



## Epigenetic contributions on mental health, neurodevelopmental and neurodegenerative disorders

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### Abstract

The significance of epigenetics for mental health and neurodevelopment to assess the contribution of gene–environment interactions to brain function is becoming increasingly clear. Epigenetic programming functions in respect to the interaction between genetics and the environment. It has the capability to make us thinking about the infraction of the prior assumption of independence between genotype and the environment. Some environmental factors such as diet, maternal behavior, psychosocial or chemical exposures have been shown to alter the progression of epigenetic programming in a significant way during the early development. Since epigenetically modified genes can be reclaimed, methylation silenced genes can be demethylated and histone complexes can be executed transcriptionally active by modification of acetylation and methylation of various histones through drugs and/or other dietary interventions, the rapidly growing field of epigenetics provides a perfect opportunity to design rationale therapeutic strategies. The widespread impact of epigenetic modifications suggests that understanding the underlying mechanisms of epigenetic contributions on mental health as well as neurodevelopmental and neurodegenerative disorders holds a great promise for us to be a rich source of more rationale and even personalized therapeutic interventions to treat these disorders in the near future. In this review, we discussed an emerging idea that epigenetic regulation may provide a mechanism by which environmental events can be encoded at the molecular level where they are recognized to influence brain function and also the future prospects of epigenetic therapies to decrease the burden of diseases by modulating epigenetic mechanisms in various ways.

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## Introduction

Understanding the underlying mechanisms of cognitive functions, neuronal metabolism and mental behavior has been a major goal in the field of neuroepigenetics. Among the various tightly controlled complex processes occurring at different levels, gene expression regulation is especially crucial, as some genes need to be activated while some genes must be suppressed. Epigenetic regulation of the genome involves processes which can edit genomic properties or the interactions between the genome and other elements to induce structural changes in the chromatin leading to transcriptional changes of different genes. These processes may provide a mechanism mediating interplay between genes and the environment, including the now recognized idea of gene–environment interactions.

Epigenome, derived from Greek meaning "above the genome", consists of chemical compounds that modify or mark the genome in a way that tells it what to do, where to do it and when to do it. The word "epigenetics" carries the Greek prefix "epi" (that means above, beyond, on top, after, in addition) and another word "genetics" derived from Greek "genno" (that means give birth representing the science of heredity). Epigenetics can be defined as the reversible inherited changes in gene expression that occur without any alteration in DNA sequence and these changes are enough powerful to regulate the dynamics of gene expression (Lin *et al.*, 2009). Disease susceptibility is a result of intricate interplay between one's genetic endowment and epigenetic marks imprinted on his genome by different endogenous and exogenous factors (Jaenisch *et al.*, 2003).

Three distinct but intertwined mechanisms are considered to be part of the epigenome (Ducasse *et al.*, 2006) which affect transcript stability, DNA folding, nucleosome positioning, chromatin compaction, and complete nuclear organization of the genetic material. They determine whether a gene is silenced or expressed, as well as the timing and tissue-specificity of the expression of these genes in a

synergistic and cooperative manner. These mechanisms are: DNA methylation alterations (methylation on the cytosine bases of CpG islands, loss of imprinting etc.), histone modifications (posttranslational modifications that alter their interaction with DNA and nuclear proteins, such as acetylation, methylation, phosphorylation, ribosylation etc.), and RNA interference through small, noncoding RNAs (miRNA, siRNA).

In this review, we will introduce three major environmental factors involved in influencing epigenetic programming in the brain: diet, maternal behavior and chemical exposure. We will also discuss the ways by which these environmental factors cause disruption of epigenetic processes which may give rise to abnormalities in brain function. Finally, we will discuss the potential of epigenetic therapeutic agents to complement current strategies for diagnosis, prognosis, and prediction of drug responses and assist with therapeutic decision-making of neurodevelopmental and neurodegenerative disorders.

### *Factors influencing epigenetic programming in the brain*

#### *Dietary contributions*

Epigenetic mechanisms that originated from environmental influences program the gene expression in different tissues of the brain and have an extraordinary effect on an individual's mental stability. However, these changes are reversible as enzymes that have methylating; demethylating and acetylating activities among them, which can be used during the developmental stage and in the premature postnatal cross fostering. Survey data recommend that the levels of methyl contents in the diet as well as nutritional restriction during pregnancy have a direct involvement in the epigenetic and gene expression programming in the brain (Patrick *et al.*, 2008).

DNA methylation is very common and has a constant activity in neurons (Levenson *et al.*, 2006) and diet can alter the methylation pattern by influencing the availability of methyl donors as well as DNMT activity

(Ross *et al.*, 2003). Folate, choline, and methionine are important methyl donors. Nutrients like folate, B vitamins and SAM are the key components of the methyl-metabolism pathway and can swiftly alter gene expression especially when the epigenome is first being established during early development. In rodents, it was found that the damages in the synaptosomal/mitochondrial parts of the brain caused by the accumulation of hydroperoxide which originated from lipid peroxidation, conjugated dienes, excess lactate dehydrogenase leaked from synaptosomal membrane can be treated by inactivation mechanisms of L-methionine which can be obtained from dietary sources. L-methionine is an important factor for brains aging and preventing the pathogenesis of neurodegenerative disorders and for neuron survival (Slyshenkov *et al.*, 2002). Methylene tetrahydrofolate-reductase (MTHFR) is used for the formation of methionine from Homocysteine and S-adenosyl-L-methionine through catalyzing the formation of an intermediate L-5-methyltetrahydrofolate, also known as Levomefolic acid. (Friso *et al.*, 2002). Apparently, in both early development rats and adult rats it was found that the methyl group originated from dietary choline helps in producing S-adenosyl-L-methionine which has a high possibility to change the gene expression and gives a better memory performance rather than the ones who were not provided with dietary choline. Choline deficiency in the rodents has clearly shown an impact of how the SAM levels decreased gene specific methylation but increased global methylation as it was followed by the over expression of DNMT mRNA (Kovacheva *et al.*, 2007). Therefore, supplement of choline in the prenatal and development period has shown to enlarge neuron cell proliferation, also the memory power, and potential learning in adulthood (Meck and Williams *et al.*, 2003). Selenium can play role to decrease DNMT1 protein expression and inhibit DNMT1 activity (Wurdinger *et al.*, 2007), zinc and magnesium can help to determine the effectiveness of DNA repair and DNA metabolism respectively. These bioactive components from food can also authorize the SAM formation and also further authorize the formation of CpG methylation

(Ross *et al.*, 2003) and also telomere length may be associated with folate and nicotinic acid levels (Bull and Fenech *et al.*, 2008).

In CBP knock out mice, chromatin acetylation was shown to play role in memory formation (Alarcon *et al.*, 2004). Histone Deacetylase inhibitors can be used as a treatment for memory loss (dementia) as it improves long term memory and establishes the formation of neuronal cells and neuronal sprouting from a damaged neuron in a mouse model with induced neurodegenerative disorder, which suggests that HDACi could be used in treating neurodegeneration and memory loss (Fischer *et al.*, 2007). Dietary components like diallyl disulfide, sulforaphane, and butyrate may act as HDACi (Dashwood *et al.*, 2006). Consumption of Green vegetables like Broccoli contains high levels of sulforaphane, which is identified as anticarcinogen shows that it suppresses histone deacetylase activity (HDAC) as well as couples with H3 and H4 acetylation in circulating peripheral blood mononuclear cells mice within 3–6 hours. Along with broccoli, healthy food components like biotin, garlic organosulfur compounds and Vitamin E metabolites can epigenetically bring back a normal cell from a cancer by HDAC inhibition as they can activate silenced genes in cancer cells (Dashwood and Ho *et al.*, 2007). Depression effects caused due to epigenetical by histone acetylation and subsequent treatment by Sodium butyrate in mice results in decreasing the antidepressant effects (Schroeder *et al.*, 2007). Thus, along with the source and treatment, normal neural functions disturbed due to environmental issues that can be suppressed by certain epigenetical factors obtained from dietary compounds.

Dietary polyphenols such as Epigallocatechin-3-gallate (EGCG), Genistein, Lycopene, Coffee polyphenols, Sulforaphane, Isothiocyanates, Curcumin, Rosmarinic acid, Resveratrol, Anacardic Acid, Garcinol, Green tea polyphenols, Polyphenon B and Theophylline, Allyl-derivates, Isothiocyanates (Sulforaphane and Isothiocyanates derivates), 3,3'-

Diindolylmethane Isopflavone and soy peptides, Quercetin, Dihydrocoumarin, Sanguinarine Isoflavones: genistein and 3,3'-diindolylmethane (DIM), Indole-3-carbinol and phenethyl isothiocyanate etc can act in controlling epigenetic modifications (Alexander *et al.*, 2010).

Offspring can be affected by DNA methylation and epigenetic variation if the food supplements uptake by maternal contains abnormal amounts of methyl releasing compounds (Cooney *et al.*, 2002). It was shown in Avy mouse model that the epigenetic marks established by dietary supplementation with methyl donors can be passed to the subsequent generation through the female germline and these effects are mediated by polycomb group proteins (Blewitt *et al.*, 2006). These outcomes suggest that it is possible that our mental health can be determined by not only what we eat, but also by what our parents ate. For a child's physical and mental health, behavior, and ability, a mother's nutritional status is one main factor, which is considered as an epigenetic factor. This involves appropriate body stores before a mother's conception – vitamins, minerals, proteins, and docosahexaenoic acid (House SH *et al.*, 2013). Responsibility of energy metabolism like neuronal and function signaling, synaptic plasticity and mental health on the brain also involves dietary factors that affect the molecular processes. Omega-3-fatty acid DHA in the plasma membrane of neurons can also be disrupted due to the oxidative stress, resulting damaged neuronal signals. Docosahexaenoic acid DHA is important for mental expression and interneuronal functioning as it is an important factor in plasma membrane function. The Brain derived neurotrophic factor (BDNF) are essential as it functions in neuronal metabolism and synaptic plasticity by activating signaling cascades which is completely dependent on the epigenetical factors like diet. (Gomez and Tyagi, 2013).

Recent studies have showed that nutrition can cause neurodegeneration, which was believed that it could only be caused by genetic factors. Environmental epigenetical modifications cause long-lasting effects

on individual's behavior. Studies suggest that nutritional components like choline, betanine, VitB6, VitB12 or folic acid diminish the cognitive functions which are defined as the cerebral activities involving knowledge, memory, attention and others. Choline supports the membrane functional integrity and helps in acetylcholine synthesis in cholinergic neurotransmission for normal brain development. On the other hand, choline can be an epigenetic modifier of the genome that reconstruct the neuronal gene expression, activity and also in methylation. Individuals with many neurodegenerative disorders and improper mental health were found to have dysregulated choline functions (Bekdash, 2018).

#### *Maternal behavior*

DNA methylation levels at a glucocorticoid receptor (GR) gene promoter in the hippocampus of the offspring was altered by high levels of pup-licking, grooming and arched-back nursing by rat mothers which leads to altered histone acetylation and binding of NGFI-A, a transcription factor, to the GR promoter. Though this programming by maternal behavior is stable and long lasting, but it is reversible by agents that interfere with either the methylation or histone deacetylation machinery (Weaver *et al.*, 2004). The group differences in histone acetylation, DNA methylation, NGFI-A binding, expression of the GR and hypothalamic-pituitary-adrenal responses to stress was abolished by central infusion of HDACi.

The evidence for a nongenomic transmission of individual differences in stress reactivity and maternal behavior was provided by the results of cross-fostering studies with the offspring of low- and high-LG mothers (Francis *et al.*, 1999). Similar findings were found for hippocampal GR expression and for the differences in both the  $\alpha_1$  and  $\gamma_2$ -GABAA receptor subunit expression in the amygdala. These findings indicate that individual differences in gene expression patterns and behavior can be directly linked to maternal care over the first week of life.

Evaluation of brain-paraventricular nuclear region in a mouse model showed that early life stress produced

by maternal-infant separation induces DNA methylation of AVP enhancer region causing excess production of AVP which lead to HPA responsivity and a stress-sensitive phenotype (Murgatroyd *et al.*, 2009). Exposure to maternal abuse by housing the foster dams in an unfamiliar environment with limited nesting resources resulted in decreased BDNF total mRNA in the prefrontal cortex and hippocampus of rats during adulthood associated by a persistent increase in DNA methylation in promoter regions for BDNF exons IX and IV (Roth *et al.*, 2009). These effects were reversed by central infusion of a DNA methylation inhibitor, into adult rats, which indicates that early life abuse causes methylation for gene regions regulating BDNF transcription. Females who were abused as pups displayed abusive behaviors toward their own offspring and their offspring exhibited greater brain DNA methylation of genes that impact BDNF expression also.

A chronic social defeat stress induces subordination and greater avoidance behaviors and less social interaction in mice and this depressive-like phenotype is associated with reductions in hippocampal BDNF gene expression due to long-lasting histone modifications of the BDNF gene, including a marked increase in H3-K27me2 at the BDNF P3 and P4 promoters (Tsankova *et al.*, 2006).

The nucleus accumbens, a chief brain reward center linked to depression in animals (Nestler and Carlezon, 2006) and humans (Tremblay *et al.*, 2005), was studied to compare chronic social defeat to prolonged social isolation in which histone dimethylation marks at lysine positions 9 and 27 associated with reduced gene expression (Kouzarides, 2007), and phospho-CREB (the transcriptionally active form of CREB) binding to gene promoters were evaluated. Significant differences in the relative levels of H3-K9me2 and H3-K27me2 in regions of gene promoters immediately upstream of their initiation sites were exhibited in both chronic social defeat and social isolation exposed mice. On the other hand, increased levels of phospho-CREB in the nucleus accumbens were seen due to social defeat stress and

decreased phospho-CREB levels in the nucleus accumbens was associated with social isolation. These histone methylation and phospho-CREB changes were reversed by the chronic administration of the anti-depressant, imipramine, which demonstrates the role of these epigenetic marks in the mediation of depressive behavior. Reduced hippocampal volume was observed in humans in response to chronic stress and depression which indicates that altered actin remodeling in response to stress may relate to morphological changes in the brain. Surprisingly, some of the inbred mice exhibit resilient response in which the mice resist developing the depressive phenotype. A total of 546 genes showed differential levels of H3 methylation in the susceptible versus the resilient mice. Despite the general similarity in H3 methylation between the resilient and the control mice, there were still some significant differences in methylation status between these two groups which suggest that resilience is an active process reflected by unique chromatin modification that occurs in response to a stressor. Treatment with the anti-depressant, imipramine, produced changes in H3 methylation status that also resembled to that was observed in the resilient mice, indicating that the mechanism of action of this anti-depressant involves a similar H3 chromatin modification pattern (Wilkinson *et al.*, 2009).

Global chromatin re-modeling is differentially sensitive to the duration of exposure of stress (Hunter *et al.*, 2009). Rapid and large chromatin modifications were produced due to acute stress demonstrating that these methylation marks are labile in adults, while chromatin modification in response to chronic stress was less marked. When rats were subjected to novelty, a mild psychological stressor, rapid changes in hippocampal chromatin remodeling were also seen (Chandramohan *et al.*, 2007).

Disruption of epigenetic regulatory mechanisms leads to the accumulation of aberrant epigenetic marks which disrupt neural plasticity and memory formation. For example, deregulated H4-K12 plays a

causal role in age-associated memory impairment suggesting that H4-K12 is an early biomarker for an impaired genome-environment interaction in the aging brain (Peleg *et al.*, 2010). The learned behavioral immobility response of rats in response to re-exposure to forced swimming was observed to be dependent upon chromatin remodeling within the dentate gyrus (Bilang-Bleuel *et al.*, 2005) and chromatin remodeling observed in this model of stress-induced memory appeared to involve glucocorticoid co-signaling through the GR as well as signaling via glutamate receptors (Chandramohan *et al.*, 2008).

Altered HPA stress responsiveness is associated with childhood adversity in humans, which is linked to increased risk for psycho-pathology, including suicide (Pruessner *et al.*, 2004). Significantly reduced total GR mRNA transcript from GR1F exon (the homolog of exon 17 of the rat) and increased GR gene (NR3C1) promoter DNA methylation were observed in suicide victims with a history of childhood abuse (McGowan *et al.*, 2009) and the promoters of the genes encoding rRNA were found to be heavily methylated in hippocampi from suicide victims relative to controls.

Due to epigenetic modifications, there are changes in the transcriptional activity in the experience-dependant plasticity in the hippocampal dentate gyrus (DG) which mainly deals with the arrangement of neuronal connections formed due to a person's experience. It was found in mouse that there was a difference in dorsal DG and ventral DG at transcription and methylation level as environmental factors can escalate the rate of DNA methylation in dorsal and ventral DG especially at NeuroD1 transcription site which brings a change in hippocampal volume, resulting in a different gene expression. (Zhang TY *et al.*, 2018).

#### *Chemical exposures*

Organophosphates (OPs) are potent inhibitors of acetylcholinesterase (AChE) enzyme causing toxicological effects that result from initially overstimulating, and consequently desensitizing,

cholinergic transmission. AChE is essential for rapid hydrolysis of acetylcholine at nicotinic and muscarinic synapses. Some OPs cause developmental neurotoxicity by mechanisms independent of AChE inhibition also (Jameson *et al.*, 2007). For example, the OP chlorpyrifos has been observed to increase the phosphorylation of the Ca<sup>2+</sup>/cAMP response element binding protein (CREB) in neuronal cultures at concentrations well below those that inhibit AChE (Schuh *et al.*, 2002) while tight regulation of CREB activity by Ca<sup>2+</sup>-dependent phosphorylation is critical for normal neural progenitor proliferation and differentiation, dendritic development and cognitive function (Peltier *et al.*, 2007).

Several classes of pesticides such as organochlorine (OC) insecticides, i.e., 4-alkyl-1-phenylpyrazoles, have been shown to interfere with GABA-mediated neurotransmission by binding to the type A family of GABA receptors (GABR) and consequently blocking their ability to mediate chloride fluxes. OC insecticides having polychloroalkane structures can bind to GABR in the mammalian brain and potentially block their ability to conduct Cl<sup>-</sup>, with many having nanomolar affinity for their receptor binding site (Cole *et al.*, 1986). Fipronil, like endosulfan and lindane, has been shown to be a high affinity noncompetitive antagonist for the mammalian  $\beta$ <sub>3</sub>-homopentameric GABR (GABR $\beta$ <sub>3</sub>) (Chen *et al.*, 2006).

Polyaromatic hydrocarbons can mediate their toxicity through the arylhydrocarbon receptor (AhR), such as dioxin, or through selective interactions with ryanodine receptors (RyR) in the brain (Zimanyi and Pessah, 1991). Such as, interactions of non-coplanar polychlorinated biphenyls (PCBs) with RyR, greatly sensitize the release of Ca<sup>2+</sup> from the microsomal intracellular stores (Pessah *et al.*, 2006), and are likely to contribute to imbalances in excitatory and inhibitory neurotransmission and the abnormal development of brain circuitry (Kenet *et al.*, 2007) as RyRs are physically and functionally linked to voltage gated Ca<sup>2+</sup> channels at the surface of the neuron where they form Ca<sup>2+</sup> release units responsible for



generating microdomains of signaling (Ca<sup>2+</sup> microdomains).

#### *Epigenetic therapeutic potential*

Promising *in vitro* and *in vivo* data concerning epigenetic therapeutic potential have been found in various studies, but these are still in early stage of research. Since toxicity has been a serious limitation for the use of those drugs on patients, therefore many of these trials were of small scale and further clinical trials are needed to produce more data.

The widely used DNA methyltransferase (DNMT) inhibitors are mainly cytosine analogs such as 5-azacytidine (commercially available as Vidaza) and 5-aza-2'-deoxycytidine (commercially sold as Decitabine), which are converted to deoxynucleotide triphosphates inside the cell and then incorporated into the DNA during replication in the original C positions as nucleoside analogs. Then they attach to the DNMT enzymes to block their activity, resulting in heritable demethylated DNA (Jones and Taylor 1980). Other types of DNMT inhibitors including non-nucleoside inhibitors such as procainamide, procaine and Epigallocatechin gallate (EGCG) etc. (Segura-Pacheco *et al.* 2003) and agents that target one specific DNMT enzyme (e.g. with antisense oligonucleotides) (Yan *et al.* 2003) have been developed and suberoylanilide hydroxamic acid (SAHA), phenyl butyrate etc. also have been widely used with some success in various studies.

Valproate (VPA) was found to induce the expression of REELIN silenced by methionine through demethylation (Dong *et al.*, 2007; Guidotti *et al.*, 2009). N-(2-aminophenyl)-4-[N-(pyridin-3-yl-methoxycarbonyl)aminomethyl]benzamide derivative (MS-275), a potent brain region-selective HDAC inhibitor (HDACi) expressed a 30- to 100-fold greater efficacy than VPA as an adjunctive to antipsychotics in the treatment of epigenetically induced psychiatric disorders by increasing Ac-H3-RELN and Ac-H3-GAD<sub>67</sub> promoter interaction in the frontal cortex (Simonini *et al.*, 2006). As other benzamide derivatives, such as sulpiride, are also brain-region

selective inhibitors of HDACs, they could be effective in the treatment of epigenetically induced psychiatric disorders too. Tranylcypromine, a non-selective monoamine oxidase inhibitor, has been used as antidepressant as it was found to inhibit LSD1 demethylase (Lee *et al.*, 2006) either by the activation of genes suppressed by the H<sub>3</sub>-K<sub>4</sub>Me<sub>2</sub> demethylating activity of LSD1 in the brain (Shi *et al.*, 2004) or by repressing genes activated by the H<sub>3</sub>-K<sub>9</sub>Me<sub>2</sub> demethylation activity of LSD1 (Metzger *et al.*, 2005). Contextual memory deficits were completely reversed by the administration of histone deacetylases in a mouse model of Alzheimer Disease (Kilgore *et al.*, 2010). HDAC inhibitors exerts significant neuroprotective effects through restoring acetylation levels, inducing both gene activation and repression and therefore represents a very promising therapeutic approach. For example, histone deacetylase inhibitor phenylbutyrate increased brain histone acetylation and decreased histone methylation as well as increased mRNA for components of the ubiquitin-proteasomal pathway and down-regulated caspases implicated in apoptotic cell death, and active caspase 3 immunoreactivity in the striatum in a transgenic mouse model of Huntington Disease (Gardian *et al.*, 2005). Another HDACi sodium butyrate induced hyperacetylation with the activation of specific down-regulated genes, reduced neural and brain atrophy and improved motor performance (Ferrante *et al.*, 2003).

3-deazaneplanocin A was found to deplete Polycomb group components and inhibit histone H<sub>3</sub>K<sub>27</sub> methylation in *in vitro* (Tan *et al.*, 2007). By targeting the enzyme that is responsible for removing methylation from H<sub>3</sub>K<sub>4</sub>, polyamine analogs were successful to inhibit it resulting in up-regulating silenced genes (Huang *et al.*, 2007). However, many more HDAC inhibitors are being tested in xenograft models, and at least a dozen of HDAC inhibitors are in various stages of clinical development (Cang *et al.*, 2009). Synergistic effects on transcriptional activation of HDAC inhibitors and DNMT inhibitors are being tested in clinical trials and initial results have been promising (Issa, 2007).

S-adenosylmethionine (SAM) remained useful in patients suffering from major depression because SAM increased the phosphocreatine levels in the brain (Silveri *et al.*, 2003). SAM also increased catechol-o-methyltransferase (COMT) activity and reduced aggression in a subpopulation of schizophrenic patients, and in female patients reduced depressive symptoms (Strous *et al.*, 2009). SAM was also reported to improve learning ability and long-term potentiation of excitatory postsynaptic potential and population spike impairments that were induced by exposure of the population to lead.

Studies have shown recently that supplementation with folate for a period of 3 years significantly improved the cognitive function domains which have a declining tendency with growing age. An increased level of vitamin B<sub>12</sub> in plasma can result in the reduction of risk of cognitive impairment with dementia or homocysteine-associated dementia. SAM and l-methylfolate have been suggested for providing nutritional therapy in idiopathic mental disorders instead of folic acid and vitamin B<sub>12</sub>. l-Methylfolate has been reported to improve negative, positive, and cognitive symptoms in patients suffering from schizophrenia. (Talal J *et al.*, 2018).

### Conclusion

The findings from various studies showed in this review clearly suggest that dietary factors, maternal behavior and chemical exposure can cause aberrations in the epigenome for the initiation and progression of mental and neuronal diseases. The studies described in this manuscript also provided evidence that targeting the epigenome delayed the onset and progression of the symptoms of neurodevelopmental and neurodegenerative diseases. The interplay between the epigenome and the genome will certainly drive future investigational studies of neurodevelopmental and neurodegenerative disorders to understand the mechanisms of gene-environment interactions of these diseases. We have already entered the era where epigenetics holds great prospect to resolve and explain many unsolved and unexplained questions and issues in modern biology.

Although the pharmacology of epigenetics is still in its infancy, with all the accumulated knowledge about the role of epigenetics in the progression of neurodevelopmental and neurodegenerative disorders, the design of more rational interventions to target or detect epigenetic or epigenomic changes is expected in the near future and the development of these epigenetic/epigenomic alteration-based tests and therapies will complement the science of genomics in making new inroads to effective personalized medicine. More studies of epigenetic contribution on mental health will open the new era for the possibility of epi-genotyping from the blood samples of patients. Furthermore, future studies regarding the identification of epigenetic biomarkers to first define an individual's epigenome will also allow the researchers for the tailoring of epigenetic drugs to specific epigenomes.

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