyl 4-hydroxylase (P4HB), ubiquitin-conjugating enzyme E2K (HIP2) and plastin 3 (T-plastin), and up-regulates expression of growth factor beta-3 (TGF- β 3), dihydropyrimidinase-like 3 (DPYSL3), and pyruvate kinase (PKM) after differentiation for 1 and 7 days [145].

Disturbances of the hypothalamic-pituitary-adrenal axis have been implicated in the pathophysiology of bipolar disorder and MDD. BD patients have significantly increased levels of the major pituitary hormones pro-opiomelanocortin (POMC) and galanin. Bipolar patients also show changes in proteins associated with gene transcription, stress response, lipid metabolism, and growth signaling. In contrast, MDD patients have significantly decreased levels of the prohormone-converting enzyme carboxypeptidase E and follow-up enzymatic analysis showed decreased activity of prolyl-oligopeptidase convertase. Altered prohormone processing may occur in pituitaries of MDD patients. MDD patients also have significant changes in proteins involved in intracellular transport and cytoskeletal signaling [146].

Quantitative proteomic studies identified 10 proteins that were consistently upregulated or downregulated in MDD patients. 3 proteins (ceruloplasmin, inter-alpha-trypsin inhibitor heavy chain H4 and complement component 1qC) were upregulated during the depressive status [147]. Combined proteomic and metabolomic approaches may provide a comprehensive understanding of MDD's etiology and contribute to the identification of diagnostic biomarkers. The combined analyses found significant alterations associated with cerebellar energy metabolism in animal models, including (i) abnormal amino acid metabolism accompanied by corresponding metabolic enzymatic alterations and disturbed protein turnover, (ii) increased glycolytic and tricarboxylic acid (TCA) cycle enzyme levels paralleled by changes in the concentrations of associated metabolites, and (iii) perturbation of ATP biosynthesis through adenosine accompanied by perturbation of the mitochondrial respiratory chain [148]. The differential proteomic analysis of urine samples from first-episode drug-naïve MDD subjects and healthy controls (HC) identified a total of 27 differential proteins, primarily including enzymes, plasma proteins, serpins, and adhesion molecules. The arginine recycling enzyme argininosuccinate synthase (ASS1) was confirmed to be significantly downregulated in the urine of 30 depressed subjects while remaining unchanged in plasma [149].

Post-stroke depression (PSD) is the most common psychiatric complication facing stroke survivors and has been associated with increased distress, physical disability, poor rehabilitation, and suicidal ideation. Plasma proteomics identified 6 proteins associated with lipid metabolism and immunoregulation (apolipoprotein A-IV (ApoA-IV), apolipoprotein C-II (ApoC-II), C-reactive protein (CRP), gelsolin, haptoglobin, and leucine-rich alpha-2-glycoprotein (LRG)). ApoA-IV expression was significantly upregulated in PSD as compared to stroke subjects. ApoC-II, LRG, and CRP expression were significantly downregulated in both PSD and HC subjects relative to stroke subjects. Gelsolin and haptoglobin expression were significantly dysregulated across all three groups [150].

Other psychiatric disorders

Many other psychiatric disorders exhibit epigenetic anomalies including drug abuse and addictive behaviors [151-153], alcohol spectrum disorders [154], sexual disorders [155], and post-traumatic stress disorder [156-158]. Prenatal alcohol exposure (PAE) can cause fetal alcohol spectrum disorders (FASD). Children born with FASD have unique DNA methylation defects that can be influenced by sex and medication exposure [159]. Altered DNA methylation at

the aryl hydrocarbon receptor repressor (AHRR) correlates with self-reported smoking. Smoking was associated with DNA demethylation at two distinct loci within AHRR (*cg05575921* and *cg21161138*), and methylation status at the AHRR residue interrogated by *cg05575921* was highly correlated with serum cotinine levels [72].

NEURODEGENERATIVE DISORDERS

Epigenetic dysregulation is an attractive mechanism to explain in part enigmatic areas of confusion associated with the pathogenesis of age-related neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (**Table 3**), where it may mediate interactions between genetic and environmental risk factors, or directly interact with disease-specific pathological factors [160].

Alzheimer's disease

Alzheimer's disease (AD) is the most frequent neurodegenerative disorder in the elderly population. Over 600 different genes distributed across the human genome are potentially involved in AD pathogenesis, where environmental factors and epigenomic aberrations also participate [14,161-164]. Conventional genomics do not explain in full AD pathogenesis in which epigenetics may help to understand some obscure events. Major epigenetic events may contribute to AD pathology, although evidence is still very limited [17,165-167]. Pharmaceuticals, pesticides, air pollutants, industrial chemicals, heavy metals, hormones, nutrition, and behavior can change gene expression through a broad array of gene regulatory mechanisms (gene translocation, histone modifications, DNA methylation, DNA repair, transcription, RNA stability, alternative RNA splicing, protein degradation, gene copy number, and transposon activation) [168]. Genetic variation associated with different diseases interferes with miRNA-mediated regulation by creating, destroying, or modifying miRNA binding sites. miRNA-target variability is a ubiquitous phenomenon in the adult human brain, which may influence gene expression in physiological and pathological conditions. One of the major roles of lncRNAs in the nucleus is the regulation of gene expression at the transcriptional level via histone or DNA modification [169]. Epigenetic mechanisms and miRNAs have recently been shown to closely interact with each other, thereby creating reciprocal regulatory circuits, which appear to be disrupted in AD [74]. Brain hypoperfusion-related changes in DNA methylation may also contribute to accelerate neuronal

Table 3. Selected Genomic, Epigenomic, and Proteomic markers in Neurodegenerative Disorders.

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/Histone modifications	Non-coding RNAs
Neurodegenerative disorders								
Alzheimer's disease (AD)	<i>APOE Apolipoprotein E</i>	19q13.32	996		APOE Apolipoprotein E	Hypomethylated	Reduced H3 acetylation, Decreased SIRT1, Increased HDAC6 and HDAC2 levels	Linked to AD (miR-34a, miR-34b/c, miR-107, miR-124, miR-125b, miR-137) Epigenetically regulated (let-7, miR-9, miR-132/212, miR146a, miR-148a, miR-184, miR-200, miR-200c/141)
	<i>APP Amyloid beta (A4) precursor protein</i>	21q21.3	1086	1176	A4 Amyloid beta A4 protein	Hypomethylated		
	<i>MAPT Microtubule-associated protein tau</i>	17q21.31	1094		TAU Microtubule-associated protein tau	Hypomethylated		
	<i>PSEN1 Presenilin 1</i>	14q24.2	929	1198	PSN1 Presenilin 1	Hypomethylated		
	<i>ALS2 Amyotrophic lateral sclerosis 2 (juvenile)</i>	2q33.1	1069	1394	ALS2 Alsin	Hypermethylated		
Amvotrophic lateral sclerosis (ALS)	<i>ATXN2 Ataxin 2</i>	12q24.12	926	699	ATX2 Ataxin 2	Hypermethylated		
	<i>C9orf72 Chromosome 9 open reading frame 72</i>	9p21.2		1746	C1072 Protein C9orf72	Hypermethylated	Histone methylation reduces <i>C9orf72</i> gene expression, HDACs overexpression induces neurodegeneration	miR-9, miR-23a-b, miR132, miR-134, miR-206, miR-338-3p, miR-455
	<i>FUS FUS RNA binding protein</i>	16p11.2	1087	398	FUS RNA-binding protein FUS	Arginine-methylation		
	<i>SOD1 Superoxide dismutase 1, soluble</i>	21q22.11	988	497	SODC Superoxide dismutase (Cu-Zn)	Hypomethylated		
	<i>UBQLN2 Ubiquitin 2</i>	Xp11.21	1089	1361	UBQLN2 Ubiquitin-2	Increase of DNMT1, DNMT3a, 5-methylcytosine		
Dementia with Lewy bodies (DLB)	<i>PRKAR2A Protein kinase, cAMP-dependent, regulatory, type II, alpha</i>	3p21.31	924	999	KAP2 cAMP-dependent protein kinase type II-alpha regulatory subunit	Hypomethylated, Inhibition of DNMT1		
	<i>SEPW1 Selenoprotein W, 1</i>	19q13.33	744	452	SELW Selenoprotein W	Hypomethylated	Reduced histone acetylation, Reduced histone methylation	Linked to <i>SCN4</i> (miR-7, miR-153)
	<i>SNCA Synuclein, alpha (non A4 component of amyloid precursor)</i>	4q22.1	1097	1185	SYUA Alpha-synuclein	Hypomethylated		
Frontotemporal dementia (FTD)	<i>C9orf72 Chromosome 9 open reading frame 72</i>	9p21.2		1746	C1072 Protein C9orf72	Hypermethylated	Reduced histone acetylation, Increased HDAC levels	miR-516a-3p, miR-571, miR-548b-5p, and miR-548c-5p, miR-922
	<i>GRN Granulin</i>	17q21.31	1066	356	GRN Granulin	Hypermethylated		
	<i>MAPT Microtubule-associated protein tau</i>	17q21.31	1094		TAU Microtubule-associated protein tau	Hypermethylated		
	<i>TARDBP TAR DNA binding protein</i>	1p36.22	982	2903	TADBP TAR DNA-binding protein 43			

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/Histone modifications	Non-coding RNAs
Neurodegenerative disorders	<i>PAD2</i> Peptidyl arginine deaminase	1p36.13	1036	2360	PAD2 Peptidylarginine deaminase enzyme	Hypomethylated		
	<i>HLA-DRB1</i> Major histocompatibility complex, class II, DR beta 1	6p21.32	1078	397	2B1F HLA class I histocompatibility antigen, DRB1-15 beta chain	Extensive methylation alterations	Increased histone acetylation	miR-18b, miR-96, miR-142-5p, miR-145, miR-146a, miR-155, miR-599
	<i>TNFRSF1A</i> Tumor necrosis factor receptor superfamily 1A	12p13.31	997	700	TNRI A Tumor necrosis factor receptor superfamily 1A	Increase of DNMT1, DNMT3a		
	<i>ABCA3</i> ATP-binding cassette, sub-family A (ABC1), member 3	16p13.3	2201	981	ABCA3 ATP-binding cassette sub-family A member 3	Hypomethylated		
	<i>ATP8A2</i> ATPase, aminophospholipid transporter; class I, type 8A, member 2	13q12.13	1087	1380	AT8A2 Phospholipid-transporting ATPase IB	Hypomethylated		
	<i>APBA1</i> Amyloid beta (A4) precursor protein-binding, family A, member	9q21.12	994	1188	APBA1 Amyloid beta A4 precursor protein-binding family A member 1	Hypomethylated		
	<i>CNTNAP2</i> Contactin associated protein-like 2	7q35-q36	1038		CNTP2 Contactin-associated protein-like 2	Hypomethylated		
	<i>CPLX2</i> Complexin 2	5q35.2	1050	4180	CPLX2 Complexin 2	Hypomethylated		
	<i>FAT1</i> FAT atypical cadherin 1	4q35.2	991	992	FAT1 Protocadherin Fat 1	Hypomethylated		
	<i>FHIT</i> Fragile histidine triad	3p14.2	951	382	FHIT Bis(5-adenosyl)-triphosphatase	Hypomethylated		
	<i>GSST1</i> Glutathione S-transferase theta 1	22q11.2	917	379	GSTT1 Glutathione S-transferase theta-1	Hypomethylated		
	<i>KCNH1</i> Potassium channel, voltage gated eeg related subfamily H, member 1	1q32.2	920		KCNH1 Potassium voltage-gated channel subfamily H member 1	Hypomethylated	Reduced H3 acetylation Toxin-mediated increase H3, H4 acetylation Reduced H3 methylation by PNK1	Linked to SCNA (miR-7, miR-153) Changed expression in PD (miR-10a/6, miR-34b-c, miR133b, miR212, miR495)
	<i>MAGI2</i> Membrane associated guanylate kinase, WW and PDZ domain containing 2	7q21.11	1041	2375	MAGI2 Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 2	Hypomethylated		
	<i>SMOC2</i> SPARC related modular calcium binding 2	6q27	1089	1791	SMOC2 SPARC-related modular calcium-binding protein 2	Hypomethylated		
<i>SLC12A5</i> Solute carrier family 12 (potassium/chloride transporter), member 5	20q13.12	958	2599	S12A5 Solute carrier family 12 member 5	Hypomethylated			
<i>SNC4</i> Synuclein, alpha (non A4 component of amyloid precursor)	4q22.1	1097	1185	SYUA Alpha-synuclein	Hypomethylated			
<i>TUBA3E</i> Tubulin, alpha 3e	2q21.1	700		TBA3E Tubulin alpha-3E chain	Hypomethylated			

death. Short-term, sub-lethal hypoxia results in long-lasting changes to genome-wide DNA methylation status and some of these changes can be highly correlated with transcriptional modulation in a number of genes involved in functional pathways [170].

Inflammatory mechanisms contribute substantially to secondary tissue injury after brain ischemia. Regulatory T cells (RTC) are endogenous modulators of postischemic neuroinflammation. HDACi, using trichostatin A, increases the number of RTC, boosts their immunosuppressive capacity and interleukin (IL)-10 expression, reduces infarct volumes and behavioral deficits after cortical brain ischemia, attenuates cerebral proinflammatory cytokine expression, and increases the number of brain-invading RTC. A similar effect is obtained using tubastatin, a specific inhibitor of HDAC6 and a key HDAC in *Foxp3* regulation. The neuroprotective effect of HDACi depends on the presence of *Foxp3*⁺ RTC, and in vivo and in vitro studies show that the anti-inflammatory cytokine IL-10 was their main mediator [171].

Memory decline is a seminal symptom in dementia. Gene expression is required for long-lasting forms of memory. Epigenetic mechanisms do not only provide complexity in the protein regulatory complexes that control coordinate transcription for specific cell function, but the epigenome encodes critical information that integrates experience and cellular history for specific cell functions as well. Epigenetic mechanisms provide a unique mechanism of gene expression regulation for memory processes. Negative regulators of gene expression, such as HDACs, have powerful effects on the formation and persistence of memory. HDAC inhibition transforms a subthreshold learning event into robust long-term memory and generates a form of long-term memory that persists beyond the point at which normal long-term memory fails [172]. Whereas increments in histone acetylation have consistently been shown to favor learning and memory, a lack thereof has been causally implicated in cognitive impairments in neurodevelopmental disorders, neurodegeneration and aging. As histone acetylation and cognitive functions can be pharmacologically restored by histone deacetylase inhibitors, this epigenetic modification might constitute a molecular memory aid on the chromatin and, by extension, a new template for therapeutic interventions against cognitive decline [27].

Neurons, due to their post-mitotic state, high metabolism, and longevity are particularly prone to the accumulation of DNA lesions. DNA damage has been suggested as a major contributor to both age-associated neurodegenerative diseases and acute neurological injury. The DNA damage

response is a key factor in maintaining genome integrity. It relies on highly dynamic post-translational modifications of the chromatin and DNA repair proteins to allow signaling, access, and repair of the lesion [173]. The repair of DNA lesions, particularly oxidative DNA lesions, might be altered in AD. DNA damage is paralleled by a decrease in DNA repair activities. DNA repair proteins might be inactivated by oxidative induced post-translational modifications or degradation. Activation of DNA repair pathways might generate death signals ending with neuronal apoptosis. A link between environmentally-induced epigenetic modification, oxidation, and repair of AD-related genes has been proposed [174]. Early life exposure of rodents and primates to xenobiotics may enhance the expression of genes associated with AD, repress the expression of others, and increase the burden of oxidative DNA damage in the aged brain. Epigenetic mechanisms that control gene expression and promote the accumulation of oxidative DNA damage are mediated through alterations in the methylation or oxidation of CpG dinucleotides. Environmental influences occurring during brain development inhibit DNA-methyltransferases, thus hypomethylating promoters of genes associated with AD, such as the *APP*. This early life imprint may persist and be triggered later in life to increase the levels of APP and A β . Increased A β levels promote the production of reactive oxygen species, which damage DNA and accelerate neurodegenerative events. These early life perturbations may result in hypomethylation as well as hypermethylation of genes. The hypermethylated genes are rendered susceptible to A β -enhanced oxidative DNA damage because methylcytosines restrict repair of adjacent hydroxyguanosines [175].

Studies performed in brains and peripheral tissues of both AD patients and individuals affected by mild cognitive impairment (MCI) revealed that oxidative DNA damage is one of the earliest detectable events during the progression from healthy aging to dementia. Some authors have suggested that mutations or polymorphisms in DNA repair genes might impair DNA repair. However, this hypothesis does not seem to be confirmed by recent genetic association studies. The growth arrest and DNA damage-inducible (*Gadd*) 45 proteins have been associated with numerous cellular mechanisms including cell-cycle control, DNA damage sensation and repair, genotoxic stress, neoplasia, and molecular epigenetics. *Gadd45*-related genes have been implicated in a host of normal and aberrant CNS processes, including early and postnatal development, injury, cancer, memory, aging, psychiatric disease, and neurodegenerative disorders. The proteins act through a variety of molecular signaling cascades including the MAPK cascade, cell-cycle

control mechanisms, histone regulation, and epigenetic DNA demethylation [176].

Brain aging and AD are associated with epigenetic dysregulation at various levels [177]. Twin studies in AD support the notion that epigenetic mechanisms mediate the risk for AD. However, it is still not fully clear whether the observed epigenetic changes actually represent a cause or a consequence of the disease [23].

DNA Methylation of pathogenic genes. Many AD-related genes contain methylated CpG sites in their promoter regions, and a genome-wide decrease in DNA methylation has been reported in AD [17,166]. Methylation status of repetitive elements (i.e. *Alu*, *LINE-1* and *SAT- α*) is a major contributor of global DNA methylation patterns. The study of global DNA methylation levels for long interspersed nuclear element 1 (*LINE-1*) repetitive sequences in patients with AD and controls did not provide clear results. In one study, no differences in *LINE-1* methylation levels between patients and controls were found [178] whereas in another study *LINE-1* methylation was found increased in AD patients compared with healthy volunteers [179]. In AD, both hypomethylation and hypermethylation of specific genes have been reported [17]. DNA methylation of the *APP* promoter was found to be decreased in the brain of autopsy cases older than 70 years of age as compared with younger cases [180]. The intracellular domain of *APP* (*AICD*) has emerged as a key epigenetic regulator of gene expression controlling a diverse range of genes, including *APP* itself, the amyloid-degrading enzyme *neprilysin*, and *aquaporin-1* [181]. Abnormal processing of neuronal cell membrane APP is accompanied by elevated human serum and CSF levels of 24-hydroxycholesterol, an endogenous ligand of Liver X receptor (LXR- α). There is an epigenomic pathway that connects LXR- α activation with genes involved in the regulation of aberrant A β production leading to the generation of toxic and inflammatory mediators responsible for neuronal death. LXR- α activation by its specific endogenous or exogenous ligands results in the overexpression of the *PAR-4* gene and suppression of the *AATF* gene through its inherent capacity to regulate genes coding for SREBP and NF- κ B. Overexpression of the *PAR-4* gene is accompanied by aberrant A β production followed by ROS generation and subsequent neuronal death. A β -induced heme oxygenase-1 can ensure cholesterol-oxidation to provide endogenous ligands for the sustained activation of neuronal LXR- α -dependent epigenomic pathways leading to neuronal death in AD [182].

Presenilin1 (*PSEN1*) is modulated by DNA methylation in neuroblastoma cells and Alzheimer's mice in an experimental

model of nutritionally altered one-carbon metabolism. Studies performed on human neuronal cell cultures revealed that folate and other B-vitamins deprivation from the media resulted in epigenetic modification of the *PSEN1* gene [183].

Several pathogenic genes (*APP*, *PSI*, *APOE*, *BACE*) and many other AD-related susceptibility genes contain methylated CpG sites. The promoterregion of the *APP* gene is hypomethylated, this contributing to a potential enhancement of A β production; however, some authors have reported non-relevant changes in APP methylation, with an epigenetic drift in AD samples [184]. *BACE* and *PSI* expression is enhanced after folate deprivation-induced hypomethylation and restored when folate deficiency is supplemented with SAM. A β may induce genome-wide hypomethylation accompanied by upregulation of genes involved in neuroinflammation (*TNF*) and apoptosis (*caspase-3*), which contribute to A β production, the process thus entering into a vicious circle [17].

The *APOE* gene exhibits a bimodal structure, with a hypomethylated CpG-poor promoter and a fully methylated 3'-CpG-island, containing the sequences for the *APOE4*-haplotype. According to Wang et al. [17,184], aberrant epigenetic changes in this CpG-island may contribute to LOAD pathology. A hypermethylated CpG-island is present within the *APOE* gene. The *APOE4* sequence may change the epigenetic function of the methylated 3'-CpG islands in the *APOE4* allele by the C to T transition that is involved in a loss of a methylatable CpG unit [184]. *APOE4* carriers show a dose-dependent risk, and the relative mRNA level of *APOE4* is increased in AD compared to controls, indicating that variability in the neuronal expression of *APOE* contributes to disease risk [185].

Clusteringene (*CLU*) (apolipoproteinJ, ApoJ), together with *APOE*, influence both A β aggregation and clearance. *CLU* levels are increased in AD and may be associated with brain atrophy, disease severity, and clinical progression. The promoter region of *CLU* contains a CpG-rich methylation domain. The demethylating effect of 5-aza-2'-deoxycytidine in prostate cancer cell lines increases the expression of *CLU* [186].

Hyperphosphorylated tau is responsible for the formation of NFTs. Changes in methylation status differ among transcription factor binding sites of tau promoter. Binding sites for GCF (granulocyte chemotactic factor), responsible for repression of GC-rich promoters, were found to be hypomethylated, whereas binding sites for the

transcriptional activator *SP1* (specificity factor 1) were hypermethylated [187]. High levels of Hcy may induce tau hyperphosphorylation, NFT formation, and SP formation via inhibition of methyltransferases and hypomethylation of protein phosphatase 2A (PP2A), a dephosphorylating enzyme of phosphorylated tau [188]. In transgenic APP^{swe}/presenilin (PS) 1 (A246E) mice, *PP2A* methylation at L309 site is decreased, in parallel with increased tau phosphorylation at Tau-1 and PHF-1 sites. A β 25-35 induces demethylation and enhances tau phosphorylation [189]. Hypomethylation of *PP2A* may lead to tau hyperphosphorylation and NFT formation [17].

Sánchez-Mut et al. [190] studied 12 distinct mouse brain regions according to their CpG 5'-end gene methylation patterns, and the DNA methylomes obtained from the cerebral cortex were used to identify aberrant DNA methylation changes that occurred in two mouse models of AD. They translated these findings to patients with AD and identified DNA methylation-associated silencing of three target genes: thromboxane A2 receptor (*TBXA2R*), sorbin and SH3 domain containing 3 (*SORBS3*), and spectrin beta 4 (*SPTBN4*). These hypermethylation targets suggest that the cyclic AMP response element-binding protein (CREB) activation pathway and the axon initial segment might contribute to AD pathology.

Several components of the cell cycle (P16, P21, P27, P53, RB1, cyclinB2, alternate open reading frame (ARF) protein product) and apoptosis pathways (caspase1, 3, 7, 8, 9) are regulated by DNA methylation and appear upregulated in AD neurons. *SORBS3* (*vinexin*, *SCAM-1* or *SH3D4*), encoding a cell adhesion molecule expressed in neurons and glia, is progressively hypermethylated with age. *SI00A2*, a member of the S100 family of calcium binding proteins, which exhibits an age-dependent decrease in DNA methylation later in life, is also hypermethylated in AD [17].

Chaperones may have a crucial role in AD due to their involvement in protein quality control, folding, and degradation. Silva et al. [191] investigated the mRNA and promoter DNA methylation levels of two chaperones, *HSPA8* and *HSPA9*, in postmortem brain tissue (entorhinal and auditory cortices and hippocampus) from healthy elderly and AD subjects as well as in peripheral blood of healthy elderly and AD patients. No changes were observed in peripheral *HSPA8* and *HSPA9* expression between elderly controls and AD. A significant downregulation of *HSPA8* and *HSPA9* was observed in AD across the three brain regions compared to the controls.

Summarizing, DNA methylation changes are present in AD-related genes; some of these genes are hypermethylated (*MTHFR*, *Nephrilysin*, *MAPT*, *APOE*, *SORB3*), while others have been found to be hypomethylated (*APP*, *BACE*, *PSEN1*, *PP2A*, *SI00A2*, *CREB5*) [17,23]. DNA methylation of CpG units by DNMTs disrupts the binding of transcription factors and attracts methyl-CpG-binding domain proteins that are associated with gene silencing and chromatin compaction [192].

Histone modifications. A small bulk of recent information [17,27,193] suggests that histone modifications are present in AD: (i) histone acetylation is reduced in AD brain tissues [194] and in AD transgenic models [27]; (ii) levels of HDAC6, a tau-interacting protein and a potential modulator of tau phosphorylation and accumulation, are increased in cortical and hippocampal regions in AD [195]; mice lacking HDAC6 are cognitively normal but reducing endogenous HDAC6 levels restores learning and memory and α -tubulin acetylation [196]; (iii) SIRT1 is decreased in the parietal cortex of AD patients, and the accumulation of A β and tau in AD brains might be related to the loss of SIRT1 [197], since SIRT1 may reduce A β production activating the transcription of *ADAM10* [198]; (iv) in the brains of twins discordant for AD, trimethylation of H3K9, a marker of gene silencing, and condensation of heterochromatin structure, are increased in the temporal cortex and hippocampus of the AD twin as compared to the twin devoid of AD neuropathology [199]; (v) phosphorylation of H3S10, a key regulator in chromatin compaction during cell division, is increased in the cytoplasm of hippocampal neurons in AD cases [200]; (vi) evidence of DNA damage, as reflected by phosphorylated H2AX at Ser139, is present in hippocampal astrocytes of AD patients [201]; (vii) long-term potentiation (LTP) and memory deficits in APP/PS1 transgenic mice might be mediated in part by decreased H4 acetylation; improving histone acetylation level restores learning after synaptic dysfunction [202]; (viii) acetylation of H3 and H4 is increased in 3xTg-AD neurons relative to non-transgenic neurons [203]; (ix) nuclear translocation of EP300 interacting inhibitor of differentiation 1 (*EID1*), a *CBP/p300* inhibitory protein, is increased in the cortical neurons of AD patients, and overexpression of *EID1* is reported to reduce hippocampal LTP and to impair cognitive function by inhibiting *CBP/p300* acetyltransferase activity and disrupting neuronal structure [204]; (x) memory formation leads to a transient increase of acetylation only in residues within H2B, H3, H4 [205,206]; (xi) HDAC inhibition induces dendritic sprouting, increases synaptic number, and improves long-term memory [207]; (xii) overexpression of neuronal HDAC2 decreases dendritic spine density, synapse number, synaptic plasticity and

memory formation, whereas HDAC2 deficiency increases synapse number and memory facilitation [208,209]; (xiii) HDAC4 is involved in learning and synaptic plasticity, and selective inhibition of HDAC4 activity may deteriorate learning and memory [210]; (xiv) treatment of hippocampal neurons with HDAC inhibitors facilitates *Bdnf* expression via hyperacetylation of histones at the *Bdnf* promoters [211,212]; (xv) histone (H3K4) methylation participates in the regulation of *Bdnf* expression and memory formation [213]; (xvi) histone methylation also facilitates memory consolidation coupled with histone acetylation; inhibition of HDACs with sodium butyrate (NaB) causes an increase in H3K4 trimethylation and a decrease in H3K9 dimethylation in the hippocampus after fear conditioning [213]; (xvii) histone H3 acetylation, methylation and phosphorylation are increased in the prefrontal cortex of Tg2576 mice, and histone H4 acetylation is increased in the hippocampal CA1 neurons of these transgenic mice [214].

Age-related differences in epigenetic acetylation and methylation of histones are associated with age-related gene regulation. In studies to quantify single cell acetylation and methylation levels across the life span in cultured hippocampal/cortical neurons from the 3xTg-AD mouse model and from non-transgenic mice, Walker et al. [203] found that in non-transgenic neurons, H3 acetylation was unchanged with age, while H4 acetylation decreased with age of the donor. Compared to non-transgenic neurons, 3xTg-AD neurons had higher levels of H3 and H4 acetylation beginning at 4 months of age. In contrast to non-transgenic neurons, 3xTg-AD neurons increased acetylation with age; 3xTg-AD neurons also responded differently to inhibition of histone deacetylases at an early age. Treatment of non-transgenic neurons with the AD peptide A β also elevated levels of acetylation. The repressive function of histone H3 lysine 9 (H3K9)-methylation increased with age in non-transgenic neurons, which was amplified further in 3xTg-AD neurons. The dominant effect of higher H3K9 methylation was supported by lower *Bdnf* gene expression in non-transgenic and 3xTg-AD mice. The epigenetic states of non-transgenic and 3xTg-AD brain neurons are profoundly different and reversible, beginning at 4 months of age when the first memory deficits are reported [203].

Nucleosome remodeling is carried out by chromatin remodeling complexes (CRCs) that interact with DNA and histones to physically alter chromatin structure and ultimately regulate gene expression. Human exome sequencing and genome-wide association studies have linked mutations in CRC subunits to intellectual disability disorders, autism spectrum disorder and schizophrenia.

There appear to be both developmental- and adult-specific roles for the neuron-specific CRC nBAF (neuronal *Brg1/hBrm* Associated Factor). *nBAF* regulates gene expression required for dendritic arborization during development, and in the adult, contributes to long-term potentiation, a form of synaptic plasticity, and long-term memory. Vogel-Ciernia and Wood [215] proposed that the *nBAF* complex is a novel epigenetic mechanism for regulating transcription required for long-lasting forms of synaptic plasticity and memory processes and that impaired nBAF function may result in human cognitive disorders.

Histone deacetylase 6 (HDAC6) expression increases significantly in the hippocampus and other relevant brain regions in both patients with AD and animal models of AD. However, when and how HDAC6 expression increases during the course of AD progression remains unclear. Increased HDAC6 expression contributes to AD-associated neurodegeneration, although beneficial effects have also been identified in some pathogenic mechanisms (axonal growth and transport, synaptic plasticity, oxidative stress, apoptosis, neuroinflammation, misfolded proteins and aggregates) [216].

Sleep disruption associated with AD is driven by epigenetic changes mediated by the histone acetyltransferase (HAT) Tip60. Tip60 functionally interacts with the AD-associated amyloid precursor protein (APP) to regulate axonal growth of *Drosophila* small ventrolateral neuronal (sLNv) pacemaker cells, and their production of neuropeptide pigment dispersing factor (PDF) that stabilizes appropriate sleep-wake patterns in the fly. Loss of Tip60 HAT activity under APP neurodegenerative conditions causes decreased PDF production, retraction of the sLNv synaptic arbor required for PDF release and disruption of sleep-wake cycles in these flies. Excess Tip60 in conjunction with APP fully rescues these sleep-wake disturbances by inducing overelaboration of the sLNv synaptic terminals and increasing PDF levels, supporting a neuroprotective role for Tip60 in these processes [217].

The sirtuins are NAD⁺-dependent histone/protein deacetylases that are similar to *Saccharomyces cerevisiae* silent information regulator 2 (Sir2). Sirtuins regulate various normal and abnormal cellular and metabolic processes, including tumorigenesis, neurodegeneration, and processes associated with type 2 diabetes and obesity. Several age-related diseases, such as AD, and longevity have also been linked to the functions of sirtuins [218].

Chromatin modification is an important epigenetic mechanism underlying neuroplasticity. A chromatin-modifying complex, containing the histone demethylase PHF8 and the acetyltransferase TIP60, is a key regulator of the activity-induced expression of *Arc*, a mediator of synaptic plasticity. Mutations in PHF8 cause X-linked mental retardation while TIP60 has been associated with AD. With synaptic activity, this dual function complex is recruited to the *Arc* promoter, where it specifically counteracts the transcriptionally repressive histone mark H3K9me2 to facilitate the formation of the transcriptionally permissive H3K9acS10P, thereby favoring transcriptional activation. Gain-of-function of the PHF8-TIP60 complex in primary rat hippocampal neurons has a positive effect on early activity-induced *Arc* gene expression, whereas interfering with the function of this complex abrogates it. The majority of common interactors of PHF8 and TIP60 are involved in mRNA processing, including PSF, an important molecule involved in neuronal gene regulation. PHF8 and TIP60 interact at the single molecule level with PSF, situating this chromatin-modifying complex at the crossroads of transcriptional activation. These data reported by Oey et al. [219] indicate that an epigenetic pathway can regulate neuronal activity-dependent gene transcription.

Non-coding RNAs. Several lncRNAs are dysregulated in AD (*Sox2OT*, 1810014B01Rik, BC200, *BACE1-AS*, *NAT-Rad18*, 17A, *GDNFOS*), Parkinson's disease (*naPINK1*, *Sox2OT*, 1810014B01Rik, BC200), and Huntington's disease (*HAR1F*, *HTTAS*, *DGCR5*, *NEAT1*, *TUG1*) [33]. miRNAs belong to the class of non-coding regulatory RNA molecules of ~22 nt length and are now recognized to regulate ~60% of all known genes through post-transcriptional gene silencing (RNA interference) (RNAi). Alterations in epigenetically regulated miRNAs may contribute to the abnormal expression of pathogenic genes in AD [33,74]. Examples of miRNAs directly linked to AD pathogenesis include miR-34a (1p36.22), miR-34b/c (11q23.1), miR-107 (10q23.31), miR-124 (8p23.1/8p12.3/20q13.33), miR-125b (11q24.1/21q21.1), and miR-137 (1p21.3); and examples of epigenetically regulated miRNAs with targets linked to AD pathogenesis are let-7b (22q13.1), miR-9 (1q22/5q14.3/15q26.1), miR-132/212 (17p13.3), miR-146a (5q34), miR-148a (7p15.2), miR-184 (15q25.1), and miR-200 (miR-200b/200a/429, 1p36.33; miR-200c/141, 12p13.31) [74].

miRNAs can be used as biomarkers to discriminate different disease forms, staging and progression, as well as prognosis [220]. A unique circulating 7-miRNA signature (*hsa-let-7d-5p*, *hsa-let-7g-5p*, *hsa-miR-15b-5p*, *hsa-miR-142-3p*,

hsa-miR-191-5p, *hsa-miR-301a-3p* and *hsa-miR-545-3p*) reported by Kumar et al. [220] in plasma, could distinguish AD patients from normal controls with >95% accuracy. Leidinger et al. [221] showed a novel miRNA-based signature for detecting AD from blood samples. Using this 12-miRNA signature, they differentiated between AD and controls with an accuracy of 93%, a specificity of 95% and a sensitivity of 92%. The differentiation of AD from other neurological diseases (MCI, multiple sclerosis, Parkinson's disease, major depression, bipolar disorder and schizophrenia) was possible with accuracies between 74% and 78%. Alexandrov et al. [222] found increased levels of miRNA-9, miRNA-125b, miRNA-146a, and miRNA-155 in the CSF and brain tissue-derived extracellular fluid from patients with AD, suggesting that these miRNAs might be involved in the modulation or proliferation of miRNA-triggered pathogenic signaling in AD brains.

AD-related SNPs interfere with miRNA gene regulation and affect AD susceptibility. The significant interactions include target SNPs present in seven genes related to AD prognosis with the miRNAs- miR-214, -23a & -23b, -486-3p, -30e*, -143, -128, -27a & -27b, -324-5p and -422a. The dysregulated miRNA network contributes to the aberrant gene expression in AD [223-225].

Several miRNAs have been identified invitro to directly regulate the *APP* mRNA, including miRNA let-7, the miR-20a family (miRs-20a, -17 and -106b), miRs-106a and 520c, miR-101, miR-16, and miRs-147, -153, -323-3p, -644 and -655 [17]. Inhibition of miR-101 overexpression reduces APP and A β load in hippocampal neurons [226]. MiR-16 targets APP to potentially modulate AD pathogenesis, and miR-16 overexpression may lead to reduced APP expression [227]. Both miR-124 and polypyrimidine tract binding protein1 (PTBP1) may alter splicing of *APP* exons 7 and 8 in neuronal cells [228]. miR-124 also regulates the expression of *BACE1* [229]. mRNA expression of *BACE1* is mediated by both miRNAs (miRs-9, -29a/b-1, -29c, -107, -298, -328 and -485-5p) and longncRNAs (*BACE1*-antisense) (*BACE1-AS*), and is repressed by miRs-29a, -29b-1 and -9 in vitro. In transgenic HEK293-APP cells, transient miR-29a/b-lower expression decreases BACE1 levels and A β production [230]. miR-29 overexpression lowers BACE1 protein levels [231]. miRNAs repress *BACE1* through direct binding to sequences in its 3' untranslated region (3'UTR), whereas miR-485-5 prepresses *BACE1* via binding to its open reading frame in exon 6. miR-107 is downregulated at intermediate stages (Braak stage3) of AD pathogenesis and might accelerate AD progression through control of *BACE1* [232]. miR-298, miR-328 and miR-195 inversely correlate with BACE1 protein, and downregulate A β levels

by inhibiting the translation of *BACE1* [233,234]. miR-125 decreases whereas *BACE1* increases in animal models [234]. Overexpression of miR-485-5p reduces *BACE1* protein levels by 30% while knockdown of miR-485-5p increases *BACE1* protein levels [235]. *BACE1-AS*, a ~2kb conserved ncRNA transcribed from the opposite strand to *BACE1* and co-expressed with *BACE1*, is up-regulated in AD, potentially promoting A β generation and AD pathogenesis. *BACE1-AS* may enhance *BACE1* mRNA stability by “masking” the binding site for miR-485-5p and preventing miRNA-induced translational repression of *BACE1* mRNA [235,236].

The RNA polymerase III-dependent ncRNA, NDM29, promotes APP amyloidogenesis and A β secretion [237]. miR-107 levels are reduced in AD temporal cortex [238,239]. Loss of miRs-9,29a/b-1, -137 and -181c (currently down-regulated in AD frontal cortex) increases A β production and serine palmitoyltransferase (SPT), the first rate-limiting enzyme in ceramide biosynthesis [240]. miRNA-106b (down-regulated in anterior temporal cortex) can influence A β metabolism either through direct regulation of APP itself, or via modulating APP trafficking, A β clearance and β -and- γ -secretase activity through regulation of the ATP-binding cassette transporter A1 (ABCA1), which is elevated in the hippocampus, correlating with cognitive decline [241]. The brain-expressed ncRNA, 17A, is up-regulated in the AD cortex, promoting A β in response to neuroinflammation injury [242].

Several miRNAs also regulate tau metabolism. The miR-132/PTBP2 pathway influences *MAPT* exon 10 splicing in brain and may contribute to AD pathogenesis. miR-132 was found to be down-regulated in some tauopathies, such as progressive supranuclear palsy (PSP), a major 4R-tauopathy, where the protein levels of the neuronal splicing factor PTBP2 were elevated [243]. miR-124, -9, -132 and -137 might regulate the 4R/3R ratio in neuronal cells [243]. Both miR-9 and miR-124 are down-regulated in AD and might affect tau. The miR-15/ERK1 pathway mediates tau phosphorylation. miR-15a is down-regulated in AD brains [244]. The miR-15 family (miR-15a, -16, -195 and -497) targets extracellular signal-regulated kinase 1 (ERK1) expression; and decreased miR-15 levels might participate in neuronal tau hyperphosphorylation. miR-26a represses mRNA of the tau kinase GSK-3 β involved in A β production and NFT formation [245,246]. miR-26a expression is also altered in AD [247]. In conditional Dicer knockout mice, with reduced brain miRNA production, tau hyperphosphorylation and altered *MAPT* splicing is observed; and reduced miRNA processing in dicer-1 knockout flies enhances tau-induced neurodegeneration [248].

SIRT1 deacetylates tau and SIRT1 deficiency increases tau acetylation and the accumulation of hyperphosphorylated tau [197,249]. miR-9, -34c and -181c repress *SIRT1* mRNA [250,251]. miR-128 modulates the expression of BAG2, the cochaperone involved in tau degradation and aggregation [252]. miR-212 is down-regulated in AD, and appears to be involved in NFT density [238,239]. miR-146a is an inflammation effector associated with immune and inflammation signalling by targeting IRAK1. miR-146a upregulation in AD brain might contribute to neuroinflammation [253,254]. miR-146a interacts with the 3'UTR of Complement factor H (CFH), a repressor of the inflammatory response, which is down-regulated in AD [255]. miRNA-146a is an inducible, 22-nucleotide, small RNA over-expressed in AD brain. Up-regulated miRNA-146a targets several inflammation-related and membrane-associated messenger RNAs (mRNAs), including those encoding complement factor-H (CFH) and the interleukin-1 receptor associated kinase-1 (IRAK-1), resulting in significant decreases in their expression. The most significant miRNA-146a-CFH changes are found in HMG cells, the ‘resident scavenging macrophages’ of the brain [256]. miR-101 interacts with cyclooxygenase-2 (COX-2), and downregulation of miR-101 might induce COX-2 upregulation in AD, enhancing the inflammatory response [226]. miR-124, -125b, -132, -134, -138 and -219 influence synaptic plasticity. miR-132 is down-regulated and miR-125bis up-regulated in different AD brain regions, probably affecting miniature excitatory postsynaptic currents (mEPSCs) [257].

The *INK4b-ARF-INK4a* locus encodes for two cyclin-dependent kinase inhibitors, p15 (INK4b) and p16 (INK4a) and a regulator of the p53 pathway, ARF. ANRIL, a non-coding RNA, is also transcribed from the locus. ARF, p15 (INK4b), and p16 (INK4a) are well-established tumor suppressors whose function is frequently disabled in human cancers. SNPs mapping in the vicinity of *ANRIL* are linked to a wide spectrum of conditions, including cardiovascular disease, ischemic stroke, type 2 diabetes, frailty and AD. The *INK4b-ARF-INK4a* locus is regulated by Polycomb repressive complexes (PRCs), and its expression can be invoked by activating signals. Other epigenetic modifiers, such as the histone demethylases JMJD3 and JHDM1B, the SWI/SNF chromatin remodeling complex, and DNMTs regulate the locus interplaying with PRCs [258].

Proteomics. There is a great interest in developing specific, sensitive, and practical tools to differentially diagnose and discriminate the different types of dementia. The currently available cerebrospinal fluid (CSF) biomarkers for AD (A β , total Tau (t-Tau), phosphorylated Tau (p-Tau)) have a

high sensitivity and specificity for AD, but there is still no test to effectively predict the development of AD in a pre-symptomatic stage [259,260]. Therefore, AD biomarkers are urgently needed for both early and accurate diagnosis and prediction of disease progression. Among peripheral candidate proteins, most AD-related proteins reported in the literature are not specific and were found to be affected by other brain disorders [261]. A β is the main constituent of senile plaques in AD. Measurement of A β 1-42 in CSF is a valuable marker in AD research, where low levels indicate AD [259]. For the past 5 years some new biomarkers have been postulated as potential diagnostic and/or prognostic candidates for AD. A novel serum proteomic approach to interrogate the low-molecular weight proteome for serum AD found 59 novel potential AD biomarkers, 4 of which showed diagnostic replicability [262]. Panel-based proteomics on plasma samples from Twins-UK subjects revealed that genetic factors explain ~26% of the variability in blood protein levels on average. The plasma level of the mitogen-activated protein kinase (MAPK) MAPKAPK5 protein was found to positively associate with the 10-year change, and the plasma level of protein MAP2K4 was found to suggestively associate negatively with the volume of the left entorhinal cortex [263]. Multiple markers were identified to be differentially expressed in the CSF of AD patients as compared with control subjects. Two of these novel markers are neuronal secretory protein VGF and neuronal pentraxin receptor-1 (NPTXR), which are decreased in AD (at baseline, 21% and 17%, respectively), with a decreased rate/year of 10.9% and 6.9%, respectively [264].

Failures in the ubiquitin-proteasome system (UPS) during aging may contribute to cellular stress and AD pathogenesis. Protein ubiquitination is one of the key modulators of AD. Mutations in ubiquitin B mRNA that result in UBB⁺¹ dose-dependently cause an impaired UPS, subsequent accumulation of UBB⁺¹ and depositions of aberrant proteins in plaques and tangles. Nuclei with substantial accumulations of tangle-bearing neurons, such as the nucleus basalis of Meynert and raphe nuclei also present high densities of UBB⁺¹-positive tangles. Areas outside the forebrain are also affected in AD [265].

A β interacts with a variety of A β -associated proteins (AAPs), some of which can form complexes with A β and influence its clearance, aggregation or toxicity. The secreted Wnt pathway protein Dickkopf-related protein 3 (Dkk-3) is a potential A β -associated protein. Dkk-3 co-localizes with A β in the brain, is expressed in neurons and in blood vessel walls, is secreted by leptomeningeal smooth muscle cells in vitro, and is abundantly present in both cerebrospinal fluid and serum, but its levels are similar in non-demented

controls and patients with AD, Lewy body dementia, and frontotemporal dementia [266].

Patients with mild cognitive impairment (MCI) who are converted into AD cases have an abnormal CSF glycosylation profile. CSF glycosylation changes may occur before the onset of the disease. Glycosyltransferase GnT-III might be involved in AD inducing specific sugar modifications in the BACE-1 glycoprotein [267].

Using cell-type specific proteomics of microdissected temporal cortex neurons from patients with AD, 400 proteins have been identified, of which 78% were neuronal and 50% were associated with AD [268]. Changes in phosphorylation levels were found in 19 proteins involved in energy metabolism, neuronal plasticity, signal transduction, and oxidative stress response in the parietal cortex of AD patients at different stages of the disease [269]. Histone post-translational modifications (PTMs) have been found in the frontal cortex of AD patients. Decreases in methylation of H2B residue K108 (25 %) and H4 residue R55 (35 %) were detected. A 91 % increase in ubiquitination of K120 on H2B was observed as well as an apparent loss in acetylation of the region near the N-terminus of H4. This study, reported by Anderson and Turko [270] is the first to demonstrate changes in methylation of H2B K108, methylation of H4 R55, and ubiquitination of H2B K120 in frontal cortex from human donors with AD.

Transgenic A β PPswe/PS1dE9 mice express a chimeric mouse/human amyloid- β protein precursor (Mo/HuA β PP695swe) and mutant human presenilin 1 (PS1-dE9) associated with early-onset AD. 15 proteins are significantly different between the A β PPswe/PS1dE9 mice and age-matched controls. The expression levels of the following proteins in A β PPswe/PS1dE9 mice were found to be at least 1.5 times higher than those in normal mice: DCC-interacting protein 13-beta, serum albumin, creatine kinase B-type, heat shock 70 kDa protein 1A, T-complex protein 1 subunit beta, adenylate kinase isoenzyme 1, pyruvate dehydrogenase E1 component subunit beta mitochondrial, and V-type proton ATPase catalytic subunit A. The expression levels of other proteins (dihydropyrimidinase-related protein 2, actin cytoplasmic 2, isoform 1 of V-type proton ATPase catalytic subunit, tubulin alpha-1C chain, F-actin-capping protein subunit alpha-2, ubiquitin carboxyl-terminal hydrolase isozyme L1, and actin cytoplasmic 1) were lower in the transgenic model. These proteins are involved in regulating various cellular functions, including cytoskeletal structure, energy metabolism, synaptic components, and protein degradation [271]. Using a redox-proteomic approach, twelve proteins were found to be significantly altered in

the levels of protein carbonyls in the hippocampus. These proteins are crucial in energy metabolism, protein folding, cell structure, signal transduction and excitotoxicity. Increased expression level of carbonyl reductase 1 (CBR1) and protein carbonyls have been observed in the hippocampi of 3 × Tg-AD mice before the appearance of A β plaques and neurofibrillary tangles (NFTs). By redox proteomics, twelve specifically carbonylated proteins were identified. Among them, alpha-enolase (ENO1) and glutamine synthetase (GS) were identified as the common targets of oxidation in the brains of 3 × Tg-AD mice, mild cognitive impairment (MCI) sufferers and AD patients. The oxidation of t-complex protein 1 subunit epsilon (CCT5) and protein disulfide-isomerase A3 (PDIA3) were reported to be associated with AD [272]. In a study of the human brain-insoluble proteome in AD by mass spectrometry, 4,216 proteins have been identified, among which 36 proteins accumulate in the disease, including U1-70K and other U1 small nuclear ribonucleoprotein (U1 snRNP) spliceosome components. Similar accumulations in mild cognitive impairment cases indicate that spliceosome changes occur in early stages of AD. Multiple U1 snRNP subunits form cytoplasmic tangle-like structures in AD but not in other examined neurodegenerative disorders, including PD and frontotemporal lobar degeneration. Comparison of RNA from AD and control brains reveals dysregulated RNA processing with accumulation of unspliced RNA species in AD, including myc box-dependent-interacting protein 1, clusterin, and presenilin-1. U1-70K knockdown or antisense oligonucleotide inhibition of U1 snRNP increases the protein level of amyloid precursor protein, indicating unique U1 snRNP pathology and implication of abnormal RNA splicing in AD pathogenesis [273]. Brain tissue from diabetic patients with cerebrovascular dementia or AD contains significant deposits of oligomerized amylin. Amylin is a pancreatic hormone that has amyloidogenic and cytotoxic properties similar to the A β peptide. Amylin is overexpressed in patients with pre-diabetic insulin resistance or obesity leading to amylin oligomerization and deposition in pancreatic islets. Amylin oligomerization was implicated in the apoptosis of the insulin-producing β -cells, and may contribute to cognitive dysfunction [274].

The tau protein is central to the etiology of several tauopathies (AD, frontotemporal dementia, progressive supranuclear palsy, post-traumatic dementia). Tau protein associates with the ribonucleoproteome, including major protein complexes involved in RNA processing and translation, and binds to several heat shock proteins, the proteasome- and microtubule-associate proteins. Expression of P301L mutant tau disrupts interactions of the C-terminal half of tau with heat shock proteins and the proteasome. Higher propensity

of P301L mutant tau to aggregate may reflect a perturbation of its chaperone-assisted stabilization and proteasome-dependent degradation [275]. MAP2c prevents arachidonic acid-induced in vitro aggregation of tau. MAP2c possesses chaperone-like activity while tau does not. Phosphorylation impairs the chaperone activity of MAP2c, implying a crucial role of chaperone in preventing tau fibrillation. MAP2c/MAP2 might be one of the regulators maintaining tau homeostasis in the cell [276]. A major step forward in understanding the role of Tau truncation would be to identify the precise cleavage sites of the several truncated Tau fragments that are present in AD brains, especially those truncated at the N-terminus. The Gln124-Tau fragment displays a stronger ability to bind and stabilize microtubules, suggesting that the Tau N-terminal domain could play a direct role in the regulation of microtubule stabilization [277].

Protein expression profiles of patients with vascular dementia (VaD) distinguished, from a total of 144 differentially expressed proteins, upregulated proteins enriched in 2 subpathways of 1 pathway, and downregulated proteins enriched in 162 subpathways of 36 pathways [278].

At present, over 1,000 different proteins have been identified in proteomic analysis of AD cases; however, interpretation of results is difficult, and a direct connection between specific proteomic profiles and AD pathogenesis is still undefined.

Parkinson's disease

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder in which genomic, environmental, cerebrovascular, and epigenetic factors are involved [279]. PD is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and presence of α -synuclein-containing protein aggregates. Over 100 genes might be involved in PD genomics of which at least 15 PD loci (*PARK1-15*) and other loci (*α -synuclein*, *leucine-rich repeat kinase 2*, *parkin*, *PTEN-induced putative kinase 1*, *DJ-1*, *ATP13A2*) might be causative [280]. Genetic etiology of PD associated with mutations in the *SNCA*, *PARK2*, *PINK1*, *PARK7* and *LRRK2* genes, whereas other loci (e.g. *LRRK2*, *MAPT*, *SCA1*, *SCA2*, *spatacsin*, *POLG1*, *GBA*) might be susceptibility genes associated with sporadic PD without family history [160,281]. Some studies suggest that common and rare genetic variation in the *PARK10* locus do not influence the risk or age at onset of clinical PD [282].

Retromer is a protein assembly that plays a central role in orchestrating export of transmembrane-spanning cargo proteins from endosomes into retrieval pathways destined

for the Golgi apparatus and the plasma membrane. A specific mutation in the retromer component VPS35, VPS35 (D620N) might link retromer dysfunction to familial autosomal dominant and sporadic PD. In cells expressing VPS35 (D620N) there is a perturbation in endosome-to-TGN transport but not endosome-to-plasma membrane recycling. The major defect of the D620N mutation lies in the association to the actin-nucleating Wiskott-Aldrich syndrome and SCAR homolog (WASH) complex, and the primary defect of the VPS35 (D620N) mutant is a decrease in affinity for the WASH complex component FAM21 [283].

Parkin is an E3-protein ubiquitin ligase, which plays an important role as a scavenger in cell metabolism. *PARK3* mutations are associated with PD. The proteomic analysis of the mutant form of the Parkin protein (Q311R and A371T), isolated from a PD patient, exhibited anomalies at the proteome level probably due to the differences in processing [284].

Genome-wide association studies have demonstrated association between SNCA variability and susceptibility to PD. Risk variants affect methylation of a putative promoter in SNCA intron 1. PD patients show significant hypomethylation as compared with controls in blood samples, and *rs3756063* is associated with SNCA methylation level in both blood and brain [285]. Methylation of the α -synuclein (*SNCA*) gene may be involved in PD pathogenesis due to altered gene expression, protein structural changes and overexpression, and protein aggregation [286]. Methylation of SNCA intron 1 is associated with decreased SNCA transcription. SNCA hypomethylation is observed in the *substantia nigra* of sporadic cases, accompanied by an increased SNCA expression [287]. Increased α -synuclein production might be the result of increased SNCA expression due to hypomethylation of the SNCA gene [286]. Furthermore, α -synuclein sequesters DNMT1, leading to DNA hypomethylation in PD and dementia with Lewy bodies [288], and overexpression of DNMT1 restores nuclear DNMT1 [286].

Maslah et al. [289] identified 10 genes among the top 1000 members of the aging-related methylation module which were associated with PD (*SLC12A5*, *ABCA3*, *FHIT*, *FAT1*, *CPLX2*, *APBA1*, *MAGI2*, *CNTNAP2*, *ATP8A2*, *SMOC2*). *MRII* and *TMEM9* were candidate genes with increased methylation, and the *GSST1*, *TUBA3E* and *KCNH1* genes showed decreased methylation. Methylation of the *HLA-DRB1*, *LRRK1*, *MMEL1*, *HLA-DQB1*, *OR12D3* and *VAV2* genes exhibited confusing results. A methylation-based EWAS in PD patients identified 20 unique genes with a sizable difference in methylation between PD and controls, while 17 were identified between PD with anxiety and

PD without anxiety. *FANCC* *cg14115740* and *TNKS2* *cg11963436* showed significant differential methylation between PD cases and controls [290].

In experimental models (1-methyl-4-phenylpyridinium (MPP⁺), paraquat, rotenone), inducing overexpression of human α -synuclein, α -synuclein translocates into the nucleus interacting with histones and inhibiting histone acetylation, and nuclear-targeted α -synuclein binds to histones and reduces histone 3 acetylation through its association with HDAC1 and SIRT2 [28,291-292].

Oxidative stress is a potential pathogenic mechanism in sporadic PD. c-Abl plays an important role in oxidative stress-induced neuronal cell death. C-Abl, a nonreceptor tyrosine kinase, is activated in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP)-induced acute PD model. Conditional knockout of c-Abl in neurons or treatment of mice with STI571, a c-Abl family kinase inhibitor, reduced the loss of dopaminergic neurons and ameliorated the locomotive defects induced by short-term MPTP treatment. p38 α is a major substrate of c-Abl and c-Abl-mediated phosphorylation is critical for the dimerization of p38 α . p38 α inhibition mitigates the MPTP-induced loss of dopaminergic neurons [293]. The oxidative stress-sensitive protein kinase C δ (PKC δ) has been implicated in dopaminergic neuronal cell death. The PKC δ gene can be regulated by histone acetylation. Treatment with histone deacetylase (HDAC) inhibitor sodium butyrate (NaBu) induces PKC δ expression in cultured neurons, brain slices, and animal models. Hyperacetylation of histone H4 by NaBu is associated with the PKC δ promoter. Deletion analysis of the PKC δ promoter mapped the NaBu-responsive element to an 81-bp minimal promoter region. Four GC boxes conferred hyperacetylation-induced PKC δ promoter activation. Sp1, Sp3, and Sp4 regulate NaBu-induced PKC δ up-regulation. NaBu does not alter the DNA binding activities of Sp proteins or their expression. Overexpression of the p300/cAMP-response element-binding protein-binding protein (CBP) potentiates the NaBu-mediated transactivation potential of Sp1/Sp3, but expressing several HDACs attenuated this effect, suggesting that p300/CBP and HDACs act as coactivators or corepressors in histone acetylation-induced PKC δ up-regulation. NaBu up-regulation of PKC δ sensitizes neurons to cell death in a human dopaminergic cell model and brain slice cultures. Histone acetylation regulates PKC δ expression to augment nigrostriatal dopaminergic cell death, which could contribute to the progressive pathogenesis of PD [294].

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene, but not in its closest paralog *LRRK1*, have been linked to autosomal dominant PD. Epidermal growth factor receptor

(EGF-R) is a *LRRK1*-specific interactor, while 14-3-3 proteins are *LRRK2*-specific. *LRRK1* and *LRRK2* can carry out distinct functions by interacting with different cellular proteins [295]. The most prevalent mutation, G2019S, results in enhanced *LRRK2* kinase activity that potentially contributes to the etiology of PD. Disease progression might be mediated by poorly characterized phosphorylation-dependent *LRRK2* substrate pathways. 776 phosphorylation sites were found to be increased or decreased by at least 50% in response to *LRRK2* kinase inhibition (*LRRK2-IN-1*) treatment, including sites on proteins previously known to associate with *LRRK2*. *LRRK2-IN-1* inhibited lipopolysaccharide-induced tumor necrosis factor alpha (TNF α) and C-X-C motif chemokine 10 (CXCL10) levels in astrocytes and also enhanced multiple neurite characteristics in primary neuronal cultures. *LRRK2-IN-1* had almost identical effects in primary glial and neuronal cultures from *LRRK2* knockout mice. *LRRK2-IN-1* may inhibit pathways of perceived *LRRK2* pathophysiological function independently of *LRRK2* [296].

Classical activation (M1 phenotype) and alternative activation (M2 phenotype) are the two polars of microglial activation states that can produce either detrimental or beneficial effects in the CNS. Histone H3K27me3 demethylase Jumonji domain containing 3 (*Jmjd3*) is essential for M2 microglia polarization. Suppression of *Jmjd3* in N9 microglia inhibits M2 polarization and simultaneously magnifies M1 microglial inflammatory responses, which leads to extensive neuron death in vitro. The suppression of *Jmjd3* in the substantia nigra (SN) causes microglial overactivation and exacerbates dopamine (DA) neuron death in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-intoxicated mouse model of PD. *Jmjd3* levels are lower in the midbrain of aged mice, where H3K27me3 levels are increased, as well as the M1/M2 ratio, suggesting that aging is a contributing factor in switching the microglia phenotypes. In the PD context, *Jmjd3* is able to enhance the polarization of M2 microglia by modifying histone H3K27me3, switching the microglia phenotypes that might influence neuroimmune dysfunction in PD [297].

LncRNAs are also important players in the pathoepigenetics of PD [33]. Nuclear factor E2-related factor 2 (Nrf2) is a key transcription factor that regulates the expression of antioxidant and detoxifying genes that provide cellular protection against various stressors, including reactive oxygen species (ROS). Nrf2 activity is tightly regulated by a cytoplasmic inhibitory protein Kelch-like ECH-associated protein 1 (Keap1). microRNA-7 (miR-7), which is highly expressed in the brain, represses Keap1 expression by targeting the 3'-untranslated region (UTR) of its mRNA in human neuroblastoma cells,

SH-SY5Y. Targeted repression of Keap1 and activation of Nrf2 pathway underlies the cytoprotective effects of miR-7 against 1-methyl-4-phenylpyridinium (MPP $^{+}$)-induced toxicity in SH-SY5Y and differentiated human neural progenitor cells, ReNcell VM [298].

Some neuronal processes involve the mechanistic/mammalian target of rapamycin complex 1 (mTORC1). Activation of mTORC1 promotes translation. Curtailing the activity of mTORC1 bidirectionally alters the expression of proteins associated with epilepsy, AD, ASD, and PD. The protein expression of PARK7 is sensitive to mTORC1 inhibition. In a mouse model of tuberous sclerosis complex (TSC), with overactive mTORC1 signaling, PARK7 protein is elevated in the dendrites and colocalizes with the postsynaptic marker PSD-95 [299]. Quantitative proteomics of protein expression profiles in the nigral tissue of PD patients and control subjects revealed the presence of 11 differentially expressed proteins, including alphaB-crystallin (*Cryab*). *Cryab* was markedly upregulated in the SN of PD brain. *Cryab* expression was also upregulated in reactive astrocytes and microglia in a neurotoxin-induced mouse PD model. Increased expression of *Cryab* was also present in cytoplasmic inclusions in a subset of glial cells in Parkinsonian brains, suggesting that *Cryab* may be involved in the glial pathology during dopaminergic neuron degeneration in PD [300].

Oxidative stress and mitochondrial dysfunction may be involved in the pathogenesis of PD. Protein alterations in PD brain are dominated by mitochondrial and lipid transport defects, and are largely independent of transcriptional changes [301]. Mutations in the mitochondrial Ser/Thr kinase PTEN-induced kinase 1 (*PINK1*) are associated with an autosomal recessive familial form of early-onset PD. *PINK1* plays important neuroprotective roles against mitochondrial dysfunction by phosphorylating and recruiting Parkin, a cytosolic E3 ubiquitin ligase, to facilitate elimination of damaged mitochondria via autophagy-lysosomal pathways. Loss of *PINK1* in cells and animals leads to various mitochondrial impairments and oxidative stress, culminating in dopaminergic neuronal death in humans. Changes in the brain proteome and phosphoproteome of mice lacking *PINK1* suggest that defects in signaling networks, energy metabolism, cellular proteostasis, and neuronal structure and plasticity are involved in the pathogenesis of familial PD. Changes in the proteome and phosphoproteome of the *PINK1* knockout mouse brain revealed alterations in key proteins associated with increased oxidative stress, aberrant cellular signaling, altered neuronal structure, decreased synaptic plasticity, reduced neurotransmission, diminished proteostasis networks, and altered metabolism, including 14-3-3 ϵ (14-3-3 protein epsilon), 3-PGDH (phosphoglycerate

dehydrogenase), ALDOA (aldolase A), APT1 (acyl-protein thioesterase 1), CaM (calmodulin), CBR3 (carbonyl reductase [NADPH]3), ENO2 (gamma-enolase), HPRT (hypoxanthine-guanine phosphoribosyltransferase), HSP70 (heat-shock-related 70 kDa protein 2), IDHc (cytoplasmic isocitrate dehydrogenase [NADP+]), MAPK1 (mitogen-activated protein kinase 1), MEK1 (MAP kinase kinase 1), MDHc (cytoplasmic malate dehydrogenase), NFM (neurofilament medium polypeptide), NSF (N-ethylmaleimide-sensitive fusion protein), PHB (prohibitin), PINK1 (PTEN-induced putative kinase 1), PPIaseA (peptidyl-prolyl cis-trans isomerase A), PSA2 (proteasome subunit alpha type-2), TK (transketolase), and VDAC-2 (voltage-dependent anion-selective channel protein 2) [302]. The proteomic analysis of the PINK1 kinase-PARKIN UB ligase mitochondrial control pathway disrupted in PD suggests that PINK1 plays a dual role by phosphorylating PARKIN on its UB-like domain and poly-UB chains on mitochondria. PARKIN activation by PINK1 produces canonical and noncanonical UB chains on mitochondria, and PARKIN-dependent chain assembly is required for accumulation of poly-phospho-UB (poly-p-UB) on mitochondria [303]. Mitochondrial complex I impairment in PD is modeled in vitro by the susceptibility of dopaminergic neurons to the complex I inhibitor 1-methyl-4-phenylpyridinium (MPP⁺). MicroRNA-7 (miR-7), which is expressed in tyrosine hydroxylase-positive nigral neurons in mice and humans, protects cells from MPP⁺-induced toxicity in dopaminergic SH-SY5Y cells, differentiated human neural progenitor ReN cell VM cells, and primary mouse neurons. RelA, a component of nuclear factor- κ B (NF- κ B), was identified to be downregulated by miR-7 using quantitative proteomic analysis. RelA mRNA is a target of miR-7 and is required for cell death following MPP⁺ exposure. RelA mediates MPP⁺-induced suppression of NF- κ B activity, which is essential for MPP⁺-induced cell death. The protective effect of miR-7 is exerted through relieving NF- κ B suppression by reducing RelA expression [304]. Mitochondrial transcription factor A (TFAM) regulates mitochondrial biogenesis, which is downregulated by extracellular signal-regulated protein kinases (ERK1/2) in cells treated chronically with the complex I inhibitor MPP⁺. Mutation of TFAM at serine 177 to mimic phosphorylation recapitulated the effects of MPP⁺ in decreasing the binding of TFAM to the light strand promoter, suppressing mitochondrial transcription. Mutant TFAM was unable to affect respiratory function or rescue the effects of MPP⁺ on respiratory complexes [305]. Mitochondrial protein profiles during dopaminergic neuronal cell death (MN9D) induced by 6-hydroxydopamine (6-OHDA) revealed several protein candidates among which TNF receptor-associated protein 1 (TRAP1), a mitochondrial molecular chaperone,

was released from the mitochondria into the cytosol in MN9D cells [306].

The proteomic analysis of chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced non-human primate animal model of Parkinsonism allowed the identification of 86 glycoproteins, 163 non-glycoproteins, and 71 phosphoproteins differentially expressed in the MPTP-treated monkeys [307]. Microarray and proteomic data have revealed abnormal expression of several genes and proteins responsible for PD. Unreported 37 PD markers were identified based on their topological significance in the networks. Of these 37 markers, 8 were significantly involved in the core functional modules and showed significant change in co-expression levels, and 4 (ARRB2, STX1A, TFRC and MARCKS) were found to be associated with several neurotransmitters, including dopamine [308].

Several candidate biomarkers in biological fluids are being pursued as blood-based biomarkers in PD (α -synuclein, DJ-1, uric acid, epidermal growth factor, apolipoprotein-A1, and peripheral inflammatory markers) [309]. Proteomic profiling followed by high-throughput targeted mass spectrometry (MS), in order to identify peptides in human cerebrospinal fluid (CSF) for PD diagnosis and disease severity correlation, characterized 14,000 unique peptides displaying differences between PD and healthy controls. Specifically, 5 peptides derived from SPP1, LRP1, CSF1R, EPHA4, and TIMP1 were identified with a sensitivity of 76.7% and a specificity of 80.0% for PD. A combination of two peptides belonging to proteins TIMP1 and APLP1 significantly correlated with disease severity [310]. Using a high-throughput shotgun proteomic strategy, 1795 nigral proteins were identified. Of them, 204 proteins displayed significant expression level changes in PD patients versus controls. These were involved in novel or known pathogenic processes including mitochondrial dysfunction, oxidative stress, or cytoskeleton impairment. The differential expression of ferritin-L and seipin was confirmed, and the neuronal localization of gamma glutamyl hydrolase and nebulin was demonstrated, suggesting a role for nebulin overexpression in PD neurodegeneration [311].

TRINUCLEOTIDE REPEAT DISORDERS

Polyglutamine disorders (**Table 4**) are caused by expansion of CAG trinucleotide repeats encoding polyglutamine tracts in specific genes [312]. The family of polyglutamine diseases includes spinal and bulbar muscular atrophy (SBMA), Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), and spinocerebellar ataxia (SCA) type 1,

2, 3, 6, 7, and 17. These disorders are caused by glutamine expansions in androgen receptor (AR), huntingtin, atrophin-1, ataxin-1, ataxin-2, ataxin-3, CACNA1A, ataxin-7, and the TATA-box binding protein (TBP), respectively [312,313]. Polyglutamine expansion in the androgen receptor (AR) is responsible for spinobulbar muscular atrophy (SBMA) that leads to selective loss of lower motor neurons. Protein arginine methyltransferase 6 (PRMT6) is a specific co-activator of normal and mutant AR and the interaction of PRMT6 with AR is significantly enhanced in the AR mutant. AR and PRMT6 interaction occurs through the PRMT6 steroid receptor interaction motif, LXXLL, and the AR activating function 2 surface. AR transactivation requires PRMT6 catalytic activity and involves methylation of arginine residues at Akt consensus site motifs, which is mutually exclusive with serine phosphorylation by Akt. The enhanced interaction of PRMT6 and mutant AR leads to neurodegeneration in cell and fly models of SBMA, indicating a direct role of arginine methylation in polyglutamine disease pathogenesis [313].

A prototypal example of neurodegeneration, in which genomic and epigenomic alterations coexist, is Huntington’s chorea-related striatal degeneration, characterized by: (i) mutations (CAG expansions) in the huntingtin (*HTT*) gene; (ii) mutant HTT-related excitotoxicity, mitochondrial dysfunction, axonal transport deficit, altered proteasome activity, and gene dysregulation; (iii) dysregulation of multiple genes;(iv)interference of nuclear localization of expanded HTT with transcription factors, co-activators, and proteins of the transcriptional machinery; (v) alteration of cytoplasmic retention of the transcriptional repressor REST, which is normally associated with wild-type HTT; (vi) alteration of transcription of multiple genes involved in neuronal survival, plasticity, signaling, and mitochondrial biogenesis and respiration; (vii) dysmorphic chromatin structure through altered post-translational modifications of histones and methylation of DNA; (viii) multiple alterations of histone post-translational modifications, including acetylation, methylation, ubiquitylation, polyamination, and phosphorylation; (ix) altered expression and regulation of non-coding miRNAs controlled by REST; and (x) concomitant de-repression of downstream mRNA targets [314,315].

Pathogenic CAG (cytosine-adenine-guanine) expansions beyond certain thresholds in the ataxin-2 (*ATXN2*) gene cause spinocerebellar ataxia type 2 (*SCA2*) and also contribute to PD, amyotrophic lateral sclerosis, and frontotemporal lobar degeneration. *ATXN2* levels are controlled by DNA methylation which influences age at onset and anticipation [316].

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/Histone modifications	Non-coding RNAs
Polyglutamine (PolyQ) diseases								
Dentatorubral pallidoluysian atrophy (DRPLA)	<i>ATN1</i> <i>Atrophin 1</i>	12p13.31	985	609	ATN1 Atrophin 1		Histone hypoacetylation ATN1 expression controlled by histone methylation	miR-137
	<i>BDNF</i> <i>Brain-derived neurotrophic factor</i>	11p14.1	1022	3213	BDNF Brain-derived neurotrophic factor	Gender-specific methylation	Decreased histone acetylation Increased histone methylation Heterochromatin condensation	Dysregulated (miR-9, miR-29b, miR-124a, miR-132) Targeting HTT (miR-125b, miR-146a, miR-150, miR-214)
Huntington’s disease (HD)	<i>HTT</i> <i>Huntingtin</i>	4p16.3	1286	937	HD Huntingtin	Extensive methylation alteration		Associated with ATXN1 (miR-19a, miR-101, miR-130a, miR-144) Associated with ATXN2 (miR-12)
	<i>ATXN1</i> <i>Ataxin 1</i>	6p22.3	1052		ATXN1 Ataxin 1			Associated with ATXN1 (miR-19a, miR-101, miR-130a, miR-144) Associated with ATXN2 (miR-12)
Spinocerebellar ataxia	<i>ATXN2</i> <i>Ataxin 2</i>	12q24.12	926	699	ATXN2 Ataxin 2	Hypermethylated	Histone acetylation Histone acetylation modulated by HDAC3	
	<i>ATXN3</i> <i>Ataxin 3</i>	14q32.12	1100	1716	ATXN3 Ataxin 3		HDAC3 modulates toxicity in a polyQ-dependent manner	Associated with ATXN3 (miR-25, miR-29a, miR-34b, miR-125b, miR-181a)
	<i>ATXN7</i> <i>Ataxin 7</i>	3p14.1	1082	1377	ATXN7 Ataxin 7			Associated with ATXN7 (miR-33-5p, miR-92a-5p, miR-375-3p)
	<i>ATXN8OS</i> <i>ATXN8 opposite strand (non-protein coding)</i>	13q21.33			ATXN8OS Putative protein ATXN8OS			

OTHER NEUROLOGICAL DISORDERS

Epigenetic and proteomic changes are frequently seen in many other CNS disorders. Transmissible encephalopathies (TSEs), such as Creutzfeldt-Jakob disease (CJD) and scrapie, are caused by prions that provoke strain-specific patterns of disease. Misfolded host prion protein (PrP-res amyloid) is believed to be the causal infectious agent. Kipkorir et al. [317] have identified host proteins bound with FU-CJD agent infectious brain particles by proteomic analysis. More than 98 proteins were differentially regulated, and 56 FU-CJD exclusive proteins were revealed after PrP, GFAP, C1q, ApoE, and other late pathologic response proteins were removed. Stripped FU-CJD particles revealed HSC70, cyclophilin B, an FU-CJD exclusive protein required by many viruses, and early endosome-membrane pathways known to facilitate viral processing, replication, and spread. Synaptosomal elements including synapsin-2 and AP180 paralleled the known ultrastructural location of 25 nm virus-like TSE particles and infectivity in synapses. Human sCJD brain particles contain 146 exclusive proteins, in addition to heat shock, synaptic, and viral pathways, and Alzheimer, Parkinson, and Huntington aggregation proteins.

Frontotemporal lobar degeneration (FTLD) comprises a spectrum of uncommon neurodegenerative diseases with an estimated prevalence of 15-22 cases per 100,000 persons. This cluster of related dementias include the behavioral variant of frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), semantic dementia (SD), FTD with motor neuron disease (FTD-MND), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). Intracellular protein aggregates are the major neuropathological hallmark of FTLD, suggesting the presence of abnormal protein metabolism or function in the disease's pathogenesis. Studies of CSF proteomics provided a set of candidate biomarkers which need further validation [318].

DNA methylation plays a key role in cell fate determination. DNA methylation at the 5 position of cytosine (5-mC) is an epigenetic marker of biological and pathological processes. 5-mC can be converted to 5-hydroxymethylcytosine (5-hmC) by the ten-eleven translocation (TET) family proteins, which is now recognized as the "sixth base" in the mammalian genome, following 5-mC, the "fifth base". 5-hmC is present in brain, embryonic stem cells, and many other tissues. 5-hmC and the TET family proteins might be involved in gene control mechanisms, DNA methylation regulation, and in the pathophysiology of human disease [319]. Cell-specific increases of 5mC and 5hmC are associated with

the death of retinal neurons during both development and degeneration, suggesting that changes in DNA methylation may play a role in modulating gene expression during the process of retinal degeneration. During retinal development, hypermethylation of retinal neurons associates with classical caspase-dependent apoptosis as well as caspase-3 independent cell death, while hypermethylation in the rd1 mouse photoreceptors is primarily associated with caspase-3-independent programmed cell death [320].

Loss of 5hmC is a hallmark of human malignancies (glioma, melanoma, myeloid tumors). In myeloid malignancies, loss of 5hmC is due to mutations within ten-eleven-translocation (*TET*) genes, enzymes being responsible for conversion of 5mC to 5hmC. There are *TET2* and *TET3* alterations in human gliomas. Kraus et al. [321] identified 7 genetic alterations within *TET2* (p.V218M, p.G355N, p.P363L, p.L1721W, p.P1723S, p.I1762V, p.H1778R). In contrast to leukemia, loss of 5hmC in glioma is not caused by *TET* gene alterations. Disrupted gene expressions or functional inhibitions of TET proteins might be responsible for the aberrant epigenome of human glioma. Subtelomeric regions dynamically change their epigenetic pattern during development and progression of several malignancies and degenerative disorders. DNA methylation levels dramatically increase at the subtelomere of Chr.8q, 21q, and XpYp in malignant glioma [322].

The Polycomb group (PcG) proteins play a critical role in histone-mediated epigenetics which has been implicated in the malignant evolution of glioblastoma multiforme (GBM). Li et al. [323] found widespread aberrant expression of the PcG members in GBM samples compared to normal brain, including upregulation of *EZH2*, *PHF19*, *CBX8* and *PHC2* and downregulation of *CBX7*, *CBX6*, *EZH1* and *RYBP*. Changes in *EZH2*, *PHF19*, *CBX7*, *CBX6* and *EZH1* occurred progressively as astrocytoma grade increased.

Brain metastatic disease is a common phenomenon in patients with breast cancer. Genomic and epigenomic events underlie breast cancer brain metastasis. Large chromosomal gains in 1q, 5p, 8q, 11q, and 20q, broad-level deletions involving 8p, 17p, 21p and Xq, amplified and overexpressed genes (*ATAD2*, *BRAF*, *DERL1*, *DNMTRB* and *NEK2A*), and deleted or underexpressed genes (*ATM*, *CRYAB*, *HSPB2*) are frequently seen in this clinical condition. Enrichment in cell cycle and G2/M transition pathways, which contained *AURKA*, *AURKB*, and *FOXMI*, are also frequent. While overall methylation levels are increased in breast cancer brain metastasis, basal-like brain metastases are associated with lower levels of methylation. Integrating DNA methylation

data with gene expression revealed defects in cell migration and adhesion due to hypermethylation and downregulation of *PENK*, *EDN3*, and *ITGAM*. Hypomethylation and upregulation of *KRT8* probably affects adhesion and permeability, as reported by Salhia et al. [324].

Nguyen [325] identified epigenetic regulation of alternative *APP* pre-mRNA splicing in the Lesch-Nyhan syndrome (LNS), showing for the first time the presence of several *APP*-mRNA isoforms encoding APP protein isoforms ranging from 120 to 770 amino acids (with or without mutations and/or deletions). New *APP*-mRNA isoforms with a deletion followed by an insertion (INDELS) in LNS and LNVs patients have been identified, suggesting a role for genomic rearrangements of *APP* gene via the Fork Stalling and Template Switching (FoSTeS) mechanism leading to INDELS. Epistasis between mutated *HPRT1* and *APP* genes could be one of the factors of epigenetic modifications responsible for genomic rearrangements of the *APP* gene.

The type III histone deacetylase sirtuin 1 (*Sirt1*) has recently emerged as a critical immune regulator by suppressing T cell immunity and macrophage activation during inflammation. Mice with genetic *Sirt1*-deletion specifically in dendritic cells (DCs) are resistant to MOG-induced experimental autoimmune encephalomyelitis (EAE). Loss of Sirt1 functions in DCs enhances their ability to produce IL-27 and interferon (IFN-β). Co-cultivation of Sirt1-null DCs with CD4⁺ T cells inhibits Th17 differentiation, which is reversed by anti-IL27 and anti-IFN-β neutralization antibodies. Sirt1 antagonizes acetylation of IRF1, a transcription factor that drives IL-27 production. Genetic deletion of *IRF1* in *Sirt1*-null DCs abolishes IL-27 production and suppresses Th17 differentiation. These data indicate that the histone deacetylase Sirt1 programs DCs to regulate Th17 differentiation during inflammation [326].

Whole brain radiotherapy (WBRT) produces unwanted sequelae. Sirtuin 2 (SIRT2) is a deacetylase expressed in the CNS. It has been postulated that a single disease pathway is responsible for radiation-induced brain injury in *Sirt2* wild-type (WT) and knockout (KO) mice at the proteomic level. Canonical pathways for Huntington's, Parkinson's, and Alzheimer's disease were acutely affected by radiation within 72 h of treatment. Although loss of Sirt2 preferentially affected both Huntington's and Parkinson's pathways, WBRT most significantly affected Huntington's-related proteins in the absence of Sirt2. Identical protein expression patterns were identified in Mog following WBRT in both Sirt2 WT and KO mice, revealing a proteomic radiation signature; however, long-term radiation effects were found

Table 5. Selected Genomic, Epigenomic, and Proteomic markers in Stroke.

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation (Promoter)	Chromatin/ Histone modifications	Non-coding RNAs
Stroke	<i>ALOX5AP</i> Arachidonate 5-lipoxygenase-activating protein	13q12.3	970	386	L5AP Arachidonate 5-lipoxygenase-activating protein	Methylation/ expression variations in MTHFR, THBS1, Era lead to risk of stroke	Perturbed histone acetylation levels associated to cell death and protective responses Abnormal chromatin remodeling leading to cell death Mutations in nucleosome remodeling enzymes increase risk of stroke High serum levels of nucleosomes are markers for risk of stroke Chromatin dynamics involved on cholesterol synthesis, transport, and metabolic pathways	Up-regulated (Has-let-7e, miR-25, miR-181a, miR-513a-5p, miR-665, miR-891, miR-933, miR-1184, miR-1246) Down-regulated (Has-let-7f, miR-15b, miR-126, miR-142-3p, miR-186, miR-519e, miR-768-5p, miR-1259)
	<i>APOC3</i> Apolipoprotein C-III	11q23.3	960	278	APOC3 Apolipoprotein C-III	High methylation levels promoting neuronal cell death		
	<i>APOE</i> Apolipoprotein E	19q13.32	996		APOE Apolipoprotein E	Abnormal DNA methylation associated with obesity, atherosclerosis, insulin resistance, autoimmunity, cancer		

to be associated with altered levels of a small number of key neurodegeneration-related proteins, identified as Mapt, Mog, Snap25, and Dnm1. The presence of Sirt2 can have significant effects on the brain proteome and its response to ionizing radiation [327].

Epigenetic changes also occur after nerve tissue injury. Epigenetic regulation of CC-chemokine ligand (*CCL*) 2 and *CCL3* participates in the peripheral sensitization leading to neuropathic pain. Kiguchi et al. [328] examined the relationship between histone H3 modification and the upregulation of these molecules using a mouse model of neuropathic pain after partial sciatic nerve (SCN) ligation (PSL). The mRNA levels of *CCL2*, *CCL3* and their receptors (*CCR2* and *CCR1/CCR5*, respectively) were increased in the injured SCN. The levels of lysine 9-acetylated histone H3 (H3K9Ac) and lysine 4-trimethylated H3 (H3K4me3) in the promoter regions of the *CCL2* and *CCL3* genes were increased in the injured SCN after PSL, indicating the enhancement of gene expression. Upregulation of *CCLs* and *CCRs* was suppressed by the histone acetyltransferase inhibitor, anacardic acid. These chemokine cascades may subsequently elicit chronic neuroinflammation following nerve injury.

Other neurological diseases in which epigenetic aberrations may be involved include multiple sclerosis [329-331], migraine [332], epilepsy [333], facioscapulohumeral muscular dystrophy [334-336], Duchennemuscular dystrophy [337], chronic pain [338,339], Hutchinson-Gilford progeria syndrome [340-342], genotoxic disorders [343,344], brain tumors [345], and stroke [346,347] (Table 5).

EPIGENETIC MENDELIAN DISORDERS

Epigenetic Mendelian disorders (EMD) are a group of multiple congenital anomaly and intellectual disability syndromes resulting from mutations in genes encoding components of the epigenetic machinery [5] (Table 6). Within this category, genetic mutations may affect writers, erasers, or readers of epigenetic marks, and chromatin remodelers, as well. Many EMD fall within the category of neurodevelopmental and imprinting disorders, and some of them may manifest in adults. EMD involving the DNA methylation machinery have been described for writers and readers of DNA methylation: (i) Rett syndrome, an X-linked disorder affecting mostly females and resulting from loss-of-function mutations in a reader of CpG methylation (*MeCP2*) (methyl-CpG-binding protein); (ii) 2q23.1 microdeletion/microduplication syndrome, and autosomal dominant syndrome with deletion/duplication in

the *MBD5* locus, encoding a methyl-CpG-binding protein; (iii) immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome, caused by homozygous or compound heterozygous hypomorphic mutations in the *DNMT3B* gene; (iv) hereditary sensory and autonomic neuropathy with dementia and hearing loss (HSAN1E) (mutations in *DNMT1* exon 20); (v) autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCADN) (mutations in *DNMT1* exon 21). EMD of the histone machinery have been described for writers, erasers, readers, and chromatin remodelers, including: (i) Kabuki syndrome, an autosomal dominant trait with mutations in mixed lineage leukemia 2 (*MLL2*) (a histone H3K4 methyltransferase) or lysine-specific demethylase 6A (*KDM6A*) genes; (ii) Rubinstein-Taybi syndrome (RTS), an autosomal dominant syndrome caused by haploinsufficiency of histone acetyltransferase enzyme genes (*CREBBP* and *EP300*); (iii) Genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson (SBBYS) syndrome (mutations in the histone acetyltransferase *KAT6B*), (iv) Widerman-Steiner syndrome (WSS) (mutations in the *MLL* gene, histone methyltransferase H3K4), (v) Kleefstra syndrome (KLFS) (mutations in *EHMT1*, histone methyltransferase H3K9), (vi) Weaver syndrome (WS) (mutations in *EZH2*, histone methyltransferase H3K27), (vii) Sotos syndrome (SS) (mutations in *NSD1*, histone methyltransferase H3K36 and H4K20); (viii) brachydactyly-mental retardation (BDMR) syndrome (haploinsufficiency of the histone deacetylase gene, *HDAC4*); (ix) Cornelia de Lange syndrome 5 (CDLS5) (X-linked) and Wilson-Turner syndrome (WTS) (X-linked) (mutations in histone deacetylase *HDAC8*), (x) Claes-Jensen syndrome (CJS) (X-linked) (mutations in *KDM5C*, histone demethylase H3K4); (xi) Kabuki syndrome (X-linked) (mutations in *KDM6A*, histone demethylase H3K27); (xii) Siderius X-linked mental retardation syndrome (MRXSSD) (mutations in *PHF8*, plant homeodomain finger protein); (xiii) Börjeson-Forssman-Lehmann syndrome (BFLS) (X-linked recessive trait, missense mutations in the *PHF6* gene, plant homeodomain finger protein); and (xiv) X-linked mental retardation and macrocephaly (mutations in *BRWD3*, bromodomain-containing protein). EMD of chromatin remodelers include the following: (i) alpha-thalassemia/mental retardation X-linked (ATRAX) syndrome (mutations in *ATRAX*, SWI/SNF ATP-dependent chromatin remodeler); (ii) 4 variants of Coffin-Siris syndrome: mental retardation autosomal dominant 14 (MRD14) (mutations in *ARID1A*), mental retardation autosomal dominant 12 (MRD12) (mutations in *ARID1B*), mental retardation autosomal dominant 16 (MRD16) (mutations in *SMARCA4*), and mental retardation autosomal dominant 15 (MRD15) (mutations in

SMARCB1); (iii) Rhabdoid tumor predisposition syndrome 2 (mutations in *SMARCA4*); (iv) Schwannomatosis (mutations in *SMARCB1*); (v) Rhabdoid tumor predisposition syndrome 1 (mutations in *SMARCB1*); (vi) Nicolaides-Baraitser syndrome (mutations in *SMARCA2*); (vii) Floating harbor syndrome (mutations in *SRCAP*, INO80/SWR1 ATP-dependent chromatin remodeler); (viii) CHARGE syndrome (mutations in *CHD7*, CHD ATP-dependent chromatin remodeler); and (ix) mental retardation autosomal dominant 21 (MRC21) (mutations in *CTCF*, chromatin-organizing zinc finger protein) [5] (Table 6).

FUTURE TRENDS

Most CNS disorders are clinical entities which, in many instances, share some common

features: (i) pathogenically, they are complex disorders in which a plethora of plural events (genomic defects, epigenetic aberrations, mitochondrial dysfunction, environmental factors) is potentially involved; (ii) many of them, especially those with a late onset, are characterized by intracellular and/or extracellular deposits of abnormal proteins; (iii) their diagnosis is difficult because they lack specific biomarkers (and their prediction is almost impossible); (iv) their treatment is symptomatic (not anti-pathogenic) and not cost-effective; and (v) the vast majority represent chronic ailments with progressive deterioration and bad prognosis [14]. The concept of epigenetics, introduced by Conrad Waddington in 1942, and its spectacular evolution, from a biotechnological perspective, has been of great help for the past 10 years in the understanding of gene regulation and expression (functional genomics), neurogenomics, and pathogenetics of CNS disorders [2,17,28,166,177] (Figure 1).

Gene expression and protein function experience profound modifications throughout the life span. It is likely that the frontier between health and disease is not only associated with specific SNP variability and epigenetic aberrations (in conjunction with environmental risks) but also with a salutary/pathogenic threshold of transformed protein accumulation in critical cells (especially in neurons). Over the past decade, progress in epigenetics and proteomics has helped to understand many aspects of pathogenic phenomena which remained obscure or unaffordable to our technical capabilities for the assessment of genomic dysfunction, epigenetic dysregulation, and abnormal protein expression. Transcription errors represent a molecular mechanism by which cells can acquire disease phenotypes. The error rate of transcription increases with cell aging, suggesting

Table 6. Epigenetic Mendelian disorders.

Disease	Defective Gene	Locus	Gene size (Kb)	Protein	Protein size (aa)	Molecular weight (kDa)	Defective Epigenetic Function	Consequence	Other Related Diseases
Hereditary sensory and autonomic neuropathy with dementia and hearing loss (HSANIE)	<i>DNMT1</i> <i>DNA (cytosine-5)-methyltransferase 1</i>	19p13.2	97.94	<i>DNMT1</i> <i>DNA (cytosine-5)-methyltransferase 1</i>	1616	183.16	DNA methylation (Writer)	Impaired targeting of DNMT1 to heterochromatin is translated into a global loss of 5-methylcytosine and increase of methylation at some gene promoters	Lymphosarcoma, lyeys-dietz syndrome, narcolepsy, cerebellar ataxia, hereditary sensory neuropathy, mutagen sensitivity, myelodysplastic syndrome, breast cancer
Autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCADN)	<i>DNMT3B</i> <i>DNA (cytosine-5)-methyltransferase 3 beta</i>	20q11.2	46.97	<i>DNMT3B</i> <i>DNA (cytosine-5)-methyltransferase 3B</i>	853	95.75	DNA methylation (Writer)	Aberrant hypomethylation of particular DNA sequences	Malignant glioma, leukemia, colorectal carcinoma, cancer, lung cancer
Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome	<i>MECP2</i> <i>Methyl CpG binding protein 2</i>	Xq28	76.18	<i>MECP2</i> <i>Methyl-CpG-binding protein 2</i>	486	52.44	Binding to methylated DNA (Reader)	Impaired binding of MECP2 or MBD5 to methylated target sequences; leading to aberrant changes on gene expression	Intellectual disability, autistic disorder, Angelman syndrome, Microcephaly, Gait apraxia
Rett syndrome	<i>MECP2</i> <i>Methyl CpG binding protein 2</i>	Xq28	76.18	<i>MECP2</i> <i>Methyl-CpG-binding protein 2</i>	486	52.44	Binding to methylated DNA (Reader)	Impaired binding of MECP2 or MBD5 to methylated target sequences; leading to aberrant changes on gene expression	Intellectual disability, autistic disorder, Angelman syndrome, Microcephaly, Gait apraxia
2q23.1 microdeletion/microduplication syndrome	<i>MBD5</i> <i>Methyl-CpG binding domain protein 5</i>	2q23.1	497.22	<i>MBD5</i> <i>Methyl-CpG-binding domain protein 5</i>	1494	159.89	Binding to methylated DNA (Reader)	Impaired binding of MECP2 or MBD5 to methylated target sequences; leading to aberrant changes on gene expression	Lagophthalmos, exposure keratitis, keratopathy

Disease	Defective Gene	Locus	Gene size (Kb)	Protein	Protein size (aa)	Molecular weight (kDa)	Defective Epigenetic Function	Consequence	Other Related Diseases
Rubinstein-Taybi syndrome (RTS)	<i>CREBBP</i> <i>CREB binding protein</i>	16p13.3	155.67	CBP CREB-binding protein	2442	265.35	Histone acetylation (Writer)	Histone acetylation (by acetylases) promotes an open chromatin conformation and a transcriptional activation. Histone methylation (by methyltransferases) is associated with transcriptional repression or activation. Defective histone methyltransferases or acetylases lead to an inappropriate chromatin conformation and regulation of those genes, which promotes the onset of the disease	Acute myeloid leukemia with t(8;16)(p11;p13) translocation, neonatal leukemia, floating-harbor syndrome, alpha-thalassemia/mental retardation syndrome, melanoma of soft parts, acute monocytic leukemia, monocytic leukemia, myeloid leukemia
	<i>EP300</i> <i>E1A binding protein p300</i>	22q13.2	88.29	EP300 Histone acetyltransferase p300	2414	264.16	Histone acetylation (Writer)		
Genitopatellar syndrome (GPS) Say-Barber-Biesecker-Young-Simpson (SBBYS) syndrome	<i>KAT6B</i> <i>K(lysine) acetyltransferase 6B</i>	10q22.2	207.69	KAT6B Histone acetyltransferase KAT6B	2073	231.37	Histone acetylation (Writer)	Blepharophimosis-intellectual disability syndrome, kat6b-related disorders, ohdo syndrome, monocytic leukemia, noonan syndrome 1, leukemia	
	<i>KMT2A</i> (<i>MLL</i>) <i>Lysine (K)-specific methyltransferase 2A</i>	11q23	90.34	KMT2A Histone-lysine N-methyltransferase 2A	3969	431.76	Histone methylation (Writer)		
Wiedemann-Steiner syndrome (WSS)	<i>EHMT1</i> <i>Euchromatic histone-lysine N-methyltransferase 1</i>	9q34.3	251.02	EHMT1 Histone-lysine N-methyltransferase EHMT1	1298	141.46	Histone methylation (Writer)	Acute biphenotypic leukemia, acute myeloid leukemia with t(9;11)(p22;q23), bilineal acute leukemia, acute myeloid leukemia with 11q23 abnormalities, precursor b-cell acute lymphoblastic leukemia, chronic neutrophilic leukemia, acute leukemia, congenital mesoblastic nephroma, intravascular large b-cell lymphoma, mesoblastic nephroma, acute myelomonocytic leukemia, primary mediastinal large b-cell lymphoma, leukemia, myelodysplastic syndrome, lymphoblastic leukemia	
Kleefstra syndrome (KLF5)	<i>EZH2</i> <i>Euchromatic histone-lysine N-methyltransferase 2</i>	7q35-q36	76.98	EZH2 Histone-lysine N-methyltransferase EZH2	746	85.36	Histone methylation (Writer)	Ezh2-related overgrowth, periodic fever, aphthous stomatitis, pharyngitis and adenitis, marshall syndrome, wrinkly skin syndrome, marshall-smith syndrome, salivary gland adenoid cystic carcinoma, chronic myelomonocytic leukemia, prostate cancer	
Weaver syndrome (WS)	<i>NSD1</i> <i>Nuclear receptor binding SET domain protein 1</i>	5q35	167.19	NSD1 Histone-lysine N-methyltransferase, H3 lysine-36 and H4 lysine-20 specific	2696	296.65	Histone methylation (Writer)	Weaver syndrome 1, 5q35 microduplication syndrome, beckwith-wiedemann syndrome due to nsd1 mutation, linedema, beckwith-wiedemann syndrome, abdominal wall defect, alpha-thalassemia/mental retardation syndrome, macroglossia leukemia, acute myeloid leukemia	

Disease	Defective Gene	Locus	Gene size (Kb)	Protein	Protein size (aa)	Molecular weight (kDa)	Defective Epigenetic Function	Consequence	Other Related Diseases
Kabuki syndrome (KS)	<i>KMT2D (MLL2) Lysine (K)-specific methyltransferase 2D</i>	12q13.12	41.17	KMT2D Histone-lysine N-methyltransferase 2D	5557	593.38	Histone methylation (Writer)	Defective MLL2 or KDM6A interferes with the upregulation of critical target genes	Spinocerebellar ataxia 2
Claes-Jensen syndrome (CJS)	<i>KDM6A Lysine (K)-specific demethylase 6A</i>	Xp11.2	239.6	KDM6A Lysine-specific demethylase 6A	1401	154.17	Histone demethylation (Eraser)	Demethylases or deacetylases associated with condensed chromatin and down regulation at target loci	X-linked syndromic mental retardation, syndromic x-linked intellectual disability due to 2q37 microdeletion syndrome, bright's hereditary osteodystrophy, neuronal intranuclear inclusion disease
Brachyactyl-mental retardation (BDMR) syndrome	<i>KDM5C Lysine (K)-specific demethylase 5C</i>	Xp11.22-p11.21	34.1	KDM5C Lysine-specific demethylase 5C	1560	175.72	Histone demethylation (Eraser)	Defects on those enzymes promote the overexpression of specific genes that favor pathological conditions	Obesity
Cornelia de Lange syndrome 5 (CDLS5) Wilson-Turner syndrome (WTS) Siderius X-linked mental retardation syndrome (MRXSSD)	<i>HDAC4 Histone deacetylase 4</i>	2q37.3	353.48	HDAC4 Histone deacetylase 4	1084	119.04	Histone deacetylation (Eraser)	Mutations on this gene are associated with impaired cell growth and differentiation	Hypogonadism, obesity
Börjeson-Forssman-Lehmann syndrome (BFLS)	<i>HDAC8 Histone deacetylase 8</i>	Xq13	243.58	HDAC8 Histone deacetylase 8	377	41.75	Histone deacetylation (Eraser)	Possible defects on transcriptional regulation	Chronic lymphocytic leukemia
	<i>PHF8 PHD finger protein 8</i>	Xp11.22	112.28	PHF8 Histone lysine demethylase PHF8	1060	117.86	Histone deacetylation (Eraser)		
	<i>PHF6 PHD finger protein 6</i>	Xq26.3	55.54	PHF6 PHD finger protein 6	365	41.29	Transcriptional regulation (Reader)		
X-linked mental retardation and macrocephaly	<i>BRWD3 Bromodomain and WD repeat domain containing 3</i>	Xq21.1	140.24	BRWD3 Bromodomain and WD repeat-containing protein 3	1802	203.59	Chromatin remodeling (Reader)		

that transcription errors affect proteostasis particularly in aging cells. Accordingly, transcription errors accelerate the aggregation of peptides and shorten the lifespan of cells [348].

Novel methodologies have allowed us to configure new pathogenic hypotheses for a better understanding of brain disorders. In this endeavor, epigenetics and proteomics have been of great benefit. Epigenetic studies have revealed the important role that epigenetic modifications have on brain development and maturation, synaptic plasticity [13], brain sex differences [43], neurodevelopment and imprinting disorders, mental disorders [38], neurodegeneration [10,17], and the new field of epigenetic Mendelian disorders [5]. Structural genomic defects cannot explain in full the pathogenesis of CNS disorders. Many old concepts related to the pathogenesis of CNS disorders should be eliminated. Parkinson's disease is not the result of a single deficiency in dopamine; Alzheimer's disease is not the consequence of a cholinergic deficit; however, the basic principles for the development of the most currently prescribed drugs for both disorders rely on a single neurotransmitter defect (enhancement of dopamine neurotransmission in Parkinson's disease, and potentiation of cholinergic transmission with acetylcholinesterase inhibitors in Alzheimer's disease). These old-fashioned pathogenic concepts are completely out-of-date, and the new conceptions on neurodegenerative disorders are based on the pathogenic cascade represented by genomic-epigenomic-transcriptomic-proteomic-metabolomic disturbances leading to a specific phenotype which in the future will require a personalized therapeutic intervention (pharmacogenomics, pharmacoepigenomics) for phenotype disease modification (Figure 1). The same must happen with most mental disorders whose psychopharmacological treatments rely on a reductionistic view based on the regulation of 6 neurotransmitters (dopamine, noradrenaline, serotonin, acetylcholine, histamine, GABA), assuming for the past 50 years that major psychiatric disorders (schizophrenia, depression, anxiety, bipolar disorder, autism, attention deficit hyperactivity disorder) are merely neurotransmitter disorders [69,83,84,349]. However, as pointed out by Riley et al. [301], systems analysis is believed to help deconvolute complex biological responses involving hundreds or thousands of genes assayed by OMICs methods. Although systems-style approaches have been applied to CNS tissues, most studies have used simple functional overview approaches resulting in the identification of differentially expressed genes, or pathways. While these approaches expanded our understanding of disease-related changes, they are not able to elucidate the complex interconnectivity of biological

Table 6. (Cont.)

Disease	Defective Gene	Locus	Gene size (Kb)	Protein	Protein size (aa)	Molecular weight (KDa)	Defective Epigenetic Function	Consequence	Other Related Diseases
Alpha-thalassemia/mental retardation X-linked (ATRX) syndrome	<i>ATRX</i> Alpha thalassaemia/mental retardation syndrome X-linked	Xq21.1	281.39	ATRX Transcriptional regulator ATRX	2492	282.58	Chromatin remodeling (Remodeler)		Mental retardation-hypotonic facies syndrome, myelodysplasia syndrome, intellectual disability syndrome, mental retardation smith fineman myers type, spastic diplegia
Mental retardation autosomal dominant 14 (MRD 14 syndrome)	<i>ARID1A</i> AT rich interactive domain 1A (SWI-like)	1p35.3	86.08	ARID1A AT-rich interactive domain-containing protein 1A	2285	242.04	Chromatin remodeling (Remodeler)		Coffin-siris syndrome, arid1a-related Coffin-siris syndrome, ovarian clear cell carcinoma, adenofibroma
Mental retardation autosomal dominant 12 (MRD 12 syndrome)	<i>ARID1B</i> AT rich interactive domain 1B (SWI-like)	6q25.1	432.93	ARID1B AT-rich interactive domain-containing protein 1B	2236	236.12	Chromatin remodeling (Remodeler)		Chromosome 6q25 microdeletion syndrome, arid1b-related Coffin-siris syndrome, nicolaides-baraitser syndrome, Coffin-siris syndrome, spinocerebellar ataxia 2, ladd syndrome, acrocephalosyndactylia
Mental retardation autosomal dominant 16 (MRD 16 syndrome)	<i>SMARCA4</i> SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	19p13.2	104.47	SMCA4 Transcription activator BRG1	1647	184.64	Chromatin remodeling (Remodeler)		Ovarian small cell carcinoma, smarca4-related Coffin-siris syndrome, Coffin-siris syndrome, tumor predisposition syndrome, peutz-jeghers syndrome, oculopharyngeal muscular dystrophy, bacteremia, choroid plexus carcinoma, primary pigmented nodular adrenocortical disease, stargardt disease
Rhabdoid tumor predisposition syndrome 2									
Mental retardation autosomal dominant 15 (MRD 15 syndrome)	<i>SMARCB1</i> SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	22q11.23; 22q11	47.55	SNF5 SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1	385	44.14	Chromatin remodeling (Remodeler)	Mutations of these proteins are associated with an altered gene expression or DNA methylation mediated by a defective chromatin conformation around specific target genes	Smarb1-related Coffin-siris syndrome, Coffin-siris syndrome, epithelioid sarcoma, rhabdoid cancer, rhabdoid meningioma, chromosome 22q deletion, monosomy 22, familial multiple meningioma, choroid plexus carcinoma, tumor predisposition syndrome, choroid plexus papilloma, retroperitoneal leiomyosarcoma, pleomorphic xanthoastrocytoma, epithelioid malignant peripheral nerve sheath tumor, malignant peripheral nerve sheath tumor, neurilemmoma, mesoblastic nephroma, congenital mesoblastic nephroma, mesenchymal chondrosarcoma, leiomyosarcoma, chondrosarcoma, hiv-1
Schwannomatosis									
Rhabdoid tumor predisposition syndrome 1									
Nicolaides-Baraitser syndrome	<i>SMARCA2</i> SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	9p22.3	178.4	SMCA2 Probable global transcription activator SNF2L2	1590	181.27	Chromatin remodeling (Remodeler)		Schizophrenia
Floating harbor syndrome	<i>SRCAP</i> Snf2-related CREBBP activator protein	16p11.2	46.98	SRCAP Helicase SRCAP	3230	343.55	Chromatin remodeling (Remodeler)		Fosniphilic angiocentric fibrosis, rubinstein-aybi syndrome
CHARGE syndrome	<i>CHD7</i> Chromodomain helicase DNA binding protein 7	8q12.2	189.26	CHD7 Chromodomain-helicase-DNA-binding protein 7	2997	335.92	Chromatin remodeling (Remodeler)		Scoliosis, hypogonadotropic hypogonadism 5 with or without anosmia, kallmann syndrome 5, chd7-related isolated gonadotropin-releasing hormone deficiency, normosmic congenital hypogonadotropic hypogonadism, omenn syndrome, esophageal atresia, tracheoesophageal fistula, choanal atresia

Disease	Defective Gene	Locus	Gene size (Kb)	Protein	Protein size (aa)	Molecular weight (KDa)	Defective Epigenetic Function	Consequence	Other Related Diseases
Mental retardation autosomal dominant 21 (MRD 21)	<i>CTCF</i> <i>CCCCTC-binding factor (zinc finger protein)</i>	16q21-q22.3	76.77	CTCF Transcriptional repressor CTCF	727	82.78	Chromatin organizing (insulator)	Defective insulator genes lead to a lack of prevention for inappropriate interactions between adjacent chromatin domains	Intellectual disability-feeding difficulties-developmental delay-microcephaly syndrome, mesoblastic nephroma, beckwith-wiedemann syndrome, cornelia de lange syndrome, silver-russell syndrome

and pathological processes present within diseased tissue. These approaches are “low resolution” descriptive methods with limited projection in terms of clarifying molecular pathogenesis, experimental follow-up, and clinical application.

Global protein profiling by mass spectrometry-based proteomics has evolved as a new hypothesis-free avenue to optimally unravel new candidate protein biomarkers involved in different CNS disorders. Technological developments and improvement of sensitivity, specificity and speed of different proteomic approaches have facilitated the discovery of an enormous number of biomarker candidates; however, most biomarkers have not yet been validated, which limit their application in clinical practice. The correct interpretation of thousands of data derived from proteomic and epigenomic analysis is an additional problem for the practical implementation of biomarkers in the clinical setting [350]. Novel neuroproteomic tools and powerful bioinformatic resources are needed to accelerate the incorporation of proteomic and epigenomic analysis to the diagnostic process [351-353].

Another important field, in which epigenetics and proteomics are contributing to its expansion, is drug development. Epigenetic drugs are becoming a fashion [9,10,354] and some of them have been approved by the FDA in recent years for the treatment of cancer [19]. However, most epigenetic drugs are pleiotropic and are not devoid of toxicity and biodynamic complications (e.g. brain penetration) [9].

The effects of drugs (pharmacokinetics and pharmacodynamics) and their therapeutic outcome in the treatment of a given disease are the result of a network of metabolomic events (genomics-epigenomics-transcriptomics-proteomics) associated with the binomial interaction of a chemical or biological molecule with a living organism. The clusters of genes currently involved in a pharmacogenomic process include pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes [14]. In practice, the expression of these genes is potentially modifiable (transcriptionally and/or post-transcriptionally) by epigenetic mechanisms which may alter (i) pathogenic events, (ii) receptor-drug interactions, (iii) drug metabolism (phase I and II enzymatic reactions), (iv) drug transport (influx-efflux across membranes and cellular barriers), and (v) pleiotropic events leading to unexpected therapeutic outcomes. The understanding of these mechanisms is the main focus of pharmacoeugenomics in order to optimize

therapeutics and advance towards a personalized medicine [9,355].

In the coming years, important achievements must be accomplished in different areas of neuroscience: (i) brain development and maturation, (ii) toxicogenomics, (iii) functional epigenomics, (iv) proteoepigenomics, (v) pathoepigenomics, (vi) predictive proteomics, (vii) diagnostic proteomics, (viii) prognostic proteomics, (ix) pharmacoepigenomics, and (x) epitherapeutics. It is likely that systems biology will dominate the -omics signatures [356]. Relevant information obtained from the ENCODE Project will be incorporated into a more versatile map of clinical neuroscience and practical medicine [29,30,357]. Development is a dynamic process that involves interplay between genes and the environment. Postnatal environment is shaped by parent-offspring interactions that promote growth and survival and can lead to divergent developmental trajectories with implications for later-life neurobiological and behavioral characteristics [358]. The impact that nutrition, emotions, drugs and environmental toxicants during prenatal development may have on brain maturation and late CNS disorders requires urgent clarification [359-361]. Important advances related to the role of epigenetics in the pathogenesis of brain disorders will occur in the near future with reliable applications. Predictive, diagnostic, and prognostic proteomics, as well as the use of biomarkers to monitor the effects of drugs will experience a profound change from the present immature stage of the field to a more specific and validated area with various applications in CNS disorders.

In therapeutics, important breakthroughs will occur in some of the following areas: (i) epigenetic drug discovery for different CNS disorders and cancer [9,10,27,193,362,363]; (ii) practical applications of pharmacogenomics [14,364] and pharmacoepigenomics [365-368] for the optimization and personalization of current drugs and new pharmacological treatments; (iii) novel therapeutic approaches to decode and resolve potential resistance mechanisms in cancer and psychiatric disorders [365,369,370]; and (iv) targeting miRNAs in prevention and treatment of brain disorders [371-373].

CONCLUSIONS

1. Epigenomic regulation is a common phenomenon of gene expression control during development, maturation and aging in physiological and pathological conditions.
2. Classical epigenetic mechanisms (DNA methylation, chromatin remodeling/histone modifications, and miRNA regulation), are among the major regulatory elements that control metabolic pathways.
3. Preconceptional parental exposure to environmental stimuli may determine the offspring's phenotype via heritable epigenetic mechanisms, and exposure to diverse external elements may condition several categories of human diseases and CNS disorders.
4. Mutations in the genes encoding elements of the epigenetic machinery can lead to epigenetic Mendelian disorders.
5. Epigenomic dysregulation contributes to the pathogenesis of neurodevelopmental, imprinting, mental, neurological, and neurodegenerative disorders.
6. Some epigenetic aberrations are conceptually reversible and can potentially be targeted by pharmacological and dietary interventions.
7. Proteomic biomarkers can be useful for both early and accurate diagnosis and prediction of CNS disease progression.
8. The correct interpretation of thousands of data derived from proteomic and epigenomic analysis is still a problem for the practical implementation of biomarkers in the clinical setting. Novel neuroproteomic tools and powerful bioinformatic resources are needed to accelerate the incorporation of proteomic and epigenomic analysis to the diagnostic process.
9. Epigenetic changes in genes involved in pharmacogenomics (pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes) can also influence drug efficacy and safety and drug resistance in brain disorders and cancer.
10. Proteomic biomarkers, novel therapeutic approaches to decode and resolve potential drug resistance mechanisms, and targeting miRNAs in prevention and treatment of brain disorders are promising developments in the field of proteoepigenomics.

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