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Review

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# DNA methylation in schizophrenia: progress and challenges

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**Abstract** Schizophrenia is a heterogeneous psychiatric disorder broadly accepted being caused by genetic and environmental factors. Although conventional genetic studies have identified some candidate genes for schizophrenia, low odds ratios and penetrance, and a lack of reproducibility have limited their explanatory power. Despite the major efforts made toward identifying environmental factors in schizophrenia, methodological limitations and inconsistent findings of epidemiological reports have obstructed attempts to identify exogenous causal factors. Epigenetic mechanisms, mediating between environment and genes, have recently been proposed to play an important role in the pathogenesis of schizophrenia. DNA methylation is the most stable and well-characterized epigenetic modification. In this paper, we briefly introduce DNA methylation mechanisms, genome-wide DNA methylation studies, and identify specific genomic methylation sites in individuals diagnosed with schizophrenia. The outline candidate genes such as *Reelin* and *COMT*, are also outlined before paying attention to the conundrum of recent researches.

**Keywords** Schizophrenia · Epigenetics · DNA methylation · *Reelin* · *Catechol-O-methyltransferase*

## 1 Introduction

Schizophrenia (SZ) comprises positive and negative symptoms, cognitive deficits, and affective symptoms. It affects approximately 1 % of the global population [1]. Although conventional genetic studies have identified some candidate genes for SZ [2], low odds ratios and penetrance, and lack of reproducibility have limited their explanatory power. Peculiarities, such as incomplete concordance between monozygotic twins, are difficult to explain purely by Mendel's laws [3, 4]. Although major efforts have been made to identify environmental factors of SZ [5], methodological limitations and inconsistent findings of epidemiological reports have obstructed attempts to identify exogenous causal factors in SZ. The study of epigenetics, especially DNA methylation, the most stable and well-characterized epigenetic modification, has revealed a mechanism by which environmental risk factors induce epigenetic alterations to genes, such as the activation or silencing of gene function involved in the etiology of SZ [6]. In this review, we will briefly describe DNA methylation mechanisms, their relevance to SZ, and the conundrum of recent researches.

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## 2 DNA methylation mechanisms

DNA methylation is catalyzed by a family of enzymes called DNA methyltransferases (DNMTs) [7]. The DNMT family includes DNMT1, DNMT3 (3a and 3b), and the newly recognized DNMT 3L. DNMT 3L is catalytically inactive but shares homology with DNMT3 [8]. DNMT1 is considered the major enzyme participating in maintaining methylation, whereas DNMT3 contributes to de novo methylation [9]. During the process of DNA methylation, DNMTs catalyze the fifth position of cytosine (5c) in a cytosine–guanine dinucleotide (CpG) and transfer a methyl group (provided by S-adenosylmethionine [10]) to 5c to produce 5-methylcytosine (5 mc). DNA methylation serves as a repressive signal in gene transcription, as it disturbs the binding of transcription factors, attracts relevant proteins and then initiates chromatin compaction leading to gene silencing [11].

Whole-genome DNA methylation studies indicate that DNA methylation mainly occurs at CpG sites, which are classified into CpG islands (CGIs), CGI shores, CGI shelves (regions flanking CGIs) according to the GC content in the genes [12]. CGIs contain greater than normal amounts of GC content. According to the location in the genes, methylated CpG sites are located mostly in promoter regions rather than in gene bodies, 3′-UTRs, or intergenic regions [13].

DNA methylation mechanisms may underlie alterations to synaptic plasticity. For instance, exposure to DNMT inhibitors leads to demethylation of many synaptic plasticity-associated genes, such as the brain-derived neurotrophic factor gene (*BDNF*) and the *Reelin* gene (*RELN*) in postmitotic neurons of the hippocampus [14]. Interestingly, levels of total DNMTs change with the induction of long-term potentiation (LTP) and LTP can enhance the demethylation state of *RELN* and *BDNF* promoters in the medial prefrontal cortex (mPFC), suggesting that alterations in DNA methylation status are involved in synaptic plasticity [15].

Not all CpG sites are methylated. There is a cell-specific distribution model of methylation in CpG sites [16]. Moreover, methylation status changes dynamically throughout the life span, following environmental changes [17]. More importantly, DNA methylation in humans can be preserved during cell meiosis and transmitted across generations [18].

## 3 The current state of DNA methylation in schizophrenia

From 2002 to 2013, the number of published empirical articles has grown rapidly (Fig. S1). The possible role of DNA methylation in SZ has been illustrated by studies of postmortem brains, peripheral blood, saliva, and rodent animal models. Depending on the research objective, various techniques are applied to analyse DNA methylation patterns, including genome-wide DNA methylation studies and methylation detection of specific sites, particular in candidate genes such as *RELN* and *catechol-O-methyltransferase* (*COMT*).

### 3.1 Genome DNA methylation in schizophrenia

Since 2007, there have been 13 published articles focusing on the alterations in whole-genome DNA methylation in SZ patients (Table S1, data from: http://www.ncbi.nlm.nih.gov/pubmed). Shimabukuro et al. [19] firstly found that genome hypomethylation in peripheral blood cells is present in male but not female SZ patients. Subsequently, hypomethylation status of peripheral blood cells was widely observed in SZ patients (but without gender differences), not only in case–control [20–24], but also in discordant twin pair studies [25, 26]. Recent advances in DNA methylation profiling have propelled us into an exciting era of investigation of the coverage of methylated sites across the whole genome. For example, using the next-generation sequencing (NGS), a recent methylome-wide association study was performed in peripheral blood cells of a large sample (759 SZ patients and 738 healthy controls). From this study, many sites that may serve as potential biomarkers of SZ were identified [27]. However, only minorities of studies have found no significant differences in genome methylation between SZ patients and healthy controls [28].

Analysis of human brain tissues provide more reliable evidence. Several studies have recently investigated genome methylation in central tissues of SZ patients [29–31]. Analysis of aberrant methylation profiles in the frontal cortex [29–31] and the anterior cingulate [29] primarily involved in SZ found that methylation disruption of numerous loci associated with neurodevelopment and neurotransmission. In addition, genome methylation in SZ patients may be affected by several factors, including medications, onset age, and illness duration. Haloperidol treatment was associated with higher levels of genome methylation compared to risperidone, clozapine, and olanzapine, and earlier onset was correlated with lower levels of genome methylation [20].

In summary, studies of both peripheral and central tissues suggest the key role of aberrant global DNA hypomethylation in the etiology and pathogenesis of SZ. These findings also suggest the use of noninvasive tissues such as peripheral blood cells as a future diagnostic indicator of SZ.