Chapter

The Role of Epigenetics in Psychosis

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Abstract

Epigenetics (genome - environment interaction) is the study of mitotically heritable, but reversible changes in gene expression without any change in DNA modifications and the chromatin structure. Transition to psychosis is a complex and longitudinal process during which epigenetic changes have been hypothesized and investigated. This process is especially important in individuals at high/ultrahigh risk for psychosis, before the development of full-blown psychosis. Psychoses is a range of complex disorders, where genetic variants explain only a portion of risk. Neuro-epigenetic mechanisms may explain the remaining share of risk, as well as the transition from susceptibility to the actual disease. There is a need for computational model of psychosis integrating genetic risk with environmental factors (epigenetic) associated with the disorder to discover its pathophysiological pathways. Epigenetic dysregulation of many genes has been widely speculated that are important factors involved in etiology, pathophysiology, and course of the psychoses, such as schizophrenia, and mood disorders with psychotic features. In addition, the role of epigenetic changes, including histone and DNA modifications and also targeting microRNAs in the treatment of psychoses is a new field of investigations.

Keywords: psychosis, epigenetic, etiology, pathophysiology

1. Introduction

Epigenetic mechanisms, link between the environment and the genome, are known to play a major role in the structure and also physiology of the human central nervous system (CNS), such as learning, memory, circadian clock and neural plasticity [1–4]. During the last decade, a huge amount of investigations in multi-omics era, including genomics, transcriptomics, proteomics, metabolomics, lipidomics, microbiomics, epigenomics, interactomics, and connectomics have pushed brain development into the "big data" era [5–10]. Multi-directional differentiation ability and self-renewal are two primary properties that characterize embryonic stem cells [11, 12]. The major cell types in the CNS, including neurons, astrocytes, and oligodendrocytes are generated from common neural stem cells (NSC) [13, 14]. There is a large number of interdependent factors, such as epigenetic modifications, pro-inflammatory cytokines, intracellular signaling pathways, and protein complexes play important role in regulating the differentiation potential and fate specification of NSC [11, 15–17]. It is known that the epigenetic mechanisms play an important role, not only in neurogenesis during the periods of fetal life and childhood, but also in neurogenesis takes place during adulthood in the mammalian brain [18].

Recent studies highlighted that microRNAs (miRNAs) as a type of epigenetic modifications, have the pivotal role in balancing the switch from self-renewal to differentiation of embryonic stem cells (ESCs) [19]. Evidence has shown that specific circular RNA (circRNA) expression patterns are significantly associated with adult stem cell self-renewal and differentiation [17]. Epitranscriptomics (chemical modifications on RNA), including N6-methyladenosine (m^6A), 2-O-dimethyladenosine (m^6A_m), N1-methyladenosine (m^1A), 5-methylcytosine (m^5C), and isomerization of uracil to pseudouridine (Ψ) has recently garnered attention, and has biological consequences, such as embryonic stem cell differentiation, brain development, and neurodevelopmental disorders [20, 21].

In the field of mental disorders, epigenetic mechanisms are thought to play a major role in the pathogenesis of the psychoses, including schizophrenia (SCZ) and bipolar disorder (BD) [22–24].

In this review article, after a brief introduction, I will discuss around: 1) the concept of epigenetics, including its definition and applications, 2) epigenetics and psychosis, including an overview of psychosis, and short references to the roles of genetics, environment, and epigenetics in psychosis, 3) the epigenetics findings in psychosis, including a dynamic approach to psychosis, epigenetic findings in prodromal phase of psychosis, in first-episode psychosis, in overt psychosis, and in methamphetamine-induced psychosis.

2. The concept of epigenetics

2.1 Definition

In as early as 1942, Conrad Waddington (as an embryologist) first defined the field. Epigenetics means "above" or "on top of" genetics. Epigenetics is the study of mitotically heritable, but reversible, changes in gene expression that occur without a change in the genomic DNA or histone sequences, principally through modifications in chromatin structure, including DNA and histone. Epigenetics is the study of how our behaviors and environment can cause changes that affect the way our genes work.

The epigenome is a dynamic concept, and refers to the biological mechanisms, which regulate gene expression (such as DNA methylation). Although the epigenome can be altered by environmental factors, but it is stable overall [25].

2.2 Epigenetic mechanisms

These mechanisms are necessary for the regulation of gene expression and chromatin architecture at a genome-wide level in mammalian, including human cells, and play critical roles in both normal human development and disorders. Epigenetic modifications are tissue specific. There are several known mechanisms for epigenetic modification. These mechanisms are DNA and histone posttranslational modifications, including methylation, acetylation, phosphorylation, and ubiquitination, and also non-coding RNAs regulation. The methylation of DNA cytosine residues at the carbon 5 position is a common epigenetic modification that is often found in the sequence context CpG [26].

2.3 Epigenetic applications

Interest in the field of epigenetics, as well as the usage of the term, have increased significantly over the last few years [27]. Up to the January of 2021,

there are 102,898 citations (29,879 reviews, 424 systematic reviews, 328 meta-analyses, and 72,267 other types of articles, including original articles) related to "epigenetics" in PubMed. In 2004, however, this number was 1017 (85 article every month), and rose to 13,125 in 2020 (1094 article every month; ~ 13 times more). In addition, there are 1,016 citations (116 reviews, 26 systematic reviews, 39 meta-analyses, and 835 other types of articles, including original articles) related to "epigenome-wide association study".

The concept of epigenetic has spread into different fields, that do not address just the genetics, such as neuroscience [28, 29], physiology [30, 31], psychiatry [32–34], addiction [35], stress [36–38], and aging [39, 40].

Complex disorders, such as endocrine, cardiovascular, skin, autoimmune, or mental disorders, result from complex interactions between genes and the environment. For example, increased DNA methylation variability may be involved in obesity [41], ischemic heart disease [42], or major depression disorder [43, 44]. Regarding the psychosis, there are 294 citations (118 reviews, 5 systematic reviews, 2 meta-analyses, and 169 other types of articles, including original articles) related to "epigenetic and psychosis", and 1058 citations (416 reviews, 13 systematic reviews, 7 meta-analyses, and 622 other types of articles, including original articles) related to "epigenetic and schizophrenia" in PubMed (accessed on January 2021).

3. Epigenetics and psychosis

3.1 An overview to psychosis

Psychotic disorders are among the frequent and disabling human disorders. In recent years, the concept of psychosis has moved from just a chronic disorder to a more dynamic paradigm. Psychosis is now conceptualized as a progressive mental disorder with transitions across several stages: early vulnerability, at-risk or ultra-high risk (UHR) mental state, first episode, and chronic disorder [25]. Schizophrenia and BD are chronic mental disorders, both considered as "major psychosis"; they are thought to share some pathogenetic factors involving dysfunctional gene x environment interactions [45]. They have heterogeneous psychiatric phenotypes, and their etiology and physiopathology still remain largely unknown [24, 46]. Psychotic disorders are highly heritable, and have polygenic inheritance underlain by pleiotropic genes [34]. So, both the genetic and environmental factors are involved in the etiology and course of the major psychoses, such as major depressive disorder (MDD), BD, and SCZ [47, 48].

3.2 An overview to the role of genetics in psychosis

Although some progress has been made in the understanding of genetic physiopathology of psychoses, and despite success in identifying cytogenetic deletions or insertions, and also genetic variants and polymorphisms associated with them, it seems that the molecular genetic findings could not yet to elucidate the exact molecular pathogenesis of different forms of psychoses [49]. Many candidate genes have been identified showing a very high genetic heterogeneity of psychoses. These genes are overrepresented in synaptic and neurotransmission pathways. Different types of common and rare genetic variants, including single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) with small or large effects have also been identified in the last years. The genetic variations may impact on local DNA methylation patterns [50]. All of these findings are important in clinical

practice as they can lead to therapeutic challenge or genetic counseling, but only a small fraction of psychosis could be easily explained by genetics [24].

3.3 An overview to the role of environmental factors in psychosis

Regarding the role of environmental factors in psychosis, many stressful life events, including obstetric complications, mother tobacco use during the pregnancy, and her physical inactivity, childhood trauma, emotional abuse, physical neglect, heightened sensitivity to stressful events, childhood and adolescent low functioning, affective comorbidities, male gender, single status, unemployment and low educational level have been reported [23, 51]. Trauma during the childhood mediates the epigenome and gene expression profile, and could provide a mechanism underling psychosis [22].

3.4 An overview to the role of epigenetics in psychosis

A large amount of epigenetic research in mental health was performed during the last decade. The results of these efforts have "revolutionary" potentials for the development of new interdisciplinary models of mental health [52]. Evidence show that the risk factors for psychosis were not solely due to the DNA sequence, but also abnormal epigenetic modifications have important role in the etiopathology of these disorders [53]. It has been widely speculated that a wide range of epigenetic modifications of the genome, such as DNA methylation, post-translational histone modifications (in particular the histone 3 lysine 4; H3L4), and non-coding RNAs (such as miRNAs) may mediate gene–environment interactions at the molecular level, and through transcription factors modulate the expression of psychiatric phenotypes, including the variability in symptom severity and family heritability [34, 46].

Several studies have investigated the epigenetic pattern, including DNA methylation pattern in patients with major psychosis in different tissues and associated this epigenetic modification with psychiatric phenotype [54–57]. The main hypothesis for the development of psychotic disorders, proposes that a combination of genetic and environmental factors, during critical periods of brain development, including prenatal and postnatal periods increase the risk for these disorders [46]. The epigenetic mechanisms are important heritable and dynamic means of regulating various genomic functions, including gene expression. These mechanisms orchestrate brain development, adult neurogenesis, and synaptic plasticity. These processes when perturbed are thought to contribute to psychosis, such as SCZ pathophysiology [58]. However, new epigenetic technologies may be able to uncover etiopathogenic mechanisms of major psychosis [59]. For example, There are significant differences were detected in both CpG and CpH modifications between patients with SCZ and healthy controls [59].

4. The epigenetics findings in psychosis

4.1 Epigenetics findings in prodromal phase of psychosis

The research about the complex interactions between the stressful life events with dysregulation of biological stress response systems (such as hypothalamic–pituitary–adrenal [HPA] axis) and genes; epigenetic changes; in one hand, and the initial emergence of psychosis, on the other hand, has increasingly focused on the prodromal phase of psychosis, the period of functional decline that precedes clinical illness [51]. In comparison with general population, childhood adversity

rates would be higher in people at UHR of psychosis [60]. Several models, such as dysfunctional cognitive patterns, and epigenetic dysregulation have been cited to explain the link between trauma and the subsequent onset of psychosis [60].

It has been estimated that around 30 to 40% of UHR individuals convert to full-blown psychosis in the following 24 to 36 months [61]. Conversion to psychosis, especially in high and/or UHR individuals is a longitudinal process during which several epigenetic changes have been described [25]. As a few examples, it has been reported that conversion to psychosis is associated with specific methylation changes in two regions, including 1q21.1 and a cluster of six CpG regions located in glutathione s-transferase mu 5 (*GSTM5*) gene (chr1p13.3) promoter [62]. Bang et al. [63] suggest that epigenetic alterations of oxytocin receptor (*OXTR*) gene, located on chromosome 3 (chr3p25.3) can be detected before the development of full-blown psychosis (**Table 1**).

Chromosomal region	Gene	Epigenetic modification	Reference
chr1p13.3	glutathione s-transferase mu 5 (*GSTM5*); six CpG regions	Methylation	[62]
Two regions of chr1q21.1	Intergenic	Methylation	[62]
chr3p25.3	oxytocin receptor (*OXTR*)	Methylation	[63]

Table 1.
An overview to the epigenetic studies in prodromal phase of psychosis.

4.2 Epigenetics findings in first-episode psychosis

The onset of psychosis is the result of complex interactions between genetic vulnerability to psychosis and response to environmental and/or developmental changes. Epigenetic modifications mediate the interplay between genes and environment leading to the onset of psychosis [62]. It has been hypothesized that the neural diathesis-stress model proposes that different stressors act on a pre-existing vulnerability and thus triggers the presenting symptoms of psychosis [64].

The global DNA hypomethylation; increased methylation and reduced gene expression of GTP cyclohydrolase 1 (*GCH1*, located on chromosome 14 [chr14q22.2]), hyperexpression of udE neurodevelopmental protein 1 like 1 (*NDEL1*, located on chromosome 17 [chr17p13.1]), AKT serine/threonine kinase 1 (*AKT1*, located on chromosome 14 [chr14q32.33]), DICER1 antisense RNA1 (*DICER1*, located on chromosome 14 [chr14q32.13]), and hypoexpression of drosha ribonuclease III (*DROSHA*, located on chromosome 5 [chr5p13.3]), catechol-O-methyltransferase (*COMT*, located on chromosome 22 [chr22q11.21]), and disturbed in schizophrenia 1 (*DISC1*, located on chromosome 1 [chr1q42.2]) have all been reported in first-episode psychosis [22].

Hypomethylation has been founded among all CpGs analyzed within the promoter of glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*) gene, located on chromosome 12 (chr12p13.1) in patients with first-episode patients with SCZ and greater LINE-1 type transposase domain-containing protein 1 (*L1TD1P1*) gene, located on chromosome 1 (chr1p31.3) methylation in patients and their siblings [65].

Human endogenous retroviruses (HERV) have been widely associated with the etiology of SCZ. The lower endogenous retroviral sequence K 2 (*ERVK2*, located on chromosome 19 [chr19q11]) methylation levels have been reported at early stages of SCZ [66].

Chromosomal region	Gene	Epigenetic modification	Reference
chr14q22.2	GTP cyclohydrolase 1 (GCH1)	Hypermethylation	[22]
chr17p13.1	udE neurodevelopmental protein 1 like 1 (*NDEL1*)	Hyperexpression	[22]
chr14q32.33	AKT serine/threonine kinase 1 (*AKT1*)	Hyperexpression	[22]
chr14q32.13	DICER1 antisense RNA1 (*DICER1*)	Hyperexpression	[22]
chr5p13.3	drosha ribonuclease III (*DROSHA*)	Hypoexpression	[22]
chr22q11.21	catechol-O-methyltransferase (*COMT*)	Hypoexpression	[22]
chr13q33.1	disturbed in schizophrenia 1 (*DISC1*)	Hypoexpression	[22]
chr12p13.1	glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*)	Hypomethylation	[65]
chr1q42.2	LINE-1 type transposase domain-containing protein 1 (*L1TD1P1*)	Hyperexpression	[65]
chr19q11	endogenous retroviral sequence K 2 (*ERVK2*)	Hypomethylation	[66]
chr12p13.1	glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*)	Hyperexpression	[67]

Table 2.
An overview to the epigenetic studies in first episode psychosis.

Working memory and executive functions impairments emerge in first-episode psychosis, and even prior to its onset. It has been reported that NMDA receptor hypofunction is a feature of early postnatal development, with epigenetic hyper-repression of the glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*), located on chromosome 12 (chr12p13.1) promoter being a contributing factor. This loss of NR2B protein may induce synaptic dysfunctions during development and may underlie early cognitive impairments in patients with SCZ (**Table 2**) [67].

4.3 Epigenetics findings in overt psychosis

Although numerous studies have examined psychosis-associated gene expression changes, epigenetic studies of psychosis are in their infancy [55]. For example, it seems that DNA methylation plays an important role in SCZ; directly as a mechanism of pathogenesis or as a risk biomarker [68]. Different epigenetic modifications have been reported in psychosis, genes implicated in dopaminergic, serotonergic, GABAergic and glutamatergic pathways [45, 46]. Specific changes in promoter DNA methylation activity of genes related to SCZ such as reelin, BDNF and GAD67, and altered expression and function of mGlu2/3 receptors in the frontal cortex have been reported [45].

Abnormal neuronal processes, including dopamine imbalance, may be the central to the pathogenesis of major psychosis. DNA methylation, transcriptomic, and genetic-epigenetic interactions in major psychosis converged on pathways of neurodevelopment, synaptic activity, and immune functions [69]. It has been suggested that hypomethylation of the enhancer at insulin-like growth factor 2 (*IGF2*, located on chromosome 11 [chr11p15.5]) may enhance dopamine synthesis associated with major psychosis. This enhancer targets the nearby tyrosine hydroxylase (*TH*, located on chromosome 11 [chr11p15.5]) responsible for dopamine synthesis [69].

Walton et al. [70] suggest that epigenetic alterations (DNA methylation) in genes implicated in neurodevelopment (such as Sp6 transcription factor; [*SP6*] gene, located on chromosome 17 [chr17q21.32]) may contribute to a brain-based biomarker (amygdala/hippocampal volume ratio) of psychotic psychopathology.

Reelin (RELN) is a large secreted extracellular matrix glycoprotein that helps regulate processes of neuronal migration and positioning in the developing brain by controlling cell–cell interactions [71]. Reelin located on chromosome 7 (chr7q22.1) is one of the most frequently studied candidates in methylation studies of SCZ [26]. Reelin is mostly synthesized in GABAergic neurons of corticolimbic structures. Reelin binds to AUP1 lipid droplet regulating VLDL assembly factor (*AUP1*, located on chromosome 2 [chr2p13.1]), apolipoprotein E (*APOE*, located on chromosome 19 [chr19q13.32]), and α3β2 Integrin receptors located on dendritic shafts and spines of postsynaptic pyramidal neurons. It has been shown that altered *RELN* expression in patients with SCZ and BD patients is associated with altered epigenetic homeostasis [72].

The loss of the human brain regions laterality (such as in temporal lobe, basal ganglia and white matter microstructure) is one of the most consistent modalities in SCZ and BD [73–75]. This loss of brain laterality corresponds to aberrant epigenetic regulation of transforming growth factor beta 2 (*TGFB2*, located on chromosome 1 [chr1q41]) and changes in transforming growth factor beta superfamily (TGFβ) signaling [76]. These findings may be potential avenues for disorders prevention/treatment.

In their metagenome-wide association study (MWAS), Aberg et al. [26] found that MINDY2 lysine 48 deubiquitinase 2 (*MINDY2*, located on chromosome 15 [chr15q21.3-q22.1]), a part of the networks regulated by microRNA (as an epigenetic regulator), is linked to neuronal differentiation and dopaminergic gene expression [77–79], that has potential relevance to SCZ.

Epigenetic alterations of oxytocin receptor (*OXTR*) gene, (located on chromosome 3 [chr3p25.3]) occur across psychotic disorders. It has been reported that patients with SCZ (especially in women) show higher levels of DNA methylation. This pattern of *OXTR* methylation is associated with poorer emotion recognition, smaller volumes in temporal-limbic and prefrontal regions [80].

Discoidin domain receptor 1 (*DDR1*) gene is located on chromosome 6 (chr6p21.33). *DDR1* hypermethylation has been found in patients with psychosis. This hypermethylation is associated with mental stress, and neutrophil-to-lymphocyte ratios [81].

The brain parvalbumin deficits are a consistent finding in SCZ and models of psychosis. Greater methylation of parvalbumin (*PVALB*) gene, located on chromosome 22 (chr22q12.3) is found in hippocampus of the patients with SCZ. The LINE-1 type transposase domain-containing protein 1 (*L1TD1P1*) gene methylation, as a measure of global methylation, is also elevated in both regions of hippocampus and prefrontal cortex in SCZ [82].

Associations between altered DNA methylation of the serotonin transporter-encoding gene (*SLC6A4*, located on chromosome 17 [chr17q11.2]), and early life events, and mood disorders have been reported. Childhood trauma exposure may be a robust environmental risk factor for psychosis. However, not all exposed individuals develop psychotic symptoms later in life [83]. Hypermethylation of the CpG site in *SLC6A4* is involved in the pathophysiology of SCZ, especially in male patients harboring low-activity 5-HTTLPR alleles [84].

Histone deacetylases (HDACs) are enzymes that regulate cognitive circuitry. HDAC expression positively correlate with cognitive performance scores [85]. Postmortem brain studies support dysregulated expression of the histone deacetylase enzymes, HDAC1 and HDAC2, as a central feature in disorders, including SCZ

Chromosomal region	Gene	Epigenetic modification	Reference
chr11p15.5	insulin-like growth factor 2 (*IGF2*)	Hypermethylation	[69]
chr17q21.32	Sp6 transcription factor; (*SP6*)	Hypermethylation	[70]
chr7q22.1	Reelin (*RELN*)	Hypoexpression	[72]
chr1q41	transforming growth factor beta 2 (*TGFB2*)	Hypoexpression	[76]
chr15q21.3-q22.1	MINDY2 lysine 48 deubiquitinase 2 (*MINDY2*)	Hypoexpression	[77–79]
chr3p25.3	oxytocin receptor (*OXTR*) gene	Hypermethylation	[80]
chr6p21.33	discoidin domain receptor 1 (*DDR1*)	Hypermethylation	[81]
chr22q12.3	parvalbumin (*PVALB*)	Hypermethylation	[82]
chr1q42.2	LINE-1 type transposase domain-containing protein 1 (*L1TD1P1*)	Hypermethylation	[65]
chr17q11.2	serotonin transporter-encoding gene (*SLC6A4*)	Hypermethylation	[83, 84]
chr1p35.2-p35.1	histone deacetylase 1 (*HDAC1*)	Hypoexpression	[85]
Chr6q21	histone deacetylase 2 (*HDAC2*)	Hypoexpression	[85]

Table 3.
An overview to the epigenetic studies in overt psychosis.

and BD [86]. It has been reported that HDAC expression is lower in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal gyrus, and higher relative HDAC expression in the cerebral white matter, pons, and cerebellum of patients with SCZ (**Table 3**) [85].

In utero exposure to diethylstilbestrol (DES), psychosis is associated with specific methylomic modifications that could impact neurodevelopment and neuroplasticity [87].

It seems that the neuronal synapses are fundamental units of mental activities. Despite the diverse origins of specific molecular dysfunctions of mental disorders, disruption of synaptic regulation, which is fundamental to behavioral adaptation to the environment, is so important. A novel class of molecular regulators of fine synaptic tuning known as long non-coding RNA (lncRNA) operates as epigenetic modifiers and enhancers of proteome diversity [88]. Non-coding RNAs, including specific microRNAs and lncRNAs provide a novel and complex mechanism of gene regulation [89]. Evidence shows remarkable alterations of the expression of lncRNAs in mental disorders, such as SCZ, suggesting the disruption of fine synaptic tuning underlying psychosis [88].

4.4 Epigenetics findings in methamphetamine-induced psychosis

Methamphetamine (MAP) causes severe substance dependence and psychosis, similar to SCZ, through the alterations in gene expression [90]. Evidence shows that epigenetic factors may play important role in methamphetamine psychosis. Nohesara et al. [91] found statistically significant DNA hypomethylation of the promoter regions of dopamine receptor D3 (*DRD3*, located on chromosome 3 [chr3q13.31]), dopamine receptor D4 (*DRD4*, located on chromosome 11 [chr11p15.5]), *MB-COMT*, and *AKT1* associated with increased expression of the corresponding genes in patients with methamphetamine psychosis. It is suggested

Chromosomal region	Gene	Epigenetic modification	Reference
chr3q13.31	dopamine receptor D3 (*DRD3*)	Hypomethylation	[90]
chr11p15.5	dopamine receptor D4 (*DRD4*)	Hypomethylation	[90]
chr22q11.21	catechol-O-methyltransferase (*COMT*)	Hyperexpression	[90]
chr14q32.33	AKT serine/threonine kinase 1 (*AKT1*)	Hyperexpression	[90]
chr7q22.1	Reelin (*RELN*)	Hypoexpression	[89]
chr10p13	tRNA aspartic acid methyltransferase 1 (*TRDMT1*)	Hypoexpression	[89]

Table 4.
An overview to the epigenetic studies in methamphetamine-induced psychosis.

that MAP can alter DNA methylation of *RELN* and tRNA aspartic acid methyltransferase 1 (*TRDMT1*, located on chromosome 10 [chr10p13]) genes in hippocampus dentate gyrus, and decrease in *RELN* mRNA in the frontal cortex. These alterations might be related to SCZ-like psychotic symptoms of MAP psychosis (**Table 4**) [90].

5. Summary and future directions

5.1 Summary

In this review article, after a brief introduction, I discussed the concepts of psychosis and epigenetics, and also references to the roles of genetics, environment, and epigenetics in psychosis. In addition, I mentioned the epigenetics findings in prodromal phase of psychosis, first-episode psychosis, overt psychosis, and also in methamphetamine-induced psychosis.

Psychotic disorders, such as SCZ and BD are among the frequent, disabling, progressive, and chronic human mental disorders, and have heterogeneous psychiatric phenotypes. Psychosis has several stages, including early vulnerability, at-risk or ultra-high risk mental state, first episode, and chronic disorder. It seems that dysfunctional genes x environment interactions influence their pathogenesis. Psychotic disorders are highly heritable, and have a polygenic inheritance pattern. Despite success in identifying cytogenetic changes, many candidate genes in synaptic and neurotransmission pathways, and also genetic polymorphisms, including SNPs and CNVs associated with psychosis, the molecular genetic findings could not yet explain its exact molecular pathogenesis. Although all of these findings are important in clinical practice, such as therapeutic challenge or genetic counseling, but only a small fraction of psychosis could be easily explained by genetics. However, the genetic variants explain only a portion of risk, and the epigenetic mechanisms may explain the remaining share of risk. In addition, many stressful environmental factors, such as obstetric complications, childhood trauma, different forms of child abuse or neglect have also been reported to play roles in the association with psychosis. These factors mediate the epigenetic modifications, and could provide a mechanism underling psychosis.

Epigenetics means "above" or "on top of" genetics. It refers to the biological mechanisms, which regulate gene expression. Epigenetics is the study of reversible changes in gene expression without any change in chromatin structure. The DNA methylation of cytosine residues at the carbon 5 position is a common epigenetic modification. Interest in the field of epigenetics has increased significantly over the last few years. It plays a key role in the structure and also physiology of the

human CNS, and also in the development of complex disorders, such as endocrine, cardiovascular, skin, autoimmune, and mental disorders. Epigenetic mechanisms, including DNA and histone modifications, and also non-coding RNAs are especially important mechanisms to detect the people with high/ultrahigh risk for psychosis.

A large amount of epigenetic research in mental health was performed during the last years, and these efforts have "revolutionary" potentials for the development of new interdisciplinary models of mental health. The main hypothesis for the development of psychotic disorders, proposes that a combination of genetic, environmental, and developmental factors increase the risk for these disorders. It has been widely speculated that a wide range of epigenetic modifications of the genome may mediate gene–environment interactions and modulate the expression of psychiatric phenotypes. There are some epigenetic dysregulations in prodromal phase of psychosis, to find the people at UHR of psychosis. During the conversion to psychosis, especially in high and/or UHR individuals, several epigenetic changes have also been described. Epigenetics findings in first-episode psychosis shows that the epigenetic modifications of many genes lead to the onset of psychosis. In addition, numerous studies have examined many psychosis-associated gene expression changes in overt psychosis, including methamphetamine-induced psychosis. For example, several epigenetic modifications in genes implicated in dopaminergic, serotonergic, GABAergic and glutamatergic pathways, have been reported in psychosis.

5.2 Future directions

Attempting to predict future is so difficult. This is particularly true in the field of psychiatry. This in mainly due to essential deficiencies in understanding the etiopathogenesis of mental disorders. For example, mapping the relationship between human epigenetics and mental and psychiatric phenotypes is a challenging task. It is essential to shift paradigm in understanding the etiology and pathophysiology of different forms of psychosis.

During the last years, a large amount of studies in multi-omics era have pushed brain development into the "big data" era, and may promise to answer major questions of psychiatry [92]. Nowadays, there are available web-based tools for integration and interpretation of omics data. Although a large amount of studies has been performed and significant progress has been made in past years, different factors, including the high heritability, clinical heterogeneity (etiological and symptomatological), and genetic and epigenetic heterogeneity of psychosis still post as major challenges to the epigenetic dissection of this complex syndrome. However, understanding of epigenetic mechanisms is important to understand the pathogenic pathways in complex disorders, including psychosis [93]. The epigenetic studies could represent a promising approach to better understanding and treating mental disorders. The methylation modifications may be used as diagnostic markers of disorder phenotype and predict the progression and response to treatment. So, the targeted epigenetic pharmacotherapy, in combination with other types of effective interventions, will be effective for future personalized psychiatry for patients [94].

Despite significant progress in identifying the mechanisms underlying psychosis, there are no valid biomarkers for both disorder phenotyping and treatment response. It seems that psychiatric diagnosis based on biomarkers will be more valid and reliable than symptoms-based diagnosis. The discovery of biomarkers, such as epigenetic biomarkers in mental disorders will help in the prevention, diagnosis, and treatment of patients with these disorders [95]. DNA methylation may play an important role in psychosis as a biomarker of risk. Blood DNA-methylation signatures show promise of serving as a biomarker of SCZ [96]. However, the sensitivity

and stability of epigenetic alterations in specific genes make them promising candidates for robust biomarkers [94, 97].

Finally, there is a need for computational model of psychosis integrating genetic risk with environmental, and developmental factors associated with the disorder to discover its pathophysiological pathways, and more accurate treatment targets for psychosis. Hopefully, the epigenetics may provide new insights into a more comprehensive interpretation of mental disorders, such as psychosis and might eventually improve the nosology, treatment, and prevention of these complex disorders.

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