Histone and DNA Methylome in Neurodegenerative, Neuropsychiatric and Neurodevelopmental Disorders

Harsha Rani and Vijayalakshmi Mahadevan

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Abstract Genome-environment interaction and epigenome plasticity significantly influence the pathogenesis of neurodegenerative and neuropsychiatric disorders. Recent advancements in the field to study genome wide chromatin modifications provide a comprehensive view of the epigenome. Dysregulation of epigenetic machinery has emerged as a major genetic driver of neuro developmental and neuro degenerative disorders, intellectual disabilities and autism spectrum disorders.

H. Rani · V. Mahadevan (✉)
Chromatin and Epigenetics Group, Institute of Bioinformatics and Applied Biotechnology (IBAB), Bangalore, India
e-mail: mviji@ibab.ac.in

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Emerging evidences point to the involvement of the epigenome in the onset and progression of Alzheimer's disease, Parkinson's disease and Huntington's disease. This review focusses on the changes in epigenetic machinery, specifically on the histone methylation and DNA methylation patterns during the onset and progression of neurodegenerative diseases and neuropsychiatric disorders. The power of epigenetic inhibitors to function as potential diagnostic and therapeutic markers is also discussed.

Keywords Epigenome · Neuropsychiatry · Brain plasticity · Epigenetic inhibitors · Schizophrenia · Huntington's disease · Alzheimer's disease · Parkinson's disease · Obsessive compulsive disorder · Bipolar disorder

1 Introduction

1.1 Dynamics of Histone Modification

Chromatin is an active and dynamic substrate for transcriptional and developmental processes and resides inside the cell nucleus in eukaryotes. The strategic and hierarchical wrapping of the 146bp of DNA around the octameric scaffold of core histones H2A, H2B, H3 and H4 forms a single unit of nucleosome (Luger et al. 1997; Kornberg 1974), which forms a higher order structure with repeating nucleosomal subunits and linker histone H1 (Luger et al. 1997). The higher order structure of chromatin is an impediment for transcription factors to gain access to DNA. Increasing evidences in the field have established chromatin as a dynamic entity that regulates gene programs and cellular functions through alteration of its structure and architecture via enzymatic modifications of histone tails or through nucleosome remodelling. Post translational modifications of histones include acetylation, methylation, phosphorylation, ubiquitination, citrullination and ADP-ribosylation that take place on the tail domains of core histones (Hottiger 2011; Cao and Yan 2012).

The sites of modifications are predominantly clustered in the first few amino acids of the core histones H3, H4, H2A and H2B though a few residues inside the core of the nucleosomes have been identified. These combinatorial patterns of histone modifications create a 'histone code' (Strahl and David Allis 2000) and control a variety of biological functions, including recruitment of DNA replication, transcription and repair (Abmayr and Workman 2012). Individual histone modifications have been shown to crosstalk with histone-enzyme interaction where nearby or distant PTMs interdependently recruit or release enzymes required for modifications (Daujat et al. 2002).

Histone methylation is a highly dynamic event which regulates diverse biological processes including cell-cycle regulation, DNA damage, stress response, development and differentiation (Pedersen and Helin 2010; Greer and Shi 2012). Methylation of histone generally occurs on arginines, lysines and histidines on the N-terminal tail of histones. Lysines can be monomethylated (me1), di-methylated(me2) or

trimethylated (me3) on their ε- amino group (Ng et al. 2009). However, arginines can either be monomethylated (me1) or symmetrically (me2s)/asymmetrically di-methylated (me2a) on their guanidinyl group. Symmetrical di-methylation of arginine refers to the addition of one methyl group to each nitrogen of the guanidinium group, whereas asymmetrical di-methylation refers to the addition of both methyl groups to one nitrogen of the guanidinium group (Borun et al. 1972). On the other hand, histidines have been found to be mono methylated although it seems to be a rare event. The effect of methylation of histones is dependent on the location of methylation residues on the histone tail and degree of methylation (Heintzman et al. 2007). SAMe (S-adenosyl methionine) is a major methyl donor which functions through cellular transmethylation pathways and methylates many substrates including those for DNA methylation and histone methylation. Generation of SAMe involves a bicyclic cellular pathway consisting of folate and methionine (1 carbon cycle). Thus, it takes part in critical epigenetic mechanism and connects nurture based metabolism with brain development (Mentch et al. 2015; Gao et al. 2018).

Genomewide location analysis (GWLA) of histone H3 methylation (me) patterns at different lysines (Ks) using Chromatin Immuno Precipitation (ChIP) revealed that these methylation patterns (unlike the acetylation marks) are predominantly enriched over broad genomic regions rather than being restricted to the promoter regions (except H3K4me). This study also provided new information on the distribution patterns of lysine methylation across the coding regions of human genes (Miao and Natarajan 2005). A study on the dynamics of distinct methylation marks (both lysine and arginine residues) in HeLa cells using heavy methyl stable isotope labelling by amino acids in cell culture (SILAC) revealed that different methylation states within the same peptide have different rates of formation and is found to be enriched mainly over broad genomic regions (Zee et al. 2010)

1.2 Readers, Writers and Erasers of Methylation Machinery

1.2.1 Epigenetic Writers

Addition of methyl groups donated from S-adenosylmethionine to histones is catalysed by histone methyl transferases (HMTs). Three families of histone methyl transferases have been classified so far which includes the SET-domain containing proteins, DOT1-l like proteins and arginine N-methyltransferase (PRMT) family proteins (Table 1). The SET domain is a sequence motif (named after Su(var) 3-9, Enhancer of Zeste, Trithorax) regulating lysine methylation and is found in several chromatin associated proteins, including members of both the Trithorax group and Polycomb group (Rea et al. 2000). The non-SET domain DOT-1 (disruptor of telomeric silencing: also called Kmt4) and its mammalian homolog, DOT1L (DOT1-like) possess histone methyltransferase activity towards histone H3Lys79. PRMT family in turn is specific for arginine methyl transferase activity (Feng et al. 2002).

Table 1 Members of the SET-domain containing family with common and unique domains of each member of the family

SET family	Members associated	Domains common to the family in addition to the SET domain	Domains unique to particular members	References
SUV39 family		Pre-SET (9 Cys, 3 Zn), post-SET ($CXCX_4C$)		Rea et al. (2000)
	SUV39H1		4 Cys, chromo	
	SUV39H2		4 Cys, chromo	
	G9a		E/KR-rich, NRSF-binding, ankyrin repeats	
	GLP1 (EuHMT1)		Same as G9a	
	ESET (SETDB1)		Tudor, MBD	
	CLLL8 (SETDB2)		MBD	
SET1 family		Post-SET ($CXCX_4C$)		Lee and Skalnik (2005)
	MLL1 (HRX, ALL1)		AT hook, Bromo PHD, CXXC	
	HRX2 (MLL4)		Same as above	
	ALR (MLL2)		PHD, ring finger	
	MLL3		PHD, ring finger	
	SET1 (ASH2)		RRM, poly-S/E/P	
	SET1L		RRM, poly-S/E/P	
SET2 family		Pre-SET (7-9 Cys); post-SET ($CXCX_4C$)		Kizer et al. (2005)
	WHSC1 (NSD2)		PWWP, PHD, HMG, ring finger	
	WHSCL1 (NSD3)		PWWP, PHD, ring finger	
	NSD1		PWWP, PHD, ring finger	
	HIF1 (HYPB)		WW	
	ASH1		AT hook, bromo, BAH, PHD	

(continued)

Table 1 (continued)

SET family	Members associated	Domains common to the family in addition to the SET domain	Domains unique to particular members	References
RIZ family	RIZ (PRDM2)		C2H2 zinc finger	Jiang and Huang (2000)
	BLIMP1 (PRDM1)		C2H2 zinc finger	
SMYD family		Post-SET ($CXCX_2C$)		Hamamoto et al. (2004)
	SMYD3		Zf-MYND	
	SMYD1		Zf-MYND	
EZ family		Pre-SET (~15 Cys)		Margueron et al. (2008)
	EZH1		2 SANT	
	EZH2		2 SANT	
SUV4-20 family		Post-SET ($CXCX_2C$)		Wu et al. (2013)
	SUV4-20H1			
	SUV4-20H2			

DOT-1 and its homologs share a conserved region with four sequence motifs-I, post I, II and III of the SAM methyl transferase. Although the catalytic domain of DOT1 proteins is structurally similar to arginine methyltransferases, these family of proteins catalyse methylation preferentially at H3K79 in the core of the nucleosome. Since H3K79 methylation plays an important role during embryonic development, over expression of Dot1 was found to disrupt telomeric silencing in yeast screens. Knock out of mDOT1L results in lethality during the time frame of organogenesis in cardiovascular development.

1.2.2 Epigenetic Erasers

Two families of demethylases including the amine oxidases and jumonji C (JmjC)-domain have been documented so far. The Jumonji C(JmjC)-domain contains iron (Fe^{2+}) and alpha-ketoglutarate-dependent dioxygenase which can reverse lysine methylation and has various functional roles in biological processes including DNA/RNA repair pathways. Demethylation of monomethyl arginines to citrulline has been shown to be catalysed by protein arginine deiminase type 4 (PADI4). However, this enzyme is not an arginine demethylase as it works on both the

methylated and unmethylated arginines (Cuthbert et al. 2004). These enzymes are highly conserved from yeast to humans and demethylate histone and non-histone substrates. The histone modifications catalysed by the Jumonji Domain are documented in Table 2.

1.3 Histone Demethylation by LSD1

The activity of LSDI enzyme is limited to di-methylated and mono-methylated lysine residues. Each demethylation cycle requires electrons to be shuttled to molecular oxygen via an FAD/FADH moiety and through production of hydrogen peroxide. Isolation of LSD1 demethylase complexes from mammalian cells revealed that it requires Co-REST, a chromatin associated transcriptional repressor, to demethylate nucleosomal substrates (Lee et al. 2005). LSD1 functions both as an activator and repressor. Association of LSD1 with Co-REST leads to transcriptional repression of neuronal genes in non-neuronal cell lineages. Association of LSD1 with androgen receptor (AR) converts LSD1 to an H3K9 demethylase, allowing it to function as transcriptional activator of androgen receptor in response to hormonal stimulus (Metzger et al. 2005).

Epigenetic mechanisms regulate the function and homeostasis of the central nervous system. Dysregulation of epigenetic machinery has emerged as a major genetic driver of neurodevelopmental and neurodegenerative disorders, intellectual disabilities and autism spectrum disorders. Such epigenomic changes cause perennial alterations in cells of the central nervous system and influence neuronal function and physiology. Brain Derived Neurotropic Factor plays a crucial role in the development, maintenance and plasticity of the CNS and has been associated with several neuropsychiatric disorders like Schizophrenia, Bipolar Disorder and depression (Cohen-Cory et al. 2010; Zagrebelsky and Korte 2014). Methylation patterns are dynamically regulated in neurons by experiential stimuli which in turn regulate memory related genes (Lattal and Wood 2013).

Emerging evidences point to the involvement of the epigenome in the onset and progression of Alzheimer's disease, Parkinson's disease and Huntington's disease. This review focusses on the changes in epigenetic machinery, specifically on the histone methylation and DNA methylation patterns during the onset and progression of neurodegenerative diseases and neuropsychiatric disorders. The power of epigenetic inhibitors as potential diagnostic and therapeutic markers is also discussed.

2 Epigenetic Alterations in Neurodegenerative Disorders

Neurodegenerative disorders manifest as neuronal disabilities accompanied by massive neuronal loss and accumulation of toxic proteins (such as β amyloid in AD and Huntingtin in HD) with progression of the disease (Forman et al. 2004).

Table 2 Epigenetic machinery of Jumonji family of proteins

Subfamily	Name	Synonym	Lysine Demethylase	Arginine Demethylase	References
JHDM1	JHDM1A	KDM2A	H3 (K36me1/2)		Frescas et al. (2008)
	JHDM1B	KDM2B	H3(K4me3/ K36me2)		He et al. (2008)
PHF2/ PHF8	JHDM1D	KDM7A	H3(K9me1/2)		Tsukada et al. (2010)
	PHF8	KDM7B	H3(K9me1/2) H4(K20me1)		Qi et al. (2010)
	PHF2	JHDM1E	H3(K9me1) H4(K20me3)		Baba et al. (2011)
JHDM2	HR		H3(K9me1/2)		Liu et al. (2014)
	JMJD1A	KDM3A	H3(K9me1/2)		Yamane et al. (2006)
	JMJD1B	KDM3B	H3(K9me1/2)		Yamane et al. (2006)
	JMJD1C	KDM3C	H3(K9me1/2)		Chen et al. (2015)
JMJD2/ JHDM3	JMJD2A	KDM4A	H3(K4me3/ K27me3/ K36me3)	H3(R2me2a)	Whetstine et al. (2006)
	JMJD2B	KDM4B	H3(K9me3/ K36me3)		Katoh and Katoh (2007)
	JMJD2C	KDM4C	H3(K9me3)		Pedersen et al. (2014)
	JMJD2D	KDM4D	H3(K9me2/3)		Krishnan and Trievel (2013)
JARID	JARID1A	KDM5A	H3(K4me2/3)		Horton et al. (2016)
	JARID1B	KDM5B	H3(K4me1/2/3)		Zhang et al. (2014)
	JARID1C	KDM5C	H3(K4me2/3)	H3(R2me1/2a/ 2s/R8me2a/2s) H4(R3me2a/2s)	Iwase et al. (2007)
	JARID1D	KDM5D	H3(K4me2/3)		Li et al. (2016)
	JARID2				Pasini et al. (2010)

(continued)

Table 2 (continued)

Subfamily	Name	Synonym	Lysine Demethylase	Arginine Demethylase	References
JmjC domain only	JMJD5	KMD8	H3(K36me2)		Hsia et al. (2010)
	JMJD7				
	TYW5				
	HSPBAP1				
	HIF1AN	FIH			
	JMJD4				
	JMJD6			H3(R2me2a/2s) H4(R3me1/2a/2s)	Chang et al. (2007)
	JMJD8				
	NO66	RIOX1	H3(K4me1/3/K36me2/3)		Eilbracht et al. (2004)
	MINA	RIOX2			
UTX/UTY	JMJD3	KDM6B	H3(K27me2/3)		Xiang et al. (2007)
	UTX	KDM6A	H3(K27me1/2/3)		Agger et al. (2007)
	UTY	KDM6C	H3(K27me3)		Walport et al. (2014)

Diseases such as Alzheimer's accumulate intracellular beta-amyloid plaques and inter cellular neurofibrillary tangles that regulate neuronal death and loss of cognitive abilities leading to dementia (Vila and Przedborski 2003). Mitochondrial alterations, defects in axonal transport and alterations in dendrite pathology are observed in neurons undergoing such transition (Schon and Przedborski 2011; Kweon et al. 2017).

The complex neuronal pathophysiology during ageing and neuronal loss strongly implies distinct roles of chromatin states in regulating neuronal function and identity. It is well established that epigenetic factors are vital regulators of ageing, lifespan and health span in yeast and *C. elegans*. It is known that histone acetylation regulates learning and decline in memory with age in mouse models of Alzheimer's disease (Kawahara et al. 2009: Gräff and Tsai 2013). Chromatin Immunoprecipitation followed by Sequencing (ChIP seq) and single cell sequencing studies have helped unravel changes in chromatin during neurodegenerative processes. Mutations in chromatin related factors, transcriptional regulators like FMR1, alterations in histone acetylome and methylome profiles are distinctly associated with neurological disorders, intellectual disabilities and autism (Bourgeron 2015; Sun et al. 2016). The ability of epigenetic mechanisms to integrate diverse environmental and physiological inputs to generate adaptive long-lasting brain functions regulates multifactorial diseases such as Parkinson's, Alzheimer's, Amylotrophic lateral sclerosis (ALS), Multiple sclerosis and even epilepsy. Ever since it has been proposed that DNA

methylation age measures the cumulative effect of an epigenetic maintenance system (EMS) and hence genomic stability, the epigenetic clock and the ratio of S-adenosyl methionine (SAM) /S-adenosylhomocysteine (SAH) have been used to measure the age of tissues based on methylation markers (Horvath 2013; Levine et al. 2015).

2.1 *Alzheimer's Disease*

Alzheimer's disease (AD) is a complex neurodegenerative disorder that involves multiple pathological processes characterized clinically by progressive loss of memory and neuronal loss. The presence of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau protein are characteristic hallmarks of Alzheimer's disease. Alzheimer's disease can be classified into late-onset AD (LOAD) and early onset AD (EOAD) depending on the age of onset of the disease. LOAD, the more common form of AD affects people above 65 years of age. Mutations in APP (Amyloid precursor protein), PS1 (Presenilin1), PS2 (Presenilin2) and APOε4 are involved in the early onset of familial AD (fAD) which occurs in less than 2% of the cases reported with AD (Wijsman et al. 2005).

Genetic linkage and association studies in the more common form of sporadic AD (sAD) have identified several genetic variants that shows mild or moderate increase in the risk of sAD (Bertram et al. 2007). A recent meta-analysis of four genome wide association studies (GWAS) totalling 17,008 cases and 37,154 controls for probing additional genetic risk factors responsible for AD identified 11 susceptibility risk loci for LOAD. These newly associated loci predicted newer pathways involving hippocampal synaptic function and axonal transport in AD patients (Lambert et al. 2013).

2.2 *Epigenetics of Alzheimer's Disease*

2.2.1 Alteration in Histone Methylation Profiles in Alzheimer's Disease

Human neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and ALS (Amyotropic Lateral Sclerosis) show significant changes in the transcription profile pointing to the involvement of dysregulated chromatin in such cases. Since ageing is a predominant risk factor in neurodegenerative diseases, chromatin alterations and epigenetic changes in ageing brains are vital targets of neurodegeneration. Aberrant changes in histone acetylation and methylation have been implicated in age related neurodegeneration (Akbarian et al. 2013; Nativio et al. 2018). Ageing models of animals show increase in the levels of H3K9me2, H3K9me3 and H3K27me3 in the cerebral cortex and hippocampal regions of these models. Active chromatin marks such as H3K27ac and H3K36me3 show decreased levels in the same regions of the brain in these animal models. Early and late pathological investigations in the hippocampus of mouse

models showed coordinated downregulation of synaptic plasticity genes and upregulation of immune response genes targeted by regulators of the electron transport system. ChIP sequencing attempted on hippocampus CK-p25 mouse models of AD and CK wild type littermates for seven histone markers (active marks, enhancers, repressive marks and marks associated with gene bodies) observed interesting behaviour of the active mark H3K4me3. In these models. 3667 of the upregulated genes corresponding to H3K4me3 peaks were enriched for immune and stimulus response while the down regulated genes corresponding to H3K4me3 peaks showed synaptic and learning functions (Gjoneska et al. 2015).

The active chromatin regulator H3K4me3 is of interest in studies of neurodegenerative disease including Alzheimer's disease because of its influence on synaptic transmission and learning and memory. Presence of H3K4me3 in the nucleus has been shown to directly influence the efficiency of post initiation processes of active transcription and is found globally (∼90%) at RNA polymerase II binding sites.

Progression of Alzheimer's disease from early to final stage has been defined on the basis of the progressive presence of NFT in successive brain regions, with stage I affecting limbic or brain stem regions, and widespread neocortical stage VI and during the end stage of the disease (Braak and Braak 1991). H3K4me3 generally localizes within the nuclear compartment of the cell along with other epigenetic regulators and co-regulates chromatin structure. However, reduced nuclear and increased cytoplasmic localization of H3K4me3 has been observed in the autopsy tissues from hippocampal regions of AD patients (Mastroeni et al. 2015). The observed cytoplasmic localization of H3K4me3 is associated with and even precedes tau markers examined in early Braak stages. The function of the ectopically present molecules in the cytoplasm is not yet known, but existing data suggest that these molecules and H3K4me3 might be involved in Tau hyperphosphorylation and axonal transport. The loss of H3K4me3 from the nucleus might be responsible for the overall decrease in the expression of synaptic genes. Brain derived neurotrophic factor (BDNF) plays an important role in memory formation. Several studies show that BDNF expression is downregulated in AD brains in humans. H3K9 methylation, a determining factor in lower *Bdnf* expression showed age dependent elevation in levels in non-transgenic neurons and further increase in cortical neurons cultured from the hippocampal regions of 3xTg-AD mouse models (Walker et al. 2012).

At initial asymptomatic stages, neurofibrillary tangles (NFT) in cerebrum are restricted to the trans-entorhinal, entorhinal cortices and CA1 region of the hippocampus. Nucleolin (NCL), nucleophosmin (NPM) are major nucleolar proteins acting as histone-binding chaperones and are required for chromatin compaction and regulation of rRNA transcription through H3K9me2. The levels of H3K9me2 and H4K12ac showed decline in CA1 and DG regions of hippocampus neurons of post mortem tissues of AD patients (Hernández-Ortega et al. 2016).

Post translational histone modifications are triggered in response to Aβ, a signalling molecule derived from dysregulated amyloid precursor protein (APP) processing. Aβ oligomers are potent signalling molecules that indirectly modulate transcription by acetylating and methylating H3 lysine residues (AcH3 and H3me2) (Lithner et al. 2013). Aβ also induces genome wide hypomethylation in cerebral

endothelial cell cultures, causing specific hypermethylation and repression of the gene for neprilysin which triggers Aβ deposition.

2.2.2 Histone Demethylases in Alzheimer's Disease

Recent work in the field has suggested a critical role for lysine demethylases in neurodegenerative diseases. Pharmacological inhibition of LSDI in a variety of neuroblastoma cells has been shown to block the mTORC1 pathway in a dose dependent manner. Inhibition of LSD1 was shown to trigger mTOR dependent activation of autophagy in neuroblastoma cells by transcriptionally activating the expression of SESN2. Chromatin Immuno Precipitation (ChIP) experiments showed direct binding of LSD1 to the Transcription Start Site (TSS) of the SESN2 promoter followed by activation of H3 acetylation and decrease of H3K27me3 in neuroblastoma cells. This establishes a novel neuroepigenetic mechanism that may offer new therapeutic routes targetting the autophagy-lysosomal pathway in neurodegeneration (Ambrosio and Majello 2018).

LSD1/KDM1A is an amine histone demethylase which in conjunction with the Co-REST complex, specifically demethylates mono-methylation and di-methylation of K4 on H3K4me1/2 but not on H3K4me3. LSD1 has many roles throughout development and can also be found in terminally differentiated cells throughout the brain. Recent studies showed that the loss of LSD1 in $LSD1^{CAGG}$ mice results in widespread hippocampus and cortex neuronal cell death. LSD1 is continuously required to prevent neuro degeneration that leads to learning and memory defects.

Gene Ontology and Gene Set Enrichment Analysis on transcriptome sequencing datasets with loss of LSD1 have implicated common pathways leading to neuronal cell death which includes activation of genes in the microglia and immune pathways, defect in oxidative phosphorylation, loss of synaptic transmission and failure to maintain cell cycle arrest. Thus loss of LSD1 affects multiple neurodegenerative pathways simultaneously with one or more of these pathways leading to neuronal cell death (Christopher et al. 2017).

2.2.3 DNA Methylation in Alzheimer's Disease

DNA methylation occurs due to the covalent addition of a methyl group from S-adenosyl methionine to the 5′ position of cytosines (5mC) linked to guanines (CpG dinucleotides). About 70% of the promoters in human genome are frequently enriched in CpGs forming the CpG islands. Recent observation suggests that the methylation status of CpGs is associated with transcription repression while methylation of CpGs in gene bodies promoted transcription. DNA methylation is dynamically regulated in the human cerebral cortex throughout the lifespan and involves differentiated neurons.

Diverse cell lines have shown lower levels of DNA methylation associated with AD. While global hypomethylation was detected in the entorhinal cortex region of

post-mortem tissues from AD patients (Liang et al. 2008) widespread hyper methylation patterns correlating with higher levels of 5hmC and 5mC were observed in the middle frontal gyrus (MFG) and the middle temporal gyrus (MTG) regions of AD patients observed in a different study (Coppieters et al. 2014). Studies on single monozygotic twins discordant for AD showed a significant loss of DNA methylation in the temporal neo-cortex neuronal nuclei of the AD twin (Mastroeni et al. 2009).

Decrease in the levels of 5hmC was observed in the post-mortem tissues of hippocampal regions of AD patients when compared to their normal controls and also in the AD twin considered for the study (Chouliaras et al. 2013). However, recent study involving genome wide profiling of 5hmC using post-mortem brain samples of AD patients identified 517 differentially hydroxylated methylated regions (DhMRs) annotated to 321 distinct genes involved in formation of neuritic plaques (NPs) and 60 DhMRs annotated to 49 distinct genes associated with the formation of neurofibrillary tangles (NFTs). This suggests a new dimension of epigenetic regulation by 5hmC that might play an important role in brain aging and neurodegenerative disorders (Zhao et al. 2017).

Various studies on neuronal cells, patient tissues and animal models have recorded aberrant alterations in DNA methylation patterns associated with multiple genes in Alzheimer's disease (Table 3). Such changes in methylation were found to differ among transcription factor binding sites of tau promoter. Folate/methionine/homocysteine metabolism plays an important role in DNA methylation mechanisms. B2 dependent MTHFR (methylenetetrahydrofolate) catalyses the conversion of 5,10 methylenetetrahydrofolate to 5-MTHF which is the methyl donor for the re-methylation of homocysteine (Hcy). Studies on post-mortem prefrontal cortex tissue and peripheral lymphocytes of AD patients show hypermethylation in the promoter region of the MTHFR gene. It is hence well established that the methylation of DNA is critical to epigenetic processes associated not only with the normal brain function and aging but also with AD. Changes in expression of individual genes aids understanding of the pathways and mechanisms involved in AD. The APOè gene represents a bimodal structure with a hypomethylated CpG- poor promoter and a fully methylated 3′ CpG- island, containing the sequence for the ε4- haplotype (genetic risk factor for LOAD) (Wang et al. 2008).

Epigenome wide association studies in prefrontal cortex and superior temporal lobe from 147 AD patient sets identified an extended region of elevated DNA methylation in the HoxA gene clusters across a 48 kb region spanning 208 differentially methylated positions (DMPs) in CpG sites adding to the growing evidence of the involvement of Hox gene in Alzheimer's disease (Smith et al. 2018).

Recent genome wide association studies (GWAS) on DNA methylation in the supratemporal gyrus of 34 patients with AD and 34 controls identified 479 autosomal differential methylated regions (DMRs), the majority of which were hypermethylated in AD cases. These identified DMRs colocalise with other functional epigenetic signatures in brain tissues, most notably hypermethylated DMRs were enriched in poised promoters, characterized by the presence of both H3K4me3 and H3K27me3 (Watson et al. 2016).

Table 3 Gene specific aberrant DNA methylation across different regions of the brain

Sl. No	Gene	Regions of the brain	Methylation status	References
1.	ANK1 Ankyrins	Human (entorhinal, temporal and prefrontal cortex	Increase in methylation in the gene body	De Jager et al. (2014), Lunnon et al. (2014)
2.	APOε4 Genetic risk factor for LOAD	Human prefrontal cortex and lymphocytes	Increase in methylation in the promoter regions	Wang et al. (2008)
3.	APP Amyloid precursor protein	Human prefrontal cortex	Decrease in methylation in promoter region	West et al. (1995), Barrachina and Ferrer (2009)
4.	TREM2 Triggering receptor expressed in myeloid cells 2	Human hippocampus	Increase in methylation in the promoter region	Celarain et al. (2016)
5.	NF-κB, COX2 Pro-inflammatory cytokines	Human frontal cortex	Decrease in methylation pattern in promoter region	Rao et al. (2012)
6.	BDNF A member of the nerve growth factor family of proteins	Human frontal cortex	Decrease in methylation pattern in the promoter region	Rao et al. (2012)
7.	CDH3 Cadherin protein	Human (entorhinal, temporal and prefrontal cortex)	Increase in methylation in the gene body	De Jager et al. (2014), Lunnon et al. (2014)
8.	CREB Transcription factor involved in synaptic plasticity and cognition	Human frontal cortex	Increase in methylation in the promoter region	Rao et al. (2012)
9.	CLU (APOJ) Clusterin (Third most associated LOAD risk gene)	Human neural cells	Unknown	Nuutinen et al. (2005)
10.	DUSP22 Dual specificity Phosphatase-22	Human hippocampus	Increase in methylation pattern in the promoter region	Sanchez-Mut et al. (2013)
11.	KDM2B Lysine demethylase of H2B	Human entorhinal, temporal and prefrontal cortex	Increase in methylation pattern in gene body	De Jager et al. (2014), Lunnon et al. (2014)
12.	MTHFR Convert 5,10—MTHF to 5-MTHF	Human pre-frontal cortex and lymphocytes	Increase in methylation in promoter region	Wang et al. (2008)

(continued)

Table 3 (continued)

Sl. No	Gene	Regions of the brain	Methylation status	References
13.	PCNT (DIP2) Pericentrin localizes to the centrosome and recruit proteins to the pericentriolar matrix	Human (entorhinal, temporal and prefrontal cortex)	Decrease in methylation in gene body	De Jager et al. (2014)
14.	PP2A Dephosphorylation of Tau	Neuroblastoma cells	Decrease in methylation in the promoter region	Vafai and Stock (2002), Zhou et al. (2008)
15.	RHBDF2, HLA-DRB5 Involved in inflammatory responses in AD	Human entorhinal, temporal and prefrontal cortex	Increase in methylation in gene body	De Jager et al. (2014)
16.	S100A2 S100 family of calcium binding proteins	Human cerebral cortex	Decrease in methylation in the promoter region	Siegmund et al. (2007)
17.	SLC2A4 Involved in neural development	Human prefrontal cortex	Increase in methylation in the promoter regions	Yu et al. (2015)
18.	SORBS3 Encoding a cell adhesion expressed in neurons and glia	Human (entorhinal, frontal cortex, temporal), APP/PS1 and 3Xtg-AD	Increase in methylation pattern in promoter region	Siegmund et al. (2007), Sanchez-Mut et al. (2013)
19.	SPTBN4 Spectrin beta 4	APP/PS1,3Xtg-AD and human frontal cortex	Increase in methylation in the promoter	Sanchez-Mut et al. (2013)
20.	TBXA2R Thromboxane A2 receptor	3Xtg-AD, APP/PS1 and human	Increase methylation in promoter region	Sanchez-Mut et al. (2013)
21.	IGFBP7 Insulin- like growth factor binding protein 7	APPPS1-21 and human frontal cortex	Increase in methylation in promoter region	Agbemenyah et al. (2014)
22.	BACE β-Site APP-cleaving enzyme	TgCRND8 Mice models	Decrease in methylation in promoter region	Fuso et al. (2008)
23.	PSEN1 Component of γ-secretase complex	TgCRN8 Mice models	Decrease in methylation in promoter region	Fuso et al. (2008)
24.	Neprilysin An Aβ degrading enzyme	Murine cerebral endothelial cells	Increase in methylation in promoter region	Chen et al. (2009)

3 Huntington's Disease (HD)

Huntington's disease is a rare and progressive neurodegenerative disorder often identified by polyglutamine (Poly Q) repeats on the genome. This disease is inherited as a fully penetrant autosomal dominant trait caused by expansion of CAG repeats within exon1 of the Huntingtin gene. A toxic gain of function (GoF) mutant of Huntingtin protein disrupts multiple intracellular pathways, leading to cognitive impairments and motor disorders, involving the hallmark feature of chorea (involuntary jerky movements of the face and limbs) and gait abnormalities accompanying progressive neurodegeneration. This mutation either leads to depletion of normal Htt (which plays an important role in endocytosis and vesicle trafficking) disrupting synaptic functions or leads to the formation of a misfolded mutant protein (mHtt) which impedes vesicular trafficking and diverse intracellular processes (Zuccato et al. 2010). This repeat instability is regulated by various epigenetic mechanisms which include changes in histone modifications, alterations in DNA methylation patterns and chromatin remodelling factors which in turn influence the degree of striatal degeneration and the age of onset of Huntington's disease (Bedford and Brindle 2012).

3.1 Histone Methylome in Huntington's Disease

Huntington's disease is characterised by transcriptional repression of key neuronal transcripts like neurotransmitters, growth factors and their receptors. Repression of dopamine receptor 2(Drd2), pre-enkephalin (Penk1), cannabinoid receptor (Cb2) and brain derived neurotrophic factor (Bdnf) are implicated in the pathogenesis of Huntington's disease. A critical event underlying transcriptional dysregulation of these key genes is the alteration in the chromatin structure in regulatory regions of these genes. Hence it is important to understand HD pathogenesis through the dimension of regulation of chromatin structure and epigenetic modifications (Zuccato and Cattaneo 2007).

Alterations in H3 methylation are implicated in cognition impairment and intellectual disabilities in Huntington's disease. Early studies of aberrant methylation of histones in HD on mice models R6/2 and N171-82Q demonstrate elevated levels of H3K9me2 and H3K9me3 in the striatum and cerebellum. The levels of histone methylation were shown to decrease on treatment with mithramycin, which prevents H3 hypermethylation in the R6/2 mouse cell line (Ferrante 2004). Mithramycin was shown to prevent brain atrophy, ventricular atrophy and striatal neuronal atrophy seen in R6/2 mice.

Chromatin immunoprecipitation on the HD locus of R6/1 and R6/2 HD transgenic mouse lines has shown correlation in the levels of H3K9me2 (heterochromatin), H3K9ac (euchromatin) and H3K4me3 (Transcription initiation) with the expression levels in the striatum and cerebellum. Also, the levels of H3K36me3 (mark associated with active transcription) and phosphorylated serine of RNA PolII

corelated strongly with CAG instability in R6/1 and R6/2 mice. Furthermore, RNA Pol II at the promoter-proximal region of the HD locus was increased in the striatum when compared to cerebellum contributing to the tissue specific instability of CAG repeats as found in HD (Goula et al. 2012).

Studies on ERG-associated with SET domain (ESET), a histone H3K9 methyl transferase has yielded interesting insights on ESET regulation of neuronal survival in HD models. The levels of ESET/SETDB1 and H3K9me3 are altered in the striatal neurons of HD patients and are insignificantly increased in caudate nucleus in HD brains as compared to control HD striatal tissue brain samples. Combined administration of mithramycin and cystamine were found to significantly reduce the expression level of ESET in R6/2 mice and H3K9me3.This combinatorial treatment also conferred extended survival (by 40%,) enhanced body weight and improved motor activity ameliorating neuropathological conditions in R6/2 mice models (Ryu et al. 2006).

ChIP sequencing experiments on NeuN-selected neuronal cell nuclei from post-mortem prefrontal cortical samples for six HD cases and six non-neurologic controls showed an average of 63% of total H3K4me3 reads mapping to transcriptional start site- proximal peaks and 36% of the distal peaks colocalizing to known enhancer sites. Distal peaks showed differential enrichment of six transcription factors and chromatin remodellers including EZH2 and SUZ12 of the PRC2 (Polycomb Repressive) complex. In HD, PRC2 inhibition is associated with upregulated H3K4me3 (Dong et al. 2015).

Knockdown of histone demethylase (JARID1C) in R6/2 mice models and human HD brains showed that mutant HTT acts to activate cell signalling pathways that impact H3K4me3, which spreads broadly downstream of the transcription start site (TSS). Reduction in the levels of JARID1C or SMCX in primary neurons was found to reverse the downregulation of key neuronal genes triggered by the expression of mutant HTT. This implies the consideration of JARID1C as a potential target for epigenetic therapy for Huntington's disease (Vashishtha et al. 2013). Genome wide mapping approach identified a large number of epigenetically altered loci in the neuronal HD genome, including loss of H3K4me3 and excessive DNA methylation on the hairy and enhancer of split 4 (HES4) promoter as well as altered expression of HES4 and its target genes MASH1 and p21 involved in striatal development. The epigenetic changes at the HES4 gene may hence be used as a novel biomarker for clinical and histopathological outcomes in Huntington's disease (Bai et al. 2014).

The involvement of chromatin remodeling complexes in the pathogenesis of Huntington's disease has been well established. Mutant form of huntingtin (mHtt) has been shown to induce the transcription of α- thalassemia/mental retardation X linked (ATRX), a DNA dependent ATPase/helicase belonging to the Rad54-like subfamily of SWI/SNF chromatin remodelling proteins. Knock down of ATRX was shown to decrease the levels of promyelocytic leukemia nuclear body (PMLNB) and H3K9me3 suggesting that ATRX mediated organization of pericentromeric heterochromatin through increase in H3K9me3 in striatal cells plays a vital role in HD pathogenesis. Elevation in the expression levels of chromatin remodeller ATRX protein in white blood cells of pre-symptomatic and symptomatic HD is a distinct epigenetic signature of Huntington's disease (Lee et al. 2012).

The modulatory polyglutamine region of the huntingtin protein facilitates the activity of epigenetic silencing complex PRC2 and its methyltransferase activity which are important for normal murine embryonic development. Full length endogenous huntingtin was found to be associated with PRC2 subunits in wildtype murine embryoid bodies and with H3K27me3 at HoxB9 while embryos lacking huntingtin showed distinct impairment of PRC2 regulation of Hox gene expression and chromatin silencing function in embryos. Lack of huntingtin protein led to impaired PRC2 epigenetic gene and chromatin silencing function in murine embryos and impaired reestablishment of global histone H3K27me3 in developing embryos, whereas full length recombinant human huntingtin specifically stimulated tri-methyl transferase activity of polycomb repressive complex 2 (PRC2) a multi protein complex with histone methyltransferase activity both in Hdh(Q111) embryoid bodies of mouse and in vitro (Seong et al. 2010).

Recent studies on HD models of *Drosophila melanogaster* showed that loss of function mutation of EZH2, the catalytic subunit of PRC2 responsible for H3K27me3 (mark for facultative heterochromatin), enhances neurodegeneration. Furthermore, epigenetic marks such as H3K27me3 (facultative heterochromatin) showed specific effects on HD pathology with reduction of demethylases Utx1 which rescues HTT induced pathology. Reduction in the levels of key methylase components of PRC2 complex led to aggressive pathology. Manipulation of enzymes which regulates histone marks representative of constitutive heterochromatin like PR-SET7 and HMT420 showed no effects on HD pathology (Song et al. 2018).

Microarray data analysis of HD brain revealed that the RE1 silencing Transcription factor (REST) bound genes are preferentially repressed in HD patients. REST, a master regulator of neuronal genes is highly expressed in immature central nervous system cells and in mature neurons, and is linked to HTT. Wild type huntingtin protein sequesters REST protein in the cytoplasm denying access of REST to its cis-regulatory elements on its target genes such as BDNF. Wild type Htt affects BDNF gene transcription by stimulating the activity of specific promoter of the complex BDNF gene. H3K4me3 enrichment was reduced at the REST/NRSF promoter II, thus suggesting that reduced transcription could be the consequence of changes in chromatin structure at REST binding site and BDNF locus (Buckley et al. 2010).

Recent studies on nuclear lamins showed increased levels of Lamin B in the putamen of Huntington's disease patients as well as in the striatum of R6/1 mouse models of HD. R6/1 mouse model showed increase in the levels of lamin B1 and B2 in the striatum and cortex from the early stages of Huntington's disease while showing elevated levels in hippocampus only at late stages. Lamin A and C were also found to be enhanced in the striatum and hippocampus at late stages but were not altered in the cortex. However, protein levels of the lamin B receptor remained unchanged (Alcala et al. 2014).

Table 4 Region wise gene expression changes in HD/HD models

Gene	Source:	HD model:	Expression status	References
Dnmt3a	Striatum	R6/2 mice	Decrease	Ng et al. (2013)
Dnmt1	STHdhQ111 cells	Cells	Decrease	Ng et al. (2013)
DNMT1	Cortex	Human	Disrupted coexpression	Narayanan et al. (2014)
DNMT3A	Cortex	Human	Disrupted coexpression	Narayanan et al. (2014)
Gadd45a	Striatum	R6/2 mice	Decrease	Tang et al. (2011)
Gadd45b	Muscle	N171-82Q mice	Decrease	Ng et al. (2013)
Gadd45g	STHdhQ111 cells	Cells	Increase	Ng et al. (2013)
Rnf4	Striatum	R6/2 mice	Decrease	Tang et al. (2011)
Rnf4	Muscle	N171-82Q mice	Increase	Jia et al. (2015)

3.2 DNA Methylation in Huntington's Disease

Several studies have observed aberrant DNA methylation patterns in Huntington's patients and HD model systems. Adenosine A_{2A} receptor ($A_{2A}R$), a GPCR which stimulates adenylyl cyclase is highly expressed in the striatum especially in the GABAergic medium sized neurons (MSNs) that express enkephalin. The receptor is severely affected in Huntington's disease (HD). Reduced levels of $A_{2A}R$ were observed in the putamen of HD patients and striatum of R6/1 and R6/2 mice model investigated at later stages of Huntington's disease. Furthermore, an increase in 5mC levels and reduction in 5hmC levels in the 5'UTR of ADORA2AR in the putamen of HD patients was observed. This has led to a gene therapy designed with DNA methyl transferase inhibitors targeted to increase the levels of A receptor in animal models. Expression levels of different genes involved in Huntington's disease specific to brain region are shown in Table 4.

5hmC plays an important role in neurodevelopment. Genome wide reduction of 5-hmC signal in the striatum and cortex of YAC128 (Yeast chromosome transgene with 128 CAG repeats) HD mice has been reported and disease specific differentially hydroxymethylated (DhMRs) in gene body have been identified. These DhMRs associated genes are involved in a number of canonical pathways including neuronal development/differentiation and neuronal function and survival. Alterations of these pathways could play role in HD, thus suggesting that reduction of 5-hmC marker is a novel epigenetic signature in HD featuring impairment of neurogenesis, neural function and survival (Wang et al. 2013).

Recent genome wide DNA methylation profiling of human cortex tissues with a subset of matched liver tissues, from a cohort of HD and control individuals identified novel site-specific differential DNA methylation patterns spanning the promoter and intragenic regions of the HTT, including a differentially methylated

CTCF-binding site in the HTT promoter. This CTCF site displayed increased occupancy in cortex tissue, with higher HTT expression than the one in the liver (De Souza et al. 2016). DNA methylation profiles investigated from whole blood of Huntington's patients however showed no recognizable changes in methylation patterns in HD implying that blood compartments are not strong enough to prove as a viable biomarker to predict age-of-onset of HD (Zadel et al. 2018).

4 Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and affects more than 6 million people across the world. The pathological hallmark of PD involves motor dysfunctions due to loss of dopamine producing neurons in nigro-striatal pathways (Braak et al. 2002), lack of control of voluntary movements, tremor, instability in postures and muscular rigidity. The loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) results in the impairment of the execution of co-ordinated movements. The disease stage is also accompanied by formation of fibrillary cytoplasmic inclusions, known as Lewy bodies which contain ubiquitin and α-synuclein.

4.1 DNA Methylation Profiles in Parkinson's Disease

Genome wide association studies (GWAS) have revealed variations in two of the familial PD genes SNCA and LRRK2 as an important risk factors for sporadic PD (Satake et al. 2009). Mutations in Parkin (Park2) and Pink1 (PTEN induced kinase protein 1) are predominant risk factors for PD (Urdinguio et al. 2009). More than 90% of clinically reported cases of PD are sporadic implying a strong interplay of epigenetic factors in the pathogenesis of Parkinson's disease (Gapp et al. 2014). SNP's in the promoter region or in the 3'UTR of the SNCA gene have been identified in PD patients. SNCA encodes presynaptic protein α-synuclein. Point mutations and multiplications of SNCA causes familial Parkinsonian syndromes with high penetrance. Investigations on the influence of epigenetic changes of SNCA expression on SNpc, putamen and cortex of sporadic PD samples of patients revealed hypomethylation of CpG islands at the promoter and intron 1 of the SNCA gene. Hypomethylation of SNCA intron1 was observed on peripheral blood samples of 490 patients with sporadic PD (de Boni et al. 2015).

High resolution methylation study on alpha synuclein gene (SNCA) reveals no significant difference in the methylation pattern of promoter and intron 1. This inconsistency might be due to the difference in sequencing techniques involved or due to different CpG sites investigated. This cannot be considered as a specific biomarker for PD as similar patterns have also been found in dementia with Lewy bodies and Alzheimer's Disease (Funahashi et al. 2017). Mislocalisation of the DNA

methyl transferase DNMT1 has been observed in post mortem brain samples of PD and LBD patient brain samples. DNMT1 was found to be sequestered in the cytoplasm leading to reduced nuclear fraction in the cells. A global hypomethylation of genes was consistent with the decreased levels of DNMT1 (Desplats et al. 2011).

DNA methylation in sporadic PD is mostly based on homocysteine cycle dysregulation. Comparison of genome wide methylation profile of sporadic PD cases with aged and sexed matched healthy controls revealed a single hypomethylated gene CYP2E1, in the putamen and cortex region of the brain during the later stages of the disease (Kaut et al. 2012). CYP2E1 is predominantly expressed in neurons and colocalized to tyrosine hydroxylase in rat substantia nigra. Enhanced CYP2E1 activity facilitates the formation of potentially toxic metabolites like isoquinolines which are structurally related to dopaminergic neuron 1—methyl 4 phenyl 1,2,3,6 tetra hydro pyridine (MPTP). Thus, altered methylation of genes such as CYP2E1 may contribute to individual susceptibility to PD.

Parkinson's patients undergo a circadian fluctuation with symptoms that involve worsening of motor symptoms during afternoon and evening. Body temperature, blood pressure and cortisol synthesis are also affected in PD. Several clock genes including period (PER1, PER2 and PER3) cryptochrome (CRY1 and CRY2), CLOCK, aryl hydrocarbon receptor nuclear translocator like (ARNT L1, also called BMAL1) and NPAS 2 have been identified in PD pathology. The promoters of seven clock genes examined through Methylation Specific PCR showed CpG islands associated with some of these genes. While most of the clock gene promoters were devoid of methylation, the methylation levels were detectable only in the CRY1 and NPAS2 promoters. The methylation frequency of the NPAS2 was significantly decreased in patients (Lin et al. 2012).

TNF-α, an important inflammatory factor has been also implicated in the pathogenesis of PD. Widespread hypomethylation of TNF-α promoter in the SNpc compared to cortex both in PD patients and in neurologically healthy controls, indicating increased susceptibility of neurons located in SNpc to TNF-α mediated inflammation. Increased concentration of plasma total homocysteine (tHcy) in patients with Parkinson's disease is responsible for cognitive impairment, neuropathy and depression in these patients.

Markers of neurodegeneration (APP, α synuclein) are also associated with cognitive impairment. Blood samples of 87 patients with PD analysed for tHcy, methylmalonic acid (MMA), vitamin B, folate, S-adenosyl methionine (SAM), S-adenosyl homocysteine (SAH), and amyloid-β showed that PD patients with no cognitive impairment had a higher plasma SAM/SAH ratio than with patients with mild or severe cognitive impairment. This relates the cognitive function in patients with Parkinson disease to a higher methylation potential (SAM/SAH ratio) and higher plasma vitamin B6. Vitamin B6 on cognitive function shows an indirect relation to enhanced methylation status and reduction in amyloid β production. The concentrations of tHcy, MMA, and SAH in plasma were higher in patients receiving single treatment with L-dopa compared to the other treatment groups. cognitive function in patients with Parkinson disease was related to a higher methylation potential (SAM/SAH ratio) and higher plasma vitamin B6 (Obeid et al. 2009).

More recent analysis of blood samples from PD patients and controls suggest an increased age acceleration preceding the onset of motor and non-motor symptoms which can be used as a biomarker for PD (Horvath and Ritz 2015).

Epigenome wide association studies (EWAS) from blood samples of PD patients and PD patients with anxiety led to the identification of more than 12,000 genes with differential methylation patterns. These genes are involved in brain centric pathways such as neuroactive ligand-receptor interaction, neutrotrophin signalling, in neurodevelopment and in neuronal apoptosis (FANCC and TNKS2) (Moore et al. 2014). Recent studies on mitochondrial DNA (mtDNA) showed a significant loss of 5-methyl cytosine levels in the D-loop region of mitochondria found in substantia nigra in Parkinson's disease suggesting that mtDNA epigenetic modulation plays an important role in various neurodegenerative disorders including Parkinson's (Blanch et al. 2016).

4.2 Histone Methylation in Parkinson's Disease

Transcription factor Nurr1, which plays a key role in the development and maintenance of the midbrain dopamine cells, plays a part in the pathogenesis of PD and provide and provide an important link to chromatin modifying complexes. Nurr1 is significantly reduced in patients affected with PD. The Co-REST repressor complex which plays a critical role in Nurr1-mediated transcriptional repression, recruits a group of proteins consisting of HDACs, the histone methyl transferase G9a and LSD1, which target promoters leading to transcriptional repression (Saijo et al. 2009).

Microglial activation states can produce either detrimental or beneficial effects in the Central Nervous System. Dysregulated microglial activation state amplifies neuronal damage and contributes to the pathogenesis of Parkinson's disease. Microglial activation states have been classified into two major phenotypes M1 (classical activation) and M2 (alternative activation). Activated microglia are present in the vicinity of degenerating neurons in the substantia nigra regions of PD patients. These activation states may change throughout the pathological process of PD. H3K27me3 demethylase Jumonji domain containing 3 (Jmjd3) plays an important role in M2 polarization. Suppression of Jmjd3 in murine N9 microglial cells and in the substantia nigra region of C57BL/6 mice model for PD inhibited M2 polarisation. The inhibition of M2 polarisation and exaggerated M1 microglial inflammatory responses led to extensive neuronal death. This suggests that Jmjd3 is able to enhance the polarization of M2 microglia by modifying histone H3K27me3, which plays a pivotal role in the switch of microglia phenotypes contributing to the pathogenesis of PD (Tang et al. 2011). PINK 1, which functions as a regulator of mitochondrial homeostasis and apoptosis, encodes PINK1 protein which interacts and phosphorylates ectoderm development Polycomb histone methylated modulator (EED/WAIT 1), inducing relocalisation of EED/WAIT1 to

mitochondria. This interaction may regulate H3K27 tri methylation through positive and negative effects on EED/WAIT1 (Berthier et al. 2013).

Recent investigation using αS (alpha- synuclein) transgenic *Drosophila melanogaster* and human neuroblastoma SH-SY5Y cells showed that αS selectively enhances H3K9 mono- and di-methylation. Epigenetic silencing affects the neural cell adhesion molecule L1 and the synaptosomal-associated protein SNAP25. Eukaryotic Histone Methyl Transferase 2 (EHMT2) might be a key regulator of this modification. Further investigation on REST target genes harbouring RE1 sites, revealed that the promoter region of *SNAP25* occupied with H3K9me2 upon overexpression of αS results in reduced gene expression and ultimately lower protein levels. Thus overexpression of alpha synuclein alters the distribution of histone marks on genes associated with the REST complex resulting in disturbed synaptic activities (Sugeno et al. 2016).

5 Regulation of Histone Methylation in Neuro psychiatric Disorders

5.1 Epigenetics of the Neuropsychiatric Disorders

Neuropsychiatric disorders represent a complex and heterogenous group of disorders involving a variety of factors that regulate pathophysiology of such diseases. Hence, it is difficult to correlate the pathophysiology of these disorders to a single gene. There is significantly increasing evidence that epigenetic mechanisms mediate gene-environment interactions during critical periods of the lifespan and manifest as mental illness (Kendler 2001; McEwen 2000). Though the influence of epigenetic mechanisms on neuropsychiatric disorders are primarily been understood through alteration in acetylation patterns and DNA methylation, the role of histone methylation in regulating Schizophrenia, ADHD, OCD and Bipolar Disorders are emerging in the field.

Alterations in brain transcriptomes in mood and psychosis spectrum disorders are associated with alterations in histone lysine methylation and other epigenetic regulators of gene expression. Cognition decline is often associated with age-dependent decline of synaptic function in brain regions such as hippocampus and prefrontal cortex which are crucial for memory formation and consolidation. Human prefrontal cortex (PFC) plays an important role in complex cognitive behaviour, personality, decision making and orchestration of thoughts and actions. Both the hippocampus and prefrontal cortex regions of the brain are frequently impacted in the neural circuitry of mood and psychosis spectrum disorders. Histone methyl transferase MLL1 is predominantly expressed in the anterior subventricular zone (SVZ) and olfactory bulb of the hippocampus and facilitates proliferation and neurogenesis of Neural Stem Cells (Lim et al. 2009).

5.2 *Schizophrenia*

Schizophrenia is one of the major psychiatric disorders whose onset begins at adolescence, though cognitive disturbances are evident at much earlier phases. Schizophrenia is highly heterogeneous and manifests through major symptoms like psychosis with delusions, hallucinations and disorganised thoughts, cognitive dysfunction and depressed mood and negative symptoms including anhedonia, social withdrawal and poor thought and speech output (Ibrahim and Tamminga 2011). The dopamine hypothesis of Schizophrenia states that the hyperactivity of dopamine D2 receptor neurotransmission in subcortical and the limbic brain regions contribute to positive symptoms of Schizophrenia while the negative and cognitive symptoms are caused due to hypo-functionality of dopamine D1 receptor neurotransmission in the prefrontal cortex (Carlsson and Lindqvist 2009). Further, alterations in GABAergic mRNA expression play a key role for prefrontal dysfunction in Schizophrenia and other neuro developmental disorders.

Anti-psychotics prescribed for Schizophrenia target the dopaminergic or serotonergic receptor system and show therapeutic value in nearly 75% of the patients. The disabling and significant feature of Schizophrenia is cognitive impairment for which no pharmacological intervention has shown therapeutic benefits so far.

5.2.1 Histone Methylation in Schizophrenia

In human brain, glutamatergic neurotransmission is mediated through ligand-gated ion channels, NMDA (*N*-methyl-D-aspartate), AMDA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), kainate (KA) and G-protein coupled metabotropic receptors (m-GluR). Gene promoter specific histone lysine methylation is involved in developmental regulation and maintenance of expression of ionotropic and metabotropic glutamate receptors. Native ChIP assays on cerebral cortex region of samples from diverse age groups have identified histone methylation marks at proximal promoters of 16 ionotropic and metabotropic glutamate receptors (GRIN1, 2A-D, GRM1, 3, 4, 6, 7) genes. H3K4me2 and H3K4me3 (active chromatin marks) showed significant correlation with mRNA levels in immature and mature cerebral cortex while H3K27me3 and H4K20me3 (Silencing Chromatin marks) were upregulated in adult cerebellum and do not correlate with transcription. Differential histone H3-K4 methylation at gene promoters of glutamate receptor gene could thus be considered as a chromatin marker for transcriptional dysregulation in various neuropsychiatric disorders (Stadler et al. 2005).

Hypometabolism and altered gene expression in the prefrontal cortex are associated with negative symptoms and cognitive deficits of Schizophrenia. Cellular metabolism regulates chromatin structure including covalent histone modifications, myelination and other functions. Studies involving histone and gene transcript profiling in the post-mortem prefrontal cortex of 41 subjects with Schizophrenia and 41 matched controls identified high levels of H3R17me associated with

downregulated metabolic gene expression in the prefrontal cortex of a subset of subjects with Schizophrenia (Akbarian et al. 2005).

Study involving peripheral blood lymphocytes from 19 healthy controls and 25 patients with Schizophrenia has provided evidence that this disease is associated with a restrictive chromatin state. Elevated levels of H3K9me2 were observed in Schizophrenia patients as compared to controls. Pharmacological treatment with Trichostatin A (inhibitor of class I, II and IV HDACs effectively preventing the deacetylation of H3K9) decreases the levels of H3K9me2 in lymphocyte cultures from patients with healthy controls (Gavin and Sharma 2009).

In contrast to the methylation patterns observed in specific gene promoters, an interesting study on Schizophrenia patients showed an overall increase in the levels of H3K9me2 in both the lymphocyte and post mortem parietal cortex of patients with Schizophrenia as compared to their non-psychiatric controls. The mRNA expression profiles of G9a and GLP responsible for bulk of genomic H3K9me2 modification and SETDB1, (the only euchromatic HMT to specifically di or tri-methylate H3K9) was also significantly increased thus positively correlating with H3K9me2 levels in the brain regions investigated. Sex-dependent restrictive epigenome studies on 74 participants, (40 patients with Schizophrenia (19 women, 21 men) and 34 healthy individuals (19 women, 15 men) indicate that men with Schizophrenia expressed the highest levels of G9a, SETDB1 mRNA and H3K9me2 protein levels as compared to women (Chase et al. 2013). These studies establish histone methyl transferases as potential therapeutic targets for Schizophrenia and for diagnosis of the disorder.

Maturation of human PFC and rodent cerebral cortex are accompanied by progressive increase in GABAergic mRNA levels, including *GAD1*, which encodes a key enzyme for GABA synthesis. These developmentally regulated changes in mRNA levels were associated with chromatin remodeling at *GAD1*/*Gad1* and other GABAergic gene loci, which correlate with increase in trimethylation of H3K4 in both systems. Post mortem samples from dorso-rostral pole of the frontal lobe of Schizophrenia patients showed significant deficits for *GAD1* mRNA and elevation in H3K4me3 levels in females, but not in males. Decrease in GAD1 mRNA levels corresponded to a decrease in H3K4me3 levels (open chromatin mark) and increase in the levels of the repressive mark H3K27me3. MLL1 is expressed in cortical interneurons and regulates H3K4 methylation at GABAergic gene promoters. Study on male C57BL/6 mice using clozapine (an atypical anti-psychotic drug) showed threefold increase in GAD1 associated H3K4me3 in comparison to the controls. MLL1 occupancy at the Gad1 promoter showed a significant twofold increase after a single dose of clozapine. Thus, clozapine induced histone methylation at the GAD1 locus increases MLL1 expression and its recruitment to the GABAergic promoter (Huang et al. 2007).

A recent study that interrogated histone modifications associated with open chromatin in neurons versus the dorsolateral prefrontal cortex and anterior cingulate cortex of Schizophrenia patients has provided interesting insights on the epigenetic implications of cell-type specific genome organisation and function in the human brain and other tissues. 157 reference maps were generated from dorsolateral

prefrontal cortex (PFC), anterior cingulate cortex (ACC) from neuronal (NeuN+), neuron depleted (NeuN-) and bulk tissue chromatin for epigenetic marks H3K4me3 and H3K27ac. Non-neuronal chromatin was concordant with epigenomic signatures of cortical homogenates from multiple sources investigated in the study while a significant epigenomic distance was observed in histone methylation and acetylation profiles obtained from ACC and PFC neurons. H3K4me3 and H3K27ac signatures in neuronal chromatin were significantly overrepresented by risk variants for Schizophrenia and other neuropsychiatric disorders (Girdhar et al. 2018).

Exome sequencing data from 231 Schizophrenic patients and 34 control trios, identified two de novo loss of function (LoF) variants in the SETD1A gene (which encodes a subunit of histone methyl transferase) which provide evidence for a more general role of chromatin regulators in Schizophrenia (Takata et al. 2014; Girdhar et al. 2018). Recent study involving whole-exome sequences of 4264 Schizophrenia patients identified a strong genome wide association between loss of function (LoF) variants and Schizophrenia risk in SETD1A implying epigenetic dysregulation in the H3K4 methylation pathway in Schizophrenia (Singh et al. 2016).

Whole genome association studies from peripheral venous blood of a homogeneous population of China (119 Schizophrenia patients, 119 recruited from homogenous population in China) identified JARID2 (Jumonji AT rich interactive domain 2) within the Schizophrenia susceptibility locus on chromosome 6p22 to confer genetic risk in multiple populations (Liu et al. 2009). JARID2 plays an essential role for binding of PcG proteins (PRC 2) to target genes leading to transcriptional repression through catalysing the di and tri methylation of H3K27. GABAergic neuronal markers including GAD67 and REELIN (RELN) have been shown to be markedly downregulated in Schizophrenia. REELIN (RELN) an extracellular matrix glycoprotein that controls neuronal cell migration and the lamination of the corticolimbic structures during embryonic development plays a major role in brain development and maturation. Post mortem brain cohorts have demonstrated reduced RELN expression (by 50%) in the prefrontal cortex (PFC), temporal cortex, hippocampus and caudate nuclei of patients with Schizophrenia (Guidotti et al. 2000).

An interesting study on pregnant Swiss Albino ND4 mice models exposed to prenatal restraint stress (PRS) showed that offspring born from stressed mothers display Schizophrenia like behavioural endophenotypes as compared to their controls (offspring born from mothers without stress). Decrease in levels of RELN, GAD67 and BDNF expression and increased levels of DNMT1 and DNMT3a were observed in the GABAergic neurons of the frontal cortex and hippocampus of the offspring born from PRS exposed mice (Matrisciano et al. 2013). Heterozygous reeler mice haplo-insufficient in RELN when treated with HDAC inhibitors Trichostatin-A and Valproic Acid for 15 days showed increase in DNA demethylase activity and restored RELN expression.

GAD67 is an enzyme that catalyses the decarboxylation of glutamate to form GABA in chandelier type GABA interneurons and is associated with working memory deficits in Schizophrenia (Lewis et al. 2005). Neurons in the dorsolateral prefrontal cortex (DLPFC) of post mortem samples of Schizophrenics showed a pronounced decrease in GAD mRNA levels in the neurons of layer I (40%) and layer

II (48%) and an overall 30% decrease in the layer III to VI (Akbarian 1995). The decrease in the level of GABAergic transmission in Schizophrenia is associated with the increased expression of DNMT1. mRNA levels of DNMT1, DNMT3a and DNMT3b were measured in Broadman's area 10 (BA 10), Caudate nucleus (CN) and putamen from post mortem Schizophrenia patient samples. A two fold increase in the mRNA levels of DNMT1 was observed in GABAergic neurons of BA10 layers and the neurons of CN and PT in SCZ while increased expression of DNMT3a was restricted to cortical layer I and II GABAergic neuron in SCZ (Zhubi et al. 2009).

5.3 Bipolar Disorders

Bipolar disorder is a chronic depressive condition characterized by manic-depressive illness, unusual shifts in mood and energy, activity levels and hypomanic episodes reflecting in inability to carry out day to day tasks. Four basic types of bipolar disorders have been documented, with majority of patients being diagnosed either with Bipolar Disorder I (BPI) manic or mixed episodes or Bipolar Disorder II (BPII) with depressed episodes.

5.3.1 Histone Methylation in Bipolar Disorders

The Synapsin family of neuronal phosphoproteins composed of three genes (SYN1, SYN2 and SYN3) are involved in synaptogenesis, synaptic transmission and synaptic plasticity and play significant roles in several disorders such as Schizophrenia, Bipolar disorder and epilepsy. Recent investigations using Chromatin Immuno Precipitation assays on the Broadmann Area 10 (BA10) of the prefrontal cortex of post mortem brains of 13 BD patients showed significant increase in the expression profiles of synapsin variants (SYN1a and SYN2a). The upregulation in the synapsin genes corresponded to a significant enrichment of H3K4me3 (open chromatin mark) levels at the synapsin promoters (Cruceanu et al. 2013).

Depressive illness is correlated with dysregulation of epigenetic regulatory mechanisms, particularly the transcriptionally repressive di-and tri -methylation of histone 3 lysine 9 (H3K9me2/me3) in nucleus acumens (NAc), region involved in the development of anhedonia, the hallmark for depression. Study on C57B1/6 male mice models showed that repeated cocaine abuse potentiated depressive behaviour through reduction in H3K9me2 and G9a/GLP levels in NAc which enhances susceptibility to subsequent social stress.

Lysine demethylases, specifically the Jumonji domain containing demethylases 2 (JmjD2) family that act on H3K9 and H3K36 methylation machinery are critical epigenetic regulators of etiopathology of depression and related disorders. Study on C7B1/6 mice model showed that except JmjD2, the expression of all other known members of JmjD2a, b and c were downregulated in depressed mice in the NAc

region of the mice. Systemic administration of JMJD inhibitor (DMOC) induces depression like symptoms in mice resulting in significant increase in the levels of H3K9me2 and H3K9me3 in NAc region (Pathak et al. 2017). However, direct correlation of these epigenetic dysregulation with bipolar disorder has not been studied yet.

Genome wide association studies across over 60,000 participants from the Psychiatric Genomics Consortium investigating common pathways across Schizophrenia, Bipolar disorder and major depression revealed the strongest association with histone methylation. Histone H3-K4 methylation featured among the top-hits in the Bipolar disorder along with association of multiple immune and neuronal signalling pathways (The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium 2015).

Bipolar disorders and other major psychosis disorders involve dysfunction in GABAergic neurotransmission. Downregulation of glutamic acid decarboxylase regulatory network (GAD1) causes a decrease in the expression of the glutamic acid decarboxylase and impaired gamma aminobutyric acid neurotransmission in brain. The decreased GABAergic neurotransmission is related to the cognitive dysfunction.

DNA methylation changes play a role in the pathophysiology of psychotic disorders. Epigenetic association study targeting GAD1 regulatory network genes from post mortem hippocampal human brain tissue of 8 patients with Bipolar disorder identified DNA methylation patterns to be distinct across circuit locations within the tri-synaptic pathway. 11% of CpG sites within GAD1 regulatory network were identified as DMPs suggesting that DNA methylation is an active process in the dysregulation of GABAergic inter neuronal function. Genes MSX1, CCND2 and DAXX with differential methylation profiles within the GAD1 regulatory network were identified in disease association. *MSX1* encodes Msh homeobox 1 and is a regulator of early central nervous system and craniofacial development and is unique to the hippocampus. *MSX1* is expressed at higher levels in the adult hippocampus than in the foetal hippocampus. It interacts with SUZ12, a component of the Polycomb Repressive Complex 2, to direct H3K27me3 to targeted genomic locations (Ruzicka et al. 2015).

Genome wide methylome analysis from peripheral blood samples of three patients with bipolar disorders using Methyl-DNA immunoprecipitation in association with high-throughput sequencing (MeDIP Seq), identified thousands of differentially methylated regions preferentially located in promoter 3'UTRs and 5'UTR of the genes. Distinct patterns of aberrant DNA methylation around Transcription Start site (TSS) were observed frequently upto 2kb from CGI (CpG island shores) as well as in promoters that lack CGIs. Furthermore, changes in 56 genes obtained from peripheral blood showed consistency with post-mortem brain samples including DNMT1, CACNA1S, PRAME, MYT1L and STAB1. Among these genes CACNA1S on 1q32 and PRAME on 22q11.22 are considered as hotspots for Bipolar Disorders (Li et al. 2015).

Post mortem frontal cortex (Broadmann area 9) shows upregulation of mRNA and protein levels of neuroinflammatory and Arachidonic acid (AA) cascade markers such as AA selective calcium-independent cytosolic phospholipase

A_2(cPLA$_2$), secretory PLA$_2$ (sPLA$_2$-IIA and cyclooxygenase-2 (COX2) along with the loss of synaptic proteins synaptophysin and debrin in patients with Bipolar disorders. Epigenetic modifications are associated with upregulated mRNA and protein levels of AA cascade, neurotrophic and synaptic protein markers. Increased Cox-2 expression in the BD corelated with hypomethylated state of the Cox-2 CpG promoter region. However, other AA cascade markers did not have DNA promoter methylation changes. Furthermore, global hypermethylated DNA in BD brains was observed suggesting decreased transcriptional activity in these disorders. These changes were also associated with significant increase in H3 phosphorylation suggesting an onset of apoptosis (Rao et al. 2012).

A recent study which analysed the methylation status of peripheral venous blood from 150 patients with bipolar disorders identified low levels of methylation at the promoter region of COMT(Catechol- O methyltransferase) and PPIEL (Peptidyl -prolyl isomerase E like). Lower levels of methylation of COMT and PPIEL can hence be closely related to Bipolar disorder and could regulate the level of dopamine (Zhang et al. 2018).

5.4 Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) is a chronic neuro developmental and psychiatric disorder characterized by uncontrollable recurring thoughts and behaviours and affects 3% of the general population. The glutamatergic system which includes glutamate ionotropic receptor NMDA types (GRINs) are the most central nodes with highest degree of connections. 57 such genes are involved in 29 pathways with greatest number of genes involved in hetero trimer G protein signalling pathways and others including the dopaminergic, serotonergic, GABAergic, opioidergic, adrenergic, cholinergic and glutamatergic systems involved in the pathogenesis of the disease (Bozorgmehr et al. 2017).

Whole exome sequencing studies involving 20 simplex OCD parent-child trios have estimated the rate of de-novo (DN) single nucleotide variation in OCD was 2.51×10^{-8} per base per generation. This study also identified 19 DN SNVs (11 missense mutations and one nonsense mutation). Most of the genes harbouring DN SNVs in OCD were located in the human brain and revealed enrichment of immunological and CNS functioning and development pathways (Cappi et al. 2016a).

5.4.1 DNA and Histone Methylation in Obsessive Compulsive Disorder

A Genome wide DNA methylation study of OCD of 65 patients from Chinese Han population with OCD resulted in identification of 2190 unique genes differentially methylated between OCD and healthy control subjects. 4013 of these loci were located in CpG islands and 2478 were in promoter regions.

Pathway enrichment analysis revealed the involvement of actin cytoskeleton, cell adhesion molecules, actin binding, transcription regulator activity to be associated with the risk of OCD (Yue et al. 2016). Gamma aminobutyric acid (GABA) B receptor1 in blood samples at birth, estrogen receptor 1(ESR1), the myelin oligodendrocyte glycoprotein (MOG) and the brain derived neurotrophic factor (BDNF) in blood samples at the time of diagnosis showed significant association with OCD (Nissen et al. 2016).

Recent study investigating the common and unique architecture of ASD, SCZ, BD and OCD identified 10 genes (BDNF, CACNA1C, CHRNA7, DRD2, HTR2A, MAOA, MTHFR, NOS1AP, SLO6A3 and TPH2) to be commonly associated with the aetiology of the disease. These genes are predominantly involved in the dopaminergic and serotonergic pathways, the voltage gated calcium ion channel gene network, folate metabolism, regulation of hippo signalling pathway and the regulation of gene silencing and expression. Hippo signalling pathway was found to be commonly associated with these neuropsychiatric disorders, implicating neural development and neuronal maintenance as key factors in disorder psychopathology (O'Connell et al. 2018; Zhang et al. 2018).

Oxytocin, the most abundant neuropeptide in the brain which acts as a neuromodulator and hormone to its G-protein coupled receptor (OXTR) is linked to neuro-behaviour functions. Oxytocin has been found to be associated with the pathophysiology of OCD. DNA methylation studies from peripheral blood leucocytes on 43 OCD patients and 34 healthy controls investigating methylation pattern of OXTR revealed hypermethylation in CpG Sites of two sequences targets located in the exon III, suggesting that at some critical point of development, environmental factors led to hypermethylation of the OXTR in OCD patients (Cappi et al. 2016b).

Histone methylation patterns in OCD are yet to be investigated in detail. However increase in anxiety and deficits in cognition and memory could be linked to SETDB1 expression in brain. Increased expression and activity of SETDB1 histone methyltransferase in forebrain neurons is associated with an antidepressant-like phenotype in behavioural paradigms related to anhedonia, despair and helplessness. Chromatin conformation capture (3C) and SETDB1 ChIP revealed a loop formation tethering the *NR2B/Grin2b* promoter to the SETDB1 target site positioned 30kb downstream of the transcription start site. SETDB1 -mediated repressive histone methylation at *NR2B/Grin2b* was associated with decreased NR2B expression in hippocampus and ventral striatum, suggesting the role for neuronal SETDB1 in the regulation of affective and motivational behaviours through repressive chromatin remodelling at a select set of target genes (Jiang et al. 2010).

Behavioural problems, including OCD have been shown to be associated with LoF mutations in SETD5. SETD5 encodes a histone methyltransferase that lies within the critical interval for 3p25.Analysis of blood samples of children and young adults recruited to the genetics of learning disability study with moderate to severe intellectual disability provide evidence that the loss of function SETD5 is a relatively frequent cause of intellectual diability and the affected individuals showed phenotypic similarity to those previously reported with a deletion in the critical region of 3p25 (Grozeva et al. 2014).

6 Genome Wide Changes in Autism Spectrum Disorders

Autism spectrum disorders (ASD) are a group of early-onset neurodevelopmental syndromes characterized by symptoms of two categories—defective behavioural impairments including social communication problems and restrictive repetitive behaviours. Neuropathological alterations in autism include megalencephaly (whole brain enlargement) and increased head circumference including increased cortical thickness and abnormalities in cortical morphology. Genetic contribution to autism comes from the studies of mono-zygotic (identical) and di-zygotic (fraternal) twins which showed that the monozygotic twins have a 50% or higher concordance for autism and dizygotic twins have 3% probability for autism.

Autism is a complex disorder that involves large number of genes associated with disease risk and involves interplay of common and rare variants. Whole-Exome Sequencing studies involving 3871 autism cases and 9937 ancestor matched or parental controls using Transmission and De novo association (TADA) identified 33 autosomal genes with false discovery ratio (FDR)$<$ 0.1 and 107 genes with FDR $<$0.3. Out of the total 33 genes, 15 are known ASD risk genes, 11 have been reported previously with mutations but were not classified as true risk genes while 7 are novel genes. The newly discovered genes include ASH1L and MLL3 which play an important role in chromatin remodelling. However, the 107 gene sets with FDR $<$0.3 show evolutionary constraint and incur de novo loss of function mutations in 5% of autistic patients. Furthermore, many genes identified in this study encode proteins for synaptic, transcriptional and chromatin remodeling pathways (De Rubeis et al. 2014).

Primary causes of ASD are highly heterogeneous, however it appears to converge on shared downstream epigenomic changes associated with specific functions. These shared chromatin alterations could in turn be responsible for some of the shared symptoms of ASD.

A genome wide study that involved the redistribution process of H3K4me3 during the transition from early infancy ($<$1) to older ages. This study identified two fold change (503 increased loci and 208 decreased loci) in the genome transcription start site. Furthermore, overlap of 711 differentially obtained H3K4me3 peaks in autistic patients with previously annotated autism risk loci showed significant correlation thus confirming significant overlap between genetic and epigenetic risk architecture in autism (Shulha et al. 2012).

Recent evidence for shared pathways and functional themes among differentially acetylated loci in the autism spectrum disorders comes from the histone acetylome wide association study (HAWAS) that involves chromatin immunoprecipitation sequencing (ChIP-seq) of H3K27ac mark on post-mortem samples from ASD patients. This study revealed aberrations (over 5000 enhancer/promoter loci) in histone acetylation patterns which are widespread in ASD cerebral cortex. Function enrichment analysis of differentially acetylated (DA) peaks in prefrontal cortex and temporal cortex showed similar functional profiles. The increased levels of H3K27ac, showed strong enrichment for genes related to ion channels, synaptic

function and epilepsy/neuronal excitability all of which was previously dysregulated in this disorder and the decreased acetylation pattern was found to be associated with digestive tract morphogenesis, chemokine signaling, HDAC activity and immune responses to microglia. Furthermore, correlating histone acetylation with genotype, greater than 2000 histone acetylation quantitative trait loci (haQTLs) were discovered including casual variants for psychiatric diseases (Sun et al. 2016). Recent study involving genome wide integrative analysis of miRNA expression in postmortem brain from ASD patients and controls, identified miRNAs like has-miR-21-3p and co-regulated modules that are disrupted in ASD. This include hsa-miR-21-3p miRNA the second most abundant miRNA in ASD (Wu et al. 2016).

Despite remarkable advances in genetics and genomics the etiology of around 70% of ASD cases remains unknown. The epigenome-wide association study integrated with the transcriptome study in blood samples from the cohort of idiopathic ASD patients showed significant hypomethylation pattern caused by rare meSNVs at six loci as well as a few clustered epimutations in single-ASD patient. Furthermore, this study also revealed a significant load of deleterious mutations affecting ERMN in ASD as compared with controls thus suggesting ERMN as a novel gene involved in ASD (Homs et al. 2016).

Parallel study involving multiple gene expression profile comparisons with human Alu-inserted genes in ASD samples identified four studies that showed association between Alu-inserted genes and differentially expressed genes (DEGs) in ASD. It was further identified that intronic Alu insertion corresponded DEGs in ASD. Biological functions associated with 320 DEGs with Alu insertion significantly associated with neurodevelopmental disorders and neurological functions involved in ASD. Alu methylation analysis using combined restriction analysis (COBRA) of lympho blastoid cell lines and Alu expression analysis using qRT-PCR also showed that the dysregulation of Alu methylation and expression was not observed in all cases but only in ASD subgroups. This suggests that the classification of ASD individuals into subgroups will help reduce heterogeneity and may lead to the discovery of novel mechanisms associated with Alu element in ASD subgroups (Saeliw et al. 2018).

7 Conclusion

7.1 Therapeutic Interventions Based on the Histone and DNA Methylome and the Challenges

Neurodegenerative and neuropsychiatric disorders present complex aetiology and are regulated by combinations of genetic and environmental risks. Since epigenetic events are the regulators of environmental impact on the genome, investigating epigenetic regulation in the brain is a key to understand the onset and progression of neurodegenerative and neuropsychiatric disorders. The histone and DNA

methylome have provided novel and newer insights into mechanisms of neural development, disease and ageing. Emerging evidences on mutations and functional alterations in the epigenetic machinery have increased our understanding of Alzheimer's disease, Parkinson's disease and Huntington's disease, besides neuropsychiatric disorders. Genome wide alterations in epigenetic modifications therefore show potential to be developed as biomarkers for brain disorders.

DNA methylation patterns on specific genes have been explored as epigenetic markers for Parkinson's disease. However, DNA methylation levels at the α-synuclein intron 1 promoter from substantia nigra of PD patients and blood from PD patients had observed conflicting results. Hence minor differences in DNA methylation levels in patient tissues and selection of genomic loci and CpG sites pose significant challenges in the development of epigenetic biomarkers. The specificity and robustness of α-synuclein based epigenetic biomarkers can be enhanced by reducing variability across patient groups, by analyzing subtypes of PD and by employing this biomarker for early diagnosis.

It is well established that changes in DNA methylation influence the expression of APP, PS1 and Aβ which are intermediates in Alzhiemer's Disease and the hypomethylation of promoters of PS1 leads to over expression of Aβ (Mulder et al. 2005). Hence DNA methylation is a viable target for therapy in Alzhiemer's Disease. Administration of S-adenosyl methionine adjunct to regular antidepressants has been shown to improve cognitive symptoms and memory in patients with depression (Levkovitz et al. 2012).

In neuropsychiatric disorders like Schizophrenia, the clinical manifestations initiate at the prodromal stage followed by a first episode in adolescence and deteriorate further after this episode. Since Schizophrenia shows fluctuating changes with increasing episodes, the identification of epigenetic biomarkers like DNA methylation or demethylation in peripheral blood cells could potentially help in prophylactic treatment leading to the prevention of prodromal phase or the onset of the first epidome or a relapse.

A major challenge in the management of neurodegenerative and neuropsychiatric disorders is early diagnosis. There is no established criterion for early and accurate detection of these disorders through reference value of biomarkers from patient blood or cerebral spinal fluid or through imaging approaches. Epigenetic alterations on the histone and the DNA methylome offer potential diagnostic tools for these diseases and would aid screening of such modifications at early stages and further reversal through epigenetic therapy.

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