Harris *et al.*[142] 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,[140] 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 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.[143] Mutations in the genes encoding elements of the epigenetic machinery can lead to an epigenetic Mendelian disorder.[144] Epigenetic marks contribute to natural human variation[145] and configure the emerging field of neuroepigenetics.[141] Not only nuclear DNA, but also mitochondrial DNA may be subjected to epigenetic modifications related to disease development, environmental exposure, drug treatment and aging.[146] Some epigenetic modifications are conceptually reversible and can potentially be targeted by pharmacological and dietary interventions.[13–16,147]

Age-related neuropsychiatric disorders (from neurodevelopment to aging) are complex diseases in which genomic defects, together with environmental factors and epigenetic alterations, may be involved.[17] Most of these disorders exhibit proteoepigenomic changes resulting from primary genomic traits and/or secondary epigenetic events that induce pathogenic (structural, functional, conformational) changes in key proteins.[148] Consequently, neuroepigenetic perturbations in genes involved in brain development, maturation and aging may alter gene expression and protein synthesis (and conformational protein configuration) leading to neurodevelopmental, neuropsychiatric, and neurodegenerative disorders.[149]

5.4.1 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[150] and brain aging might be influenced by epigenetic changes in the neuronal microenvironment.[151,152]

5.4.1.1 DNA Methylation

Age- and tissue-dependent DNA hypo- and hyper-methylation has been reported.[153] It appears that global loss of DNA methylation predominates in aged cells. DNMT1, which maintains DNA methylation of CpGs, decreases