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REVIEW ARTICLE

Epigenetic mechanisms in schizophrenia and other psychotic disorders: a systematic review of empirical human findings

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Abstract

Schizophrenia and other psychotic disorders are highly debilitating psychiatric conditions that lack a clear etiology and exhibit polygenic inheritance underlain by pleiotropic genes. The prevailing explanation points to the interplay between predisposing genes and environmental exposure. Accumulated evidence suggests that epigenetic regulation of the genome may mediate dynamic gene–environment interactions at the molecular level by modulating the expression of psychiatric phenotypes through transcription factors. This systematic review summarizes the current knowledge linking schizophrenia and other psychotic disorders to epigenetics, based on PubMed and Web of Science database searches conducted according to the PRISMA guidelines. Three groups of mechanisms in case–control studies of human tissue (i.e., postmortem brain and bio-fluids) were considered: DNA methylation, histone modifications, and non-coding miRNAs. From the initial pool of 3,204 records, 152 studies met our inclusion criteria (11,815/11,528, 233/219, and 2,091/1,827 cases/controls for each group, respectively). Many of the findings revealed associations with epigenetic modulations of genes regulating neurotransmission, neurodevelopment, and immune function, as well as differential miRNA expression (e.g., upregulated miR-34a, miR-7, and miR-181b). Overall, actual evidence moderately supports an association between epigenetics and schizophrenia and other psychotic disorders. However, heterogeneous results and cross-tissue extrapolations call for future work. Integrating epigenetics into systems biology may critically enhance research on psychosis and thus our understanding of the disorder. This may have implications for psychiatry in risk stratification, early recognition, diagnostics, precision medicine, and other interventional approaches targeting epigenetic fingerprints.

Introduction

Schizophrenia is a complex mental disorder affecting around 0.5−1% of the global population, causing high personal distress and economic costs [1]. It is linked to substantial morbidity [2], significantly diminished life expectancy [3], and poor clinical and societal recovery rates [4]. Schizophrenia is characterized by a broad phenotype

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including "positive" symptoms, reflecting disturbed contact with reality, often taking the form of hallucinations and delusions, and/or "negative" symptoms, such as anhedonia, avolition, and attentional impairment. Its underlying causes include environmental and genetic factors, pointing to a multifarious etiology [5].

Genome research has revealed an additional layer of regulation of genes and gene-associated proteins, i.e., epigenetics, which encompasses meiotically and mitotically heritable alterations in chromatin function and structure [6]. For example, the role of epigenetics in cancer is evident across most stages of tumor development and progression stages [7]. Epigenetic mechanisms also regulate important brain-related functions, such as neurogenesis, neurodegeneration, neuronal activity, and cognition [8], serving as a promising avenue for unraveling the etiology of complex traits and diseases of the central nervous system [9].

Epigenetics may be particularly relevant for understanding schizophrenia and other psychotic disorders. Despite intensive research efforts, insufficient biological markers have yet been identified [10], with findings often lacking consistency and referring to competing hypotheses. Notably, the estimated heritability of schizophrenia and other psychotic disorders is high (60–80%) [11]. However, non-Mendelian irregularities [12], a concordance rate in monozygotic twins reaching 50% [13], the discovery of many rare variants with low penetrance [14], including hundreds or even thousands of contributing risk loci with small effect sizes [15], and genetic overlap with other psychiatric and neurodevelopmental disorders [16], cumulatively make the genetic pattern far from clear. This stimulates many questions about the ways in which genes are regulated and globally orchestrated in health and disease. Notably, the primary suggested environmental risk factors for schizophrenia are in action during periods critical for early neurodevelopment, when crucial epigenetic reprogramming events drive cell replication and tissue differentiation [17]. The environment may continue to shape epigenetics into early adulthood and across lifespans, with epigenetic mechanisms possibly acting as downstream effectors of environmental signals. On the other hand, epigenetic marks may also record altered gene expression [18]. However, as opposed to the conserved nature of DNA sequences, epigenetics may operate through the regulation of genomic function independently [19]. The dynamic and interactive nature of epigenetics may thus contribute to the multi-level etiology of most psychiatric conditions, including psychosis. Although the integration of antipsychotics in clinical practice has revolutionized symptom management, many patients still experience incomplete responses to medication, side effects, and/or cognitive deficits [20]. The epigenome may also be a dedicated target of future pharmacological intervention [21]. Notably, several antipsychotics, such as clozapine and haloperidol, have been found to influence epigenetic signaling [22]. Accordingly, epigenetics may provide a functional interface between genotype and phenotype, offering a platform for harmonizing disparate findings between biological pathways and environmental exposures [5]. Given the above rationale, epigenetics presents molecular processes valuable for understanding schizophrenia and other complex polygenic psychotic disorders.

DNA methylation, post-translational histone modification, and RNA interference, particularly through microRNAs (miRNAs), are three epigenetic mechanisms (Fig. 1). DNA methylation, the most documented epigenetic mechanism, implies the covalent transfer of a methyl group (CH_3) to the fifth position of the cytosine ring. By blocking the binding of transcription factors at gene promoters and by altering chromatin structure, methylation constitutes a crucial regulator of gene expression and gene silencing [23]. However, the association between methylation and gene expression is far more complex and may differ in directionality (i.e., typically being inverse for promoters [24] and commonly negative for gene methylation [25], with other sequence regions also influencing this link [26]), as well as varying among cells, tissues, diseases, and symptoms. Histone modifications, referring to modifications to the proteins that package and order DNA into nucleosomes, most often involve histones 3 (H3) and 4 (H4). Such occurrences may be transcriptionally permissive or repressive, depending on the residues and the added modifying groups [27]. The third epigenetic category involves miRNAs, which are single-stranded non-coding RNAs that engage in posttranscriptional repression or mRNA destabilization of many targeted genes [28]. These mechanisms were chosen based on their important regulatory roles within the nervous system [29]. Non-coding RNAs are epigenetic modulators that may also be targets of epigenetic modification [30]. There is growing evidence indicating that they may be underlying elements in the pathology of psychiatric diseases [31].

After surveying the published literature, we summarize the current understanding and determine the quality of the association between an extended phenotype of schizophrenia and other psychotic disorders (excluding bipolar disorder) and epigenetic regulation. To our knowledge, there are only two systematic reviews in this field, a conceptually driven narrative review [32] and a comparison of DNA methylation in schizophrenia and bipolar disorder limited to peripheral tissues [33]. The current systematic review considers several epigenetic mechanisms in their tissue-specific contexts, including both brain and peripheral tissues (i.e., blood or saliva). Global methylation represents the total genomic

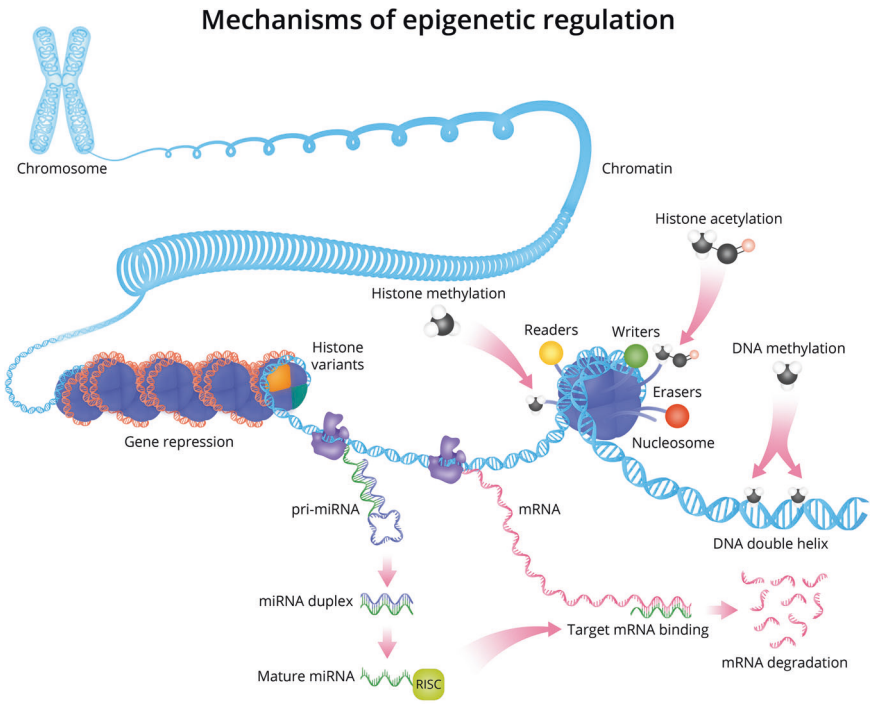

Fig. 1 Overview of epigenetic regulatory mechanisms. Methylation involves the addition of methyl groups to DNA sequences. Histone modifications (usually through methylation or acetylation) exert effects through the relaxation or compaction of nucleosomes, thereby activating or repressing transcription, respectively. MicroRNAs (miRNAs) affect gene expression as a post-transcriptional mechanism, through the inhibition of protein translation or the destabilization of target transcripts. miRNAs are transcribed as primary precursor molecules (pri-miRNA) that undergo nuclear cleavage. The miRNA duplex binds to RNA-induced silencing complexes (RISCs), while the mature miRNA assembles into RISCs, which catalyze the degradation of messenger RNAs (mRNAs).

methylation status, while candidate gene studies focus on predefined genes. Thanks to the advent of high-throughput sequencing methods, more extensive DNA methylation maps can be developed in a hypothesis-free manner. Histone modifications and miRNAs constitute two separately analyzed categories, adding to the broad spectrum of epigenetic control over the genome reviewed in this work.

Materials and methods

Study identification and eligibility criteria

The present study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34]. PubMed and Web of Science searches were conducted using the predifined search terms (see Supplementary Material) to find studies published by January 15, 2019. Retrieved records were screened according to the following inclusion criteria: (a) record content type for original experimental articles; (b) study population for studies of human tissue; (c) diagnosis for schizophrenia or other psychotic disorders including schizophreniform and schizoaffective disorders (bipolar disorder was not considered); (d) study design for case–control studies with healthy controls as a comparator group; (e) target mechanisms for reports on DNA methylation, histone modification, and miRNA expression; (f) focus variables for epigenetic studies using case–control design for the primary study objective (focal point on unrelated variables, e.g., medication or method validation, led to exclusion); (g) record language and format for peer-reviewed articles with their main text in English.

Data extraction

The following information was extracted from each included study: (1) sample size and sex (cases, controls); (2) mean age and standard deviation (standard error, alternatively); (3) diagnostic instrument; (4) ancestry (country); (5) antipsychotic medication; (6) tissue source; (7) method; (8) main findings from case–control contrasts. Some category-specific data were also retrieved: gene/locus, gene expression–methylation relationship, histone residues, miRNA expression status, secondary findings, and biological functionality.

Quality assessment and risk of bias

The quality of each individual study was determined independently by two authors (LS, VJ) using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment of

Case–Control Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). In cases of disagreement, a consensus opinion was reached (for 9% of the included studies). Two indices of interrater reliability were used, percent agreement and kappa statistic [35], to additionally account for the agreement expected by chance.

Results

Summary of included studies

From the initial pool of 3,204 retrieved records, after elimination of duplicates, there remained 2,161 potentially eligible records. The titles and abstracts were screened for content, and 295 underwent a full-text evaluation, which was also conducted for any study whose exclusion was questioned. Reasons for exclusion and a flowchart of record processing are given in the Supplementary Material (Table S1, Fig. S1). In total, 152 studies (reported in 142 articles; 10 records included data on two mechanisms or tissues examined here) met our criteria concerning in total 27,713 individuals (14,139 cases; 13,574 controls). In most studies (76%), the diagnosis followed DSM-III, DSM-IV, or DSM-5 criteria. Patients diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, and other psychotic disorders were included in 139, 8, 2, and 2 studies, respectively, and a single study included cases with a diagnosis of postpartum psychosis. Eighty-nine studies described findings from medicated (36 studies) or mostly medicated (37 studies) cases (60–97% of each sample), one from an equally medicated and unmedicated group (50–50%), 22 from unmedicated (21 studies) or mostly unmedicated (1 study) cases, while forty studies did not report the medication status.

Article quality and interrater reliability

According to the NHLBI guidelines, the quality of 71% of the included studies were rated fair ($n = 108$), 9% were rated good ($n = 14$), and 20% were rated poor ($n = 30$). The agreement for quality between the two assessors was 92.54% (high), while Cohen's kappa was $\kappa = 0.75$ (moderate). The main limitations encountered were unclearly defined sample characteristics and neglect of potential confounders (items 2 and 12, Supplementary Material, Tables S2, S3).

DNA methylation

Global methylation

Of the 10 global methylation studies, three assayed brain tissue and seven assayed blood (Table 1A). Three reports calculated average or threshold beta values from a genome-wide assay [36–38], two investigated LINE-1 elements [39–41], and two used either a luminometric methylation assay [42] or *Hpa*II/*Msp*I restriction-based evaluation [43], while two older studies utilized high-performance liquid chromatography [44] or radiolabeled [^{3}H]dCTP-extension assays [45]. Four studies revealed no differences, while three found higher methylation levels and the remaining three found lower methylation levels for cases related to controls.

Candidate gene approach

Among 64 candidate gene studies, 22 focused on post-mortem brain tissue, 38 on blood, and 4 on saliva (Table 1B). The majority investigated promoter regions (primary regulatory units), 35 of 64 studies focused on genes related to the following main neurotransmission systems: dopaminergic (18 studies), GABAergic (12 studies), serotonergic (9 studies), glutamatergic (4 studies), and cholinergic (1 study). Methylation status was quantified primarily by pyrosequencing/methylation-specific PCR. There were 27 hypermethylation and 20 hypomethylation effects, 3 simultaneous region-dependent lower and higher methylation effects (indicated by ↓ and ↑, respectively), and 14 results revealing no differences (indicated by x). The following genes were the top six with significant effects: *BDNF* (3↓, 1↑, 3x), *MB-COMT* (4↓, 1x), *COMT* (2↑, 1↓, 2x), *RELN* (3↑, 5 ×), and *HTR2A* (2↑, 1↓). Hypomethylation of *MB-COMT* was the most consistent finding in this category.

Genome-wide methylation

Among 29 genome-wide methylation studies, 14 investigated brain tissue and 15 investigated bio-fluid (i.e., blood) (Table 1C). Fifteen studies utilized 450 K arrays, while five and one used 27 and 12 K arrays, respectively. Four studies utilized methyl-CpG binding domain protein-enriched sequencing, while another four used methylated DNA immunoprecipitation with sequencing. Overall, these studies identified numerous differentially methylated CpGs, often including additional analyses to determine functional associations with genes.

Histone modification

Only seven studies (Table 2) met our criteria for post-translational histone modifications, three in the brain and four in lymphocytes. Changes occurring at residues H3K4, H3K9, H3K14, H3K27, H3S10, or H4K12, including (di-/tri-)methylation, acetylation, and phosphorylation, were examined. Three families of assays, ELISA kits,

Table 1 Details of studies reporting DNA methylation in association with schizophrenia and other psychotic disorders.

Global DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Measure of global methylation	Method	↑ ↓ X	Main findings	Secondary findings
	Cases	CTRLS	Cases	CTRLS									
Brain postmortem tissue													
Alelú-Paz et al. [36]	SZ(sci): 19 (19/0)	HC: 3 (3/0)	80.72 ± 9.46	75.00 ± 8.66	DSM-IV-TR	NR (Spain)	NR	DLPFC, AC, HIPP	Number of methylated ($\beta \geq 0.75$) and unmethylated ($\beta \leq 0.20$) CpG sites	Illumina Infinium HumanMethylation 450 K BeadChip	↑	Significantly more methylated CpG sites in SZ (overall); Significantly more methylated CpG sites for DLPFC and HIPP in SZ; Significantly more unmethylated CpG sites for AC in SZ	–
Fachim et al. [41]	SZ: 15 (11/4)	HC: 16 (11/5)	52.60 ± 18.18	67.25 ± 12.73	RDC	NR (UK)	*M*	PFC, HIPP	LINE-1 methylation	BPS	↑	SZ-associated hypermethylation for PFC and HIPP	–
Viana et al. [37]	SZ: 41	HC: 47	–	–	DSM	NR (UK, Canada)	NR	PFC, STR, HIPP, CBL (LNDBB, DBCBB)	Average beta-value for all CpG sites from 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	X	No significant differences for any of the brain regions	–
Biofluid													
Bromberg et al. [45]	SZ: 28 (10/18)	HC: 26 (10/16)	39 ± 13.7	42 ± 10.0	DSM-IV	NR (Israel)	*M*	Leukocytes	Digest of genomic DNA by restriction enzymes (*Hpa*II, *Msp*I, *Dpn*I)	Radiolabeled [^{3}H]dCTP-extension assay	X	No significant difference	Methylation lower in SZ smokers and higher in SZ females
Jiang et al. [43]	SZ: 264 (150/114)	HC: 221 (134/87)	43.99 ± 0.76	35.96 ± 0.60	NR	Asian (China)	*M*	Leukocytes	Global 5mC and 5hmC levels	*Hpa*II/*Msp*I restriction-based EpiMark 5hmC/5mC Analysis Kit and FPDM	↑	SZ-associated increased 5mC levels; SZ- and male-associated increased 5hmC levels (but decreased levels in female SZ)	Positive correlation between global 5hmC levels and age in HC; Negative correlation in SZ
Li et al. [39]	SZ: 92 (62/30)	HC: 92 (62/30)	40.54 ± 10.50	40.28 ± 9.84	DSM-IV	Asian (China)	*M* ≈ 88%	PBMCs	LINE-1 methylation (S1, S2, S3)	BS-OLE assay	↓	SZ-associated hypomethylation for S1 and S3	Significant female-dependent and age-related increase in LINE-1 methylation in HC; non-significant for SZ
Melas et al. [42]	SZ: 177 (87/90)	HC: 171 (–/–)	51.6 ± 9.1	–	DSM-IV	NR (Sweden)	*M*	Leukocytes	HpaII/MspI (CCGG sites)	Luminometric methylation assay (LUMA)	↓	SZ-associated hypomethylation	Haloperidol medication associated with higher methylation; Early onset associated with lower methylation
Misiak et al. [40]	SZ(FE): 48 (21/27)	HC: 48 (23/25)	25.92 ± 5.16	26.08 ± 2.76	DSM-IV ICD-10 (OPCRIT)	Caucasian (Poland)	*M* ≈ 77%	Leukocytes	LINE-1 methylation	COBRA PCR, restriction digestion and quantitation	X	No significant difference for the SZ(FE) vs. HC contrast	Significantly lower LINE-1 methylation for the SZ(FE) subgroup with a history of childhood trauma
Nishioka et al. [38]	SZ(FE): 18 (11/7)	HC: 15 (10/5)	22.8 ± 4.5	23.3 ± 4.0	DSM-IV SIPS	Asian (Japan)	*M*	PBMCs	Average beta for all CpG sites from 27 K arrays	Illumina Infinium HumanMethylation27 BeadChip Kit	↓	SZ(FE)-associated lower methylation for all CpG sites and inside CpG sites (but no differences for outside CpG sites)	No differences between males and females
Shimabukuro et al. [44]	SZ: 210 (124/86)	HC: 237 (108/129)	–	–	DSM-IV	Asian (Japan)	*M*	Leukocytes	% mC content	HPLC	X	No significant difference	Sex- and age-dependent effects; Significant hypomethylation for males, decreasing with age

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Brain postmortem tissue																
Abdolmaleky et al. [57]	SZ: 5 (5/0)	HC: 5 (5/0)	45.4 ± 2.61	46.0 ± 2.74	NR	*NR* (USA)	U	Frontal lobe [BA9, BA10] (HBTRC)	GABAergic	***RELN***	P	BS, MSP	↑	SZ-associated hypermethylation at *RELN* promoter	–	Inverse (*RELN*)
Abdolmaleky et al. [53]	SZ: 35 (26/9) +5 (5/0)	HC: 35 (26/9) +5 (5/0)	42.5 ± 8.47 45.4 ± 2.61	44.2 ± 7.63 46.0 ± 2.74	NR	Caucasian ≈ 97% (USA)	*M* 80%	Frontal lobe [BA46, BA9, BA10] (SMRI, HBTRC)	Dopaminergic	***MB-COMT***	P	BS, MSP	↓	SZ-associated hypomethylation at *MB-COMT* promoter	More prominent in the left frontal lobe; Associated with alcohol abuse	Inverse (*DRD1*)

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Abdolmaleky et al. [108]	SZ: 35 (26/9)	HC: 35 (26/9)	42.5 ± 8.47	44.2 ± 7.63	NR	Caucasian (USA)	*M* ≈ 91%	Frontal lobe [BA46, BA9, BA10] (SMRI)	Serotonergic	*HTR2A*	P	BS, qMSP	↑ ↓	SZ-associated hypermethylation of *HTR2A* promoter at -1438A/G polymorphic site SZ-associated hypomethylation of *HTR2A* promoter at T102C polymorphic site	Decrease of *HTR2A* expression associated with early age of disease onset	Inverse (*HTR2A* and −1438A/G polymorphic site); Positive (*HTR2A* and T102C polymorphic site)
Abdolmaleky et al. [64]	SZ: 35 (26/9)	HC: 35 (26/9)	42.5 ± 8.47	44.2 ± 7.63	NR	Caucasian (USA)	*M* ≈ 91%	Frontal lobe [BA46, BA9, BA10] (SMRI)	Serotonergic	***SLC6A4***	P	BS, qMSP (preceded by GWDMP)	↑	SZ-associated hypermethylation of *SLC6A4* promoter	Effect stronger in unmedicated cases	Inverse (*SLC6A4*)
Abdolmaleky et al. [131]	SZ: 35 (26/9)	HC: 35 (26/9)	42.5 ± 8.47	44.2 ± 7.63	NR	Caucasian (USA)	*M* ≈ 91%	Frontal lobe [BA46,BA9, BA10] (SMRI)	Other	***DTNBP1***	P	BS, qMSP (preceded by GWDMP)	X	No significant differences	Associated with age of disease onset	Inverse (*DTNBP1*)
Alelú-Paz et al. [151]	SZ(smci): 29 (29/0)	HC: 4 (4/0)	77.6 ± 10.10	68.75 ± 14.36	DSM-IV-TR	NR (Spain)	NR	DLPFC, AC, HIPP, CBL	Other (19 genes involved in major neurotransmitter systems)	*CNP*, *NG2*, *DRD1*, ***DRD4***, *SLC6A3*, ***MB-COMT***, *GABBR*, *GABBR2*, ***GAD1***, *GAD2*, ***RELN***, *GRIN1*, *GRM7*, *GRIK3*, ***SLC6A4***, ***DTNBP1***, *DISC1 HINT1*, ***BDNF***	P	BS, MSP	X	No SZ-associated differences, irrespective of cognitive deficits	–	–
Boks et al. [118]	SZ: 91 (50/41)	HC: 123 (82/41)	52.6 ± 5.2	45.9 ± 16.8	DSM-IV	Caucasian ≈ 54%, Other ≈ 46%)	NR	DLPFC (LI)	Other	*DUSP22*	P	GWDMP (450 K BeadChip array)	↑	SZ-associated hypermethylation	–	No correlation (but significantly lower *DUSP22* transcript levels in SZ)
Cheah et al. [122]	SZ: 22 (18/4)	HC: 23 (15/8)	52.5 ± 22.7	70.2 ± 9.2	NR	NR (USA)	M 90%	PFC [BA10, BA46] (HBSFRC)	BDNF	***BDNF***	P I, E V	GWDMP (450 K BeadChip array)	↓	SZ-associated differences for *cg3* and *cg6*	No sigificant effects after adujsting for age and post-mortem interval	Positive (for *cg5*)
Cheah et al. [65]	SZ: 22 (18/4)	HC: 23 (15/8)	52.5 ± 22.7	70.2 ± 9.2	NR	NR (USA)	M 90%	PFC [BA10, BA46] (HBSFRC)	Serotonergic	*HTR2A*	P I, E I	GWDMP (450 K BeadChip array)	↑	SZ-associated hypermethylation of *cg5*, *cg7*, *cg10*	–	Significant negative correlation (*HTR2A*)
Dempster et al. [152]	SZ: 15 (9/6)	HC: 15 (9/6)	44.2	48.1	DSM-IV	Caucasian 90%, Asian ≈ 7%, Other ≈ 3% (USA)	M ≈ 97%	CBL (SMRI)	Dopaminergic	***COMT***	P	BPS	X	No significant differences	–	None
Fachim et al. [41]	SZ: 15 (11/4)	HC: 16 (11/5)	52.60 ± 18.18	67.25 ± 12.73	RDC	*NR* (UK)	M	PFC, HIPP	GABAergic	*PVALB*	P	BPS	↑	SZ-associated hypermethylation in HIPP for CpG2 and CpG4	–	–
Grayson et al. [58]	SZ: 15 (6/9)	HC: 15 (7/8)	48.07 ± 15.67	55.07 ± 13.62	NR	Others (USA)	NR	OC, PFC [BA9, BA10] (SFNC, HBTRC)	GABAergic	***RELN***	P	BS	↑	SZ-associated hypermethylation of *RELN* promoter at positions -134 and -139 (4 CpG sites)	–	–
Huang et al. [63]	SZ: 14 (5/9)	HC: 14 (5/9)	58.7 ± 5.5	60.5 ± 5.2	NR	NR (USA)	NR	PFC	GABAergic	***GAD1***	P, I 2	BS	↓	SZ-associated hypomethylation of repressive H3K27me3 chromatin fraction	–	Positive (methylation and expression level of *GAD1*)
Iwamoto et al. [71]	SZ: 11 (–/–)	HC: 12 (–/–)	–	–	DSM-IV	NR (USA)	*M* ≈ 73%	PFC [BA10] (SMRI)	Other	*SOX10*	E	BS	↑	SZ-associated hypermethylation of *SOX10*	–	Inverse (expression of *SOX10* and oligodendrocyte genes)

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Keller et al. [119]	SZ: 15 (8/7)	HC: 15 (8/7)	61.73 ± 18.44	63.27 ± 17.83	NR	Caucasian ≈ 93%, Other ≈ 7% (UK, Italy)	*M* ≈ 73%	PFC, STR	BDNF	***BDNF***	P IV, I	MassARRAY, BPS	↓	SZ-associated hypomethylation of -93 CpG site in PFC ($P < 0.5$)	–	No correlation
McKinney et al. [72]	SZ + SZAD (16 + 6): 22 (17/5)	HC: 22 (17/5)	47.14 ± 2.91 (SEM)	45.14 ± 2.30 (SEM)	DSM-IV	Caucasian ≈ 70%, Other ≈ 30% (USA)	NR	STG	Other	*BAIAP2*, *DLG1*	All sites	GWDMP (450 K BeadChip array)	↓ X	SZ-associated hypomethylation of *BAIAP2;* No significant differences for *DLG1*	–	–
Mill et al. [13]	SZ: 35 (26/9)	HC: 35 (26/9)	42.6 –	44.1 –	DSM-IV	Caucasian (USA)	*M* ≈ 91%	Frontal cortex (SMRI)	Dopaminergic Glutamatergic-Other	*ARVCF*, ***BDNF***, ***COMT***, ***DRD4***, ***DTNBP1***, ***GAD1***, *GRIN2B*, *MTHFR*, *NRG1*, ***RELN***	P, E, I	BS, BPS	X	No significant SZ-associated difference in the ten tested candidate genes	Modest association between genotype and DNA methylation for *BDNF*	–
Ruzicka et al. [109]	SZ: 8 (4/4)	HC: 8 (4/4)	67.9 ± 17.3	64.1 ± 14.2	NR	NR (USA)	*M*	HIPP (CA2/3, CA1) (laser-microdissected GABAergic interneurons) (HBTRC)	GABAergic	***GAD1*** regulatory network (27 genes)	1308 CpG loci	GWDMP (450 K BeadChip array), BPS	↑ ↓	44 SZ-associated differentially methylated regions SZ-associated hypermethylation of *MSK1*, hyper- and hypomethylation of *DAXX* and *CCND2*, respectively	–	Inverse and positive
Scarr et al. [123]	SZ: 69 (51/18) (20 SZ(Def) + 49 SZ(Ndef))	HC: 63 (47/16)	44 ± 2	43 ± 2	DSM-IV DIBS	NR (Australia)	M	DLPFC [BA9]	Other (Cholinergic)	*CHRM1*	P	MassARRAY EpiTYPER	↓	SZ-associated hypomethylation of four CpG sites; No difference in methylation between two forms of SZ	No association with age, gender, suicide, tissue pH, or post-mortem interval	Decreased mRNA
Tamura et al. [60]	SZ: 35 (26/9)	HC: 35 (26/9)	43 range: 19–59	45 range: 31–60	DSM-IV	Caucasian (USA)	*M* ≈ 91%	Forebrain(SMRI)	GABAergic	***RELN***	P	MSREs PCR	X	No differences	–	Inverse (for samples prepared within 18 h after death)
Tochigi et al. [61]	SZ: 14	HC: 13	–	–	DSM-IV	NR (USA)	NR	PFC [BA10] (SMRI)	GABAergic	***RELN***	P	BPS	X	No differences	–	–
Tolosa et al. [120]	SZ: one sample for each region	HC: one sample for each region	–	–	NR	NR (Spain)	NR	STG, PHG, CG (LNDBB, UK)	Other	*FOXP2*	E SNP	BS	↑	SZ-associated hypermethylation in the left hemisphere of PHG	–	No correlation in SZ
Biofluid																
Abdolmaleky et al. [64]	SZ: 30 (–/–)	HC: 30 (–/–)	35.9 ± 8.7	36.3 ± 8.2	DSM IV-R	NR (Iran)	*M* ≈ 66%	Saliva	Serotonergic	***SLC6A4***	P	BS, qMSP (preceded by GWDMP, 27 K, 450 K BeadChip array)	↑	SZ-associated hypermethylation of *SLC6A4*	Effect stronger in unmedicated SZ	–
Abdolmaleky et al. [131]	SZ: 30 (–/–)	HC: 30 (–/–)	35.9 ± 8.7	36.3 ± 8.2	DSM III-R	NR (Iran)	*M* ≈ 66%	Saliva	Other	***DTNBP1***	P	BS, qMSP (preceded by GWDMP, 27 K, 450 K BeadChip array)	↑	SZ-associated hypermethylation of *DTNBP1*	Effect present in unmedicated SZ	–
Alfimova et al. [62]	SZ + STD + BPD + SZAD (47 + 2 + 1 + 1): 51 (24/27)	HC: 52 (26/26)	26.73 ± 6.83	27.62 ± 6.96	ICD-10	Caucasian (Russia)	*M*	Whole blood	GABAergic	***RELN***	P	Modified SMRT-BS	X	No significant SZ-associated differences	Positive correlation between methylation status in -258 to -151 bp and cognitive index	–
Boks et al. [118]	SZ: 15 (9/6)	HC: 49 (4/45)	40.1 ± 13.8	35.9 ± 17.0	DSM-IV	Caucasian (Netherlands)	NR	Whole blood	Other	*DUSP22*	P	GWDMP (450 K BeadChip array)	↑	Z-associated hypermethylation	–	–

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Carrard et al. [66]	SZ: 40 (24/16)	HC: 67 (49/18)	32 ± 8	42 ± 12	DSM-IV DIGS	Caucasian (Switzerland)	NR	Leukocytes	Serotonergic	*HTR1A*	P	HRM-PCR	↑	SZ-associated hypermethylation	No separate effect of age and sex, but their covariance was significant (analyzed together with bipolar disorder sample, $n = 58$)	–
Chen et al. [125]	SZ(P): 371 (199/172)	HC: 288 (123/165)	–	–	DSM-IV	Asian (China)	NR	Whole blood	Other	*MAOA*	P	BS	X	No significant differences	SZ(P)-associated hyper- and hypomethylation for females and hyper-methylation for males for individual CpG sites	–
Cheng et al. [50]	SZ: 60 (30/30)	HC: 30 (15/15)	29.6 ± 5.4	30.4 ± 4.0	DSM-IV	Asian (China)	*M*	Whole blood	Dopaminergic	***DRD4***	P	BPS	↑	SZ-associated and male-specific hypermethylation of *DRD4* (average)	–	Positive (*DRD4*) in 10 healthy males
Chuang et al. [153]	SZ: 64 (37/27)	HC: 63 (30/33)	49 ± 9	50 ± 17	DSM-IV	Asian (Taiwan)	NR	PBMCs	Other	*ARC gene*	P	BPS	↑	SZ-associated hypermethylation of CpG1, 3, 4, 9, 11, 16, 17, and 24	–	–
Çöpoğlu et al. [70]	SZ: 49 (33/16)	HC: 65 (46/19)	35.31 ± 10.35	35.18 ± 9.05	DSM-IV	Other (Turkey)	*M*	Whole blood	BDNF	***BDNF***	P, I 3-E 4 boundary	MSP	X	No significant differences	Association with mean duration of illness for *BDNF* gene CpG island-1 (lower in the hemi-methylated compared to the non-methylated group)	–
Dai et al. [51]	SZ: 59 (30/29) (30 SZ(P) + 29 SZ(U))	HC: 26 (12/15)	29.6 ± 5.3	–	DSM-IV	Asian (China)	*M*	Whole blood	Dopaminergic	*DRD3*	P	BPS	↑	Significant association of CpG2 with SZ	Methylation: -higher in male SZ than male HC for CpG2 and CpG3 -higher in female SZ than female HC for CpG5 -higher in male SZ(P) and male SZ (U) than male HC for CpG2 and CpG3 -lower in female SZ(U) than female HC for CpG2 and CpG3 - higher in female SZ(P) than female HC for CpG5	–
D'Addario et al. [116]	SZ: 25 (14/11)	HC: 34 (15/19)	47.70 ± 13.01	52.38 ± 12.80	DSM-IV TR	NR (Italy)	*M*	PBMCs	Cannabinoid	*CNR1*	P	BPS	↓	SZ-associated hypomethylation for average of CpG1-5 and CpG2	No sex differences Lower methylation at CpG site 2 in younger (< 40 years) SZ subjects and a trend versus older (> 40 years) SZ subjects	Higher expression in SZ
Fikri et al. [59]	SZ: 110 (71/39)	HC: 122 (89/33)	40.26 ± 8.38	37.92 ± 9.76	DSM-IV	Asian (Malaysia)	*M* (mostly)	Whole blood	Dopaminergic	***RELN***	P	MSP	↑	SZ-associated hypermethylation	–	Downregulation in methylated versus unmethylated SZ samples ($n = 9$)
Gao et al. [126]	SZ: 105 (50/55)	HC: 105 (50/55)	38.12 ± 11.62	36.70 ± 9.52	DSM-IV	Asian (China)	*M*	Leukocytes	Dopaminergic	***COMT***	P	BPS	↑	SZ-associated hypermethylation	Results driven by males; Based on the ROC curve, DNA methylation predicted the SZ risk in males	–
Gao et al. [115]	SZ(DS): 51 (51/0) SZ(NDS): 53 (53/0)	HC: 50 (50/0)	50.25 ± 6.91 48.15 ± 7.40	48.80 ± 6.55	DSM-IV	Asian (China)	*M*	PBMCs	Other	*MMP9*	E 4, E 5	BPS	↓	SZ-associated hypomethylation in SZ(DS) and SZ(NDS) relative to HC	For both SZ groups, a significant positive correlation between gene expression of MMP9 and negative symptoms	Negative correlation between exon 4 DNA methylation with gene expression of *MMP9* in SZ(DS) (after controlling for age and medication)
Ghadirivasfi et al. [128]	SZ: 63 (–/–)	HC: 76 (–/–)	–	–	DSM-IV	Other (Iran)	NR	Saliva	Serotonergic	*HTR2A*	P, E 1	BS, qMSP	↓	SZ-associated hypomethylation at T102C polymorphic site	SZ-associated (trend) hypomethylation with age in individuals with CC genotype	–
Hu et al. [132]	SZ: 100 (100/0) SZ(H): 100 (100/0)	HC: 100 (100/0)	– (range: 18–60)	– (range: 18–45)	DSM-V	Asian (China)	*U* 50% *M* 50%	Whole blood	Dopaminergic	***MB-COMT***	P	BPS	↓	Significant differences among three groups (SZ- and SZ(H)-associated hypomethylation)	No significant differences, when grouped by genotype	–
Ikegame et al. [68]	SZ: 100 (54/46)	HC: 100 (55/45)	43.1 ± 13.0	46.2 ± 12.0	DSM-IV	Asian (Japan)	NR	PBMCs	BDNF	***BDNF***	P: I, IV	BPS	↑ X	SZ-associated hypermethylation of promoter I (CpG1-72) (small effect); No significant difference for promoter IV	Effect at promoter I more prominent in males; For all CpG sites, at promoter IV hypermethylation significant only for females	–

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Kordi-Tamandani et al. [69]	SZ: 80 (–/–)	HC: 71 (–/–)	47.53 ± 10.80	46.70 ± 11.72	DSM-IV	Caucasian (Iran)	*U*	Whole blood	Dopaminergic BDNF	***BDNF***, ***SLC6A3***	P	MSP	↓ X	SZ-associated hypomethylation of *BDNF;* No significant difference for *SLC6A3*	–	Inverse (*BDNF*) Not significant for *SLC6A3* ($n_{SZ} = 17$; $n_{HC} = 17$)
Kordi-Tamandani et al. [111]	SZ: 81 (20/61)	HC: 71 (14/57)	47.53 ± 10.80	46.70 ± 11.72	DSM-IV	Caucasian(Iran)	*U*	Whole blood	Glutamatergic	*GRM2*, *GRM5*, *GRM8*, *GRIA3*	P	MSP	↑ X	SZ-associated hypermethylation of *GRM2* and *GRM5;* No significant differences for *GRM8* and *GRIA3*	–	Inverse (for *GRM2*, *GRM5*, *GRIA3*) ($n_{SZ} = 17$; $n_{HC} = 17$)
Kordi-Tamandani et al. [52]	SZ: 80 (–/–)	HC: 71 (–/–)	47.5 ± 10.80	46.79 ± 11.72	DSM-IV	Caucasian (Iran)	*U*	Whole blood	Dopaminergic	*DRD1*, *DRD2*, ***DRD4***, *DRD5*	P	MSP	↓	SZ-associated hypomethylation of *DRD2*, *DRD4*, and *DRD5*	–	Inverse (*DRD2*, *DRD4*, *DRD5*) ($n_{SZ} = 17$, $n_{HC} = 17$)
Kordi-Tamandani et al. [73]	SZ: 94 (27/67)	HC: 99 (29/70)	47.53 ± 10.80	46.70 ± 11.72	DSM-IV	Caucasian (Iran)	*U*	Whole blood	Other	*CTLA4*	P	MSP	↑	SZ-associated hypermethylation of *CTLA4*	–	Increased expression for SZ ($n = 17$)
Kordi-Tamandani et al. [154]	SZ: 80 (–/–)	HC: 71 (–/–)	47.53 ± 10.80	46.79 ± 11.72	DSM-IV	Caucasian (Iran)	*U*	Whole blood	Other	*GSTT1*, *GSTP1*	P	MSP	↑	SZ-associated hypermethylation of *GSTT1* and *GSTP1*	–	–
Li et al. [155]	SZ(TD): 35 (20/15) SZ(NTD): 35 (20/15)	HC: 34 (14/15)	45.1 ± 12.2 44.7 ± 11.2	44.4 ± 11.6	DSM-IV	Asian (China)	*M*	Whole blood	Other	*DLGAP2*	P	BPS	↑	SZ-associated hypermethylation, regardless of subgroup	–	–
Melas et al. [42]	SZ: 177 (87/90)	HC: 171 (–/–)	51.6 ± 9.1	–	DSM-IV	NR (Sweden)	*M*	Leukocytes	Dopaminergic Serotonergic	***S-COMT*** ***SLC6A4***	P	BPS	↑ X	SZ-associated hypermethylation of S-*COMT* (5 CpG sites) No difference for *SLC6A4* (8 CpG sites)	–	–
Murphy et al. [56]	SZ: 20	HC: 31	–	–	DSM-IV	NR (Canada)	NR	Whole blood	Dopaminergic	***S-COMT***	P	BS	X	No differences (with some exceptions at an individual level)	–	–
Murphy et al. [156]	SZ: 20	HC: 31	–	–	DSM-IV	NR (Canada)	NR	Whole blood	Other	*SYN III*	P	BS	X	No significant differences (partial to total methylation at cytosine 20 in HC - 22:9, in SZ - 18:2)	–	–
Nakata et al. [157]	SZ: 49 (23/26)	HC: 50 (25/25)	61.8 ± 13.3	62.0 ± 14.3	DSM-V	Asian (Japan)	NR	Leukocytes	Other (ghrelin, hormonal system)	*GHSR* *MBOA4*	P, I 1	BPS	X	No significant differeneces	–	mRNA expression of *GHS-R1a* significantly decreased in SZ mRNA expression of *GHS-R1b* and *MBOAT4* significantly increased in SZ
Nohesara et al. [54]	SZ: 20 (–/–)	HC: 25 (–/–)	–	–	DSM IV-R	NR (Iran)	NR	Saliva	Dopaminergic	***MB-COMT***	P	BS, qMSP	↓	SZ-associated hypomethylation of *MB-COMT*	Association with sex (methylation status increased with age)	–
Nour El Huda et al. [121]	SZ: 138 (103/35)	HC: 132 (101/31)	*m*: 39.05 ± 7.98 *f*: 39.83 ± 8.05	*m*: 37.42 ± 8.37 *f*: 35.94 ± 9.23	DSM-IV	Asian (Malaysia)	*M* ≈ 74%	Leukocytes	Dopaminergic	***COMT***	P	MSP	↓	SZ-associated hypomethylation	Association with sex (methylation status lower in males than in females); Differential effects for BMI and antipsychotic groups (lower for atypical antipsychotics and risperidone than typical antipsychotics)	No significant effects
Okazaki et al. [158]	SZ(A): 40 (20/20) SZ(C): 40 (20/20)	HC: 40 (20/20)	41.3 ± 12.9 39.6 ± 10.4	39.7 ± 4.7	DSM-IV	Asian (Japan)	NR	Whole blood	Other (cell-cycle genes)	*CDK4*, *MCM7*, *POLD4*	P	GWDMP (450 K BeadChip)	X	No significant differences after Bonferroni correction (significant when uncorrected)	–	mRNA expression decreased in SZ

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Ota et al. [110]	FEP (SZ + SZFD + BPD + OPD: 30 + 11 + 7 + 3): 51 (32/19)	HC: 51 (32/19)	25.43 ± 8.01	25.88 ± 7.83	DSM-IV	NR (Brazil)	*U*	Whole blood	11 neurodevelopment- and neurotransmitter-related genes, 5 housekeeping-genes	*ABAT*, *TSPO*, *CHRNA*, *CHRNB*, *CHRNE*, ***COMT***, *GABRR*, *GCH1*, *GCHFR*, *TACR2*, *NRG1; B2M*, *HPRT1*, *RPL13A*, *GAPD*, *ACTB*	P	BS	↑	FEP-associated hypermethylation of *GCH1* promoter (CpG13, CpG15, CpG16, CpG21)	Expression of *GCH1* correlated with PANSS scores	Inverse (*GCH1*)
Pesce et al. [112]	SZ(FE): 54 (28/26)	HC: 38 (22/16)	34.9 ± 8.7	41.3 ± 9.8	DSM-IV	NR (Italy)	*U*	PBMCs	Other	*SHP-1*	P II	MSP	↑	SZ(FE)-associated hypermethylation	–	Lower level of SHP-1 gene expression in SZ(FE)
Pun et al. [159]	SZ: 30 (15/15)	HC: 30 (19/11)	–	–	DSM-IV	Asian (Hong Kong)	*M*	Whole blood	GABAergic	*GABRB2*	SNP E, I	BS	↑ ↓	SZ-associated hypermethylation of CpG sites 10, 18, 22, and 25 SZ-associated hypomethylation of CpG sites 1, 9, and 13	–	–
Rubin et al. [74]	SZ: 57 (35/22) SZAD: 34 (15/19)	HC: 75 (37/38)	*m*: 33 ± 12 *f*: 39 ± 14 m: 38 ± 18 *f*: 37 ± 11	*m*: 39 ± 13 *f*: 36 ± 13	DSM-IV	Caucasian ≈ 52%, Other ≈ 48% (USA)	*M* ≈87%	Whole blood	Other	*OXTR*	P	BPS	↑	SZ-associated hypermethylation (contrast SZ vs. HC and SZ vs. SZAD)	Methylation status in schizophrenia spectrum disorder linked to behavioral deficits and brain areas known for emotion processing	–
Uno et al. [160]	SZ: 7(7/0)	HC: 7(7/0)	–	–	NR	Asian (Japan)	NR	Whole blood	Other	*Shati/Nat8l*	P	BS	↓	SZ-associated hypomethylation at -1532, -1509, -1492, -1480	–	–
Venugopal et al. [161]	SZ: 47 (29/18)	HC: 47 (27/20)	31.74 ± 6.57	29.74 ± 5.09	DSM-IV	Asian (India)	*U*	Buffy coat	Other	*IL6*	P	BS	↓	SZ-associated hypomethylation	–	–
Walton et al. [55]	SZ: 82 (62/20)	HC: 102 (62/40)	33.76 ± 10.61	32.66 ± 11.43	DSM-IV	NR (USA)	*M*	Whole blood	Dopaminergic	***MB-COMT***	P	GWDMP (27 K BeadChip array)	↓	SZ-associated hypomethylation	Methylation positively correlated with signal change in the left DLPFC (fMRI memory task)	–
Xu et al. [162]	SZ: 81 (38/43) (both famine exposed and unexposed)	HC: 80 (41/39) (both famine exposed and unexposed)	–	–	ICD-10	Asian (China)	NR	Whole blood	Other	*PLA2G4C*	P	BS	↑	SZ-associated higher frequency of partial methylation of the 1CpT, but not 2CpT and 3CpT; Effect higher in famine unexposed SZ; No significant differences for famine exposure for the average of three sites between SZ and HC	–	–
Yoshino et al. [129]	SZ: 50 (24/26) + 18 (7/11)	HC: 50 (25/25) + 18 (7/11)	62.1 ± 13.3 + 33.1 ± 9.0	61.9 ± 14.2 + 33.4 ± 8.9	DSM-5	Asian (Japan)	*M* ≈ 74%	Leukocytes	Dopaminergic	*DRD2*	P	BPS	↓	SZ-associated hypomethylation of CpG2, CpG4, and CpG7 in medicated cases SZ-associated hypomethylation of CpG1-3 and CpG5-7 in unmedicated cases	SZ-associated correlation between age and methylation	–
Yoshino et al. [113]	SZ: 50 (24/26)	HC: 50 (25/25)	62.1 ± 13.3	61.8 ± 13.3	DSM-5	Asian (Japan)	*M*	Leukocytes	Other	*TREM2*	I 1	BPS	↓	SZ-associated hypomethylation on average and for CpG2-3	Age correlated with CpG4 methylation No correlations between methylation, age at onset, duration of illness, medication, and psychiatric or extrapyramidal symptoms	Inverse (*TREM2* methylation of CpG2)

Table 1 (continued)

Candidate gene DNA methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antips. medication	Tissue source (database)	Related biological system	Gene loci	Region	Method	↑ ↓ X	Main findings	Secondary findings	Gene expression–methylation relationship
	CASES	CTRLS	CASES	CTRLS												
Zhou et al. [114]	SZ(D) + SZ(ND): 53 (53/0) + 55 (55/0)	HC: 63 (63/0)	50.30 ± 6.59 49.02 ± 6.35	48.08 ± 6.34	DSM-IV	Asian (China)	*M*	PBMCs	Other	*CXCL1*	E 2	BPS	↓	SZ-associated hypomethylation of CpG1 and 2, regardless of the subgroup SZ(ND)-associated hypomethylation of CpG3	*CXCL1* gene expression associated with the negative syndrome in SZ (ND)	Inverse (*CXCL1* gene expression and E 2 average methylation in SZ (D))
Zong et al. [130]	SZ: 279 (162/117)	HC: 256 (155/101)	43.77 ± 12.43	36.88 ± 9.37	DSM-IV	Asian (China)	*M*	Leukocytes	GABAergic	*GABRB2*	P1, P2, Alu	HpaII/MspI restriction, qP-CR	↑	SZ-associated hypermethylation of P1 for males, of P2 for males + females and females, of Alu for males + females and males	*GABRB2* genotype-dependent methylation P1-5mC and P2-5mC levels correlated with age and sex Alu-5mC and P2-5hmC levels correlated with age; Associations with antipsychotic medication and family history of psychiatric disease	–

Genome-wide dna methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Method	Assay/Platform	Findings	Enrichment/pathway/network analysis
	Cases	CTRLS	Cases	CTRLS								
Brain postmortem tissue												
Alelú-Paz et al. [36]	SZ(sci): 19 (19/0)	HC: 3 (3/0)	80.72 ± 9.46	75.00 ± 8.66	DSM-IV-TR	NR (Spain)	NR	DLPFC, AC, HIPP	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	More methylated CpGs for DLPFC and HIPP; more unmethylated CpGs for AC 139 differentially methylated sites; Findings (examples): *NUBP1*, *STK32B*, *PRKCE*, *HLA-DRB5*, *HLA-B*, *FRK*	Nucleotide binding, signal transduction, axon growth and guidance, antigen processing, immune system, kinase activity
Chen et al. [78]	SZ: 39 (28/11)	HC: 43 (30/13)	43.2 range: 30–70	45.0 range: 20–60	DSM-IV	Caucasian (USA)	*M* (mostly)	CBL (SMRI)	GWDMP 27 K array	Illumina Infinium HumanMethylation 27 K BeadChip	SZ-associated differential methylation of 488 sites; Correlation between methylation and expression for *PIK3R1*, *BTN3A3*, *NHLH1*, *SLC16A7* (both SZ and BD), *RELN*, *and COMT*	Neurotransmission, neurodevelopment, adaptive immune responses
Jaffe et al. [90]	SZ: 191 (72/29)	HC: 240 (166/74)	50.1 ± 14.4	42.3 ± 16	DSM-IV	Caucasian ≈ 50% (USA)	*M* 64%	DLPFC [BA46/9]	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	Differences in 2104 CpGs; Widespread SZ-associated hypomethylation (97.1%); Highly ranked genes: *CD164*, *COPZ2*, *SUGT1*, *HAT1*, *TYW1B*.	Neurodevelopment and neurodifferentiation
McKinney et al. [72]	SZ + SZAD (16 + 6): 22 (17/5)	HC: 22 (17/5)	47.14 ± 2.91 (SEM)	45.14 ± 2.30 (SEM)	DSM-IV	Caucasian ≈ 73%, Other ≈ 27% (USA)	NR	STG	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	150 differentially methylated sites at $p < 1 \times 10^{-4}$ (top five genes: *CUEDC1*, *ACSS1*, *(ACTRT2)*, *TSPEAR*, *LARP1*); No differentially methylated sites at $p < 1 \times 10^{-7}$.	–
Mill et al. [13]	SZ: 35 (26/9)	HC: 35 (26/9)	42.6 –	44.1 –	DSM-IV	Caucasian (USA)	*M* ≈ 91%	Frontal cortex (SMRI)	12 K CpG-island microarrays genome-wide	Microarray-based DNA methylation profiling	Multiple differentially methylated loci; top five genes for males: *EXOSC7*, *GRIA2*, *ELMOD1*, *KCNJ6*, *WDR18*; top five genes for females: *C6orf84*, *HCG9*, *SLC17A7*, *NR4A2*, *AB051500*; top genes for both sex: *RPP21*, *KEL*	Mitochondrial function, brain development, signal transduction
Numata et al. [163]	SZ + SZAD (97 + 9): 106 (73/33)	HC: 110 (75/35)	46.8 ± 13.8	45.1 ± 15.1	DSM-IV	Caucasian ≈ 52.5%, Other ≈ 47.5% (USA)	*M* ≈ 62%	DLPFC	GWDMP 27 K array	Illumina Infinium HumanMethylation 27 K BeadChip	SZ-associated differentially methylated 107 CpG sites ($p < 0.05$, Bonferroni corrected) Hyper-methylation at 79 sites Genes (examples): *GRIA4*, *ASTN2*, *DCDC2*, *MRPS14*, *BRINP3*	–
Pidsley et al. [87]	SZ: 22 (12/10) (21 PFC, 20 CBL); [DC]; 18 (15/3) [RC]	HC: 24 (18/6) (23 PFC, 23 CBL); [DC]; 15 (13/2) [RC]	61 ± 16.6 45.5 ± 16.6	61.1 ± 18.9 42.3 ± 14.8	DSM	NR (UK, Canada)	NR	PFC, CBL (LBBND, DBCBB)	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	Four SZ-associated differentially methylated loci in PFC (FDR ≤ 0.05): *GSDMD*, *RASA3*, *HTR5A*, *PPFIA1*	Neuron projection, nervous system development, synaptic transmission, neurogenesis, calcium ion binding

Table 1 (continued)

Genome-wide dna methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Method	Assay/Platform	Findings	Enrichment/pathway/network analysis
	Cases	CTRLS	Cases	CTRLS								
Ruzicka et al. [164]	SZ: 8 (4/4)	HC: 8 (4/4)	67.9 ± 17.3	64.1 ± 14.2	NR	*NR* (USA)	*M*	HIPP (laser-microdissected GABAergic interneurons) (HBTRC)	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	53 differentially methylated positions (SZ vs. HC) 210 differentially methylated positions (SZ CA1 vs. SZ CA2/3) 1 differentially methylated position (SZ CA1 vs. HC CA1) 0 differentially methylated positions (SZ CA2/3 vs. HC CA2/3) Genes: *PLCH2*, *RERE*, *PLEKH01*, *SDCCAG8*, *CYP26B*, *CACNB2*, *DGKZ*, *YPEL4*, *LRP1*, *PLCB2*, *NRN1L*, *SLC12A4*, *CLC12A4*, *MYO15A*, *PPP1R16B*, *CHADL*, *LINC00634*	–
van den Oord et al. [80]	SZ: 39 (23/16)	HC: 27 (19/8)	43.3 ± 9.9	43.1 ± 7.4	DSM-IV	NR (Sweden)	NR	PFC [BA10] (SMRI)	MWAS CpG-SNP MBD-seq	MethylMiner™, SOLiD platform	Top replication of blood findings from the same study: *IL1RAP*	Interleukin 1 receptor accessory protein; inflammation
Viana et al. [37]	SZ: 41	HC: 47	–	–	DSM	NR (UK, Canada)	NR	PFC, STR, HIPP, CBL (LNDBB, DBCBB)	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	SZ-associated differentially methylated loci in each brain region; 12 passed a stringent significance threshold of $p <$ 1.66E-07; Findings (examples): *ATP6V0D1*, *DEFB115*, *ELK3*, *GBP4*, *GART*, *GRINL1A*, *(GCOM1)*, *HECW1*, *NCAM1*, *SYNPO*, *SND1*, *ZNF586*	*NCAM1* (neurodevelopment, synaptic plasticity), *SYNPO* (postsynaptic densities, dendritic spines), *PRDM9* (meiosis), *WNT5A* (neurodevelopment), *RPH3AL* (calcium-ion-dependent exocytosis), *DISC1*, *GBP4*
Wockner et al. [79]	SZ: 24 (16/7) (1 md)	HC: 24 (19/5)	51.6 ± 21.6 (1 md)	71.3 ± 9.3	DSM-IV	NR (USA, Australia)	*M* ≈ 92%	PFC (HBSFRC)	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	2929 SZ-associated differentially methylated genes (adjusted for age and post-mortem interval); Genes (examples): *AKT1*, *DTNBP1*, *DNMT1*, *NOS1*, *PPP3CC*, *SOX10*	–
Wockner et al. [165]	SZ: 22 (15/7) 20 (11/9) 18 (15/3)	HC: 24 (19/5) 23 (17/6) 15 (13/2)	51.3 ± 22.0 62.1 ± 15.9 45.5 ± 16.6	71.3 ± 9.8 62.0 ± 18.7 42.2 ± 14.9	DSM-IV *NR*	NR (USA, Australia)	NR	PFC (HBSFRC, LBBND, DBCBB)	GWDMP 450 K array	Illumina Infinium HumanMethylation 450 K BeadChip	Genes (examples): *CERS3*, *DDX43*, *DPPA5*, *LY6G5C*, *PRDM9*, *REC8PFKP*	*PRDM9* (histone methyltransferase), *REC8* (maintenance of chromosomes protein partners), *DDX43* (ATP-related RNA helicase), *DPPA5* (embryo-specific expression), *CERS3* (fatty acid constitution), *LY6G5C* (leukocyte antigen-6 gene)
Xiao et al. [91]	SZ: 5 (3/2)	HC: 6 (5/1)	53.6 ± 3.36	46.5 ± 16.02	DSM-IV-TR	Caucasian ≈ 70%, Other ≈ 30% (USA/China)	*M* 60%	Frontal cortex, AC [BA9, BA24] (SWBB)	Genome-scale MeDIP-seq	Illumina HiSeq2000	4985 differentially methylated regions in BA9 3867 differentially methylated regions in BA24; Widespread SZ-associated hypomethylation	Development, differentiation, and projections of neurons
Zhao et al. [92]	SZ: 5 (3/2	HC: 6 (5/1)	53.6 ± 3.36	46.5 ± 16.02	DSM-IV-TR	Caucasian ≈ 70%, Other ≈ 30% (USA/China)	*M* 60%	[BA9] (SWBB)	Genome-scale MeDIP-seq	Illumina HiSeq 2000	10,961 differentially methylated regions (7880 hypermethylated and 3081 hypomethylated); Findings confirmed by literature: *PLP1*, *NR4A1*, *IL1B*, *GFAP*, *APC*, *TAAR1*, *MYT1L*, *GRIP1*, *ASTN2*, *EGFR*, *CD28*, *SLC6A2*	Neurogenesis, nervous system development
Biofluid												
Aberg et al. [76]	SZ: 750	HC: 750 TR: 75	(–/–)	(–/–)	Hospital discharge register	NR (Sweden)	NR	Whole blood	MBD-seq, PS	MethylMiner™, SOLiD platform	Findings (examples): *GRIA2*, *FNDC3B*, *DCTN*, *HTRA3*, *CAMK2D*	–
Aberg et al. [77]	SZ: 759 (417/342) [DC]; 178 (110/68) [RC I]; 561 (355/206) [RC II]	HC: 738 (399/339) [DC]; 182 (120/62) [RC I]; 582 (352/230) [RC II]	53.2 ± 11.6 56.4 ± 10.7 54.5 ± 11.4	55.1 ± 11.8 58.5 ± 10.3 57.1 ± 10.9	National population register	NR (Sweden)	NR	Whole blood Buffy coat	MBD-seq	MethylMiner™, SOLiD platform	25 genes for $p < 1.15 \times 10^{-8}$ Example loci: *FAM63B*, *FCAR*, *RUNX3*, *SMAD3*, *CREB1*, *ARNT*, *ARHGAP26*, *CTAGE11P*, *TBC1D22A*, *RELN*	Hypoxia, immune system

Table 1 (continued)

Genome-wide dna methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Method	Assay/Platform	Findings	Enrichment/pathway/network analysis
	Cases	CTRLS	Cases	CTRLS								
Boks et al. [118]	SZ(FamE): 23 (18/5) SZ(FamNE): 51 (28/23) (SZ + SZFD + SZAD)	HC(FamE): 25 (10/15) HC(FamNE): 54 (21/33)	50.1 ± 0.6 46.7 ± 0.8	50.3 ± 0.5 46.8 ± 1.0	DSM-IV	Asian (China)	*M*	Whole blood	GWDMP 450K array	Illumina Infinium HumanMethylation 450 K BeadChip	SZ-associated hypermethylation *DUSP22* (p FWER = 0.01), independent of famine exposure	–
Hannon et al. [81]	SZ: 353 [DC]; SZ: 414 [RC]	HC: 322 [DC]; HC: 433 [RC]	(–/–)	(–/–)	ICD-10 DSM-IV	UK	NR	Whole blood	GWDMP 450K array	Illumina Infinium HumanMethylation 450K BeadChip	25 SZ-associated differentially methylated positions ($p < 1 \times 10^{-7}$) Top genes: *FAM126A*, *PPTC7*, *GYG1*, *SIK3*, *USP36*, *EHD1*, *ITGA11*, *FAR2*, *IL15*, *GNB5*, *TRAF3IP3*, *MED22*, *AIM2*, *FBXO10*, *DDO*, *TNFAIP8* 14 significant differences ($p < 1 \times 10^{-7}$) differences; same direction in the replication cohort, 5 additional differentially methylated positions ($p < 5 \times 10^{-5}$)	Neuronal proliferation, brain development, and immune function
Kinoshita et al. [166]	SZ: 24 (11/13)	HC: 23 (10/13)	30.9 ± 10.5	31.9 ± 9.7	DSM-IV	Asian (Japan)	*U*	Leukocytes	GWDMP 450K array	Illumina Infinium HumanMethylation 450 K BeadChip	10,747 CpG sites differentially methylated (with 0.05 FDR correction) Genes (examples): *B3GAT2*, *DGKI*, *GFRA2*, *HDAC4*, *INSIG2*, *PCM1*, *RAI1*	–
Kinoshita et al. [207]	SZ: 42 (42/0)	HC: 42 (25/17)	51.8 ± 6.7	51.9 ± 5.5	DSM-IV	Asian (Japan)	*M*	Leukocytes	GWDMP 450K array	Illumina Infinium HumanMethylation 450K BeadChip	SZ-associated homocysteine-related effects at 1,338 CpG sites ($p < 0.01$) Findings (examples): *GNAL*, *KCNH2*, *NTNG2*, *SLC18A2*	*SLC18A2*, vesicular transporter type2; *GNAL*, guanine nucleotide-binding protein G subunit α, functional changes of D1 receptor; *KCNH2*, potassium channel signaling, modulation of neuronal firing; *NTNG2*, synaptic formation/maintenance
Kinoshita et al. [144]	SZ: 63 (50/13)	HC: 42 (25/17)	48.6 ± 9.6	46.9 ± 10.2	DSM-IV	Asian (Japan)	*M*	Leukocytes	GWDMP 450K array	Illumina Infinium HumanMethylation 450K BeadChip	Significant differences at 16,220 CpG sites (SVA 0.05 FDR); at 2,552 CpG sites after adjusting for cell type proportions (SVA 0.05 FDR) 1161 sites hypermethylated for SZ	Regulation of transcription (RNA polymerase II promoter)
Li et al. [167]	SZ: 6 (2/6)	HC: 1 (–/–)	–	–	DSM-IV-TR	Other (Mexico)	*U*	Whole blood	MeDIP-Seq	Illumina HiSeq 2000	955 SZ-associated differentially methylated regions in promoters (352 hypermethylated, 603 hypomethylated) Genes (examples): *ATP1B1*, *ARHGEF5*, *REPIN1*, *NBPF1*, *ADCY1*, *SMAD3*, *ARHGAP26*, *CREB1*	KEGG pathways: neuroactive ligand-receptor interaction, long-term potentiation, oocyte meiosis, vibrio cholera infection, endocytosis, MAPK signaling pathway
Liu et al. [82]	SZ + SZFD + SZAD: 98 (73/25) SZ: 325 [RC, GEO]	HC: 108 (70/38) SZ: 394 [RC, GEO]	34 ± 11	32 ± 11	DSM-IV-TR or CASH	Caucasian ≈ 83%, Other ≈ 14%, Asian ≈ 3% (USA)	*M* ≈ 92%	Whole blood	GWDMP 27K array	Illumina Infinium HumanMethylation 27 K BeadChip	SZ-associated differences at 20 CpG sites (controlled for gender, age, race, alcohol, nicotine use, cannabis use); 16 CpG sites confirmed by validation 7 genes with significant expression changes (*CD244*, *LAXI*, *PRF1*, *FAM173A*, *CBFA2T3* upregulated in SZ; *TCN1* downregulated in SZ) Correlations with methylation status: 11 CpG sites with reality distortion symptoms, *MS4A1* with chlorpromazine equivalent dosage (positive), *MPG* and *SLC25A10* with illness duration (positive), *CBFA2T3* with SZ age onset (negative).	Inflammatory response

Table 1 (continued)

Genome-wide dna methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Method	Assay/Platform	Findings	Enrichment/pathway/network analysis
	Cases	CTRLS	Cases	CTRLS								
Montano et al. [145]	SZ: 689 (477/212); 247 (188/59) [RC]	HC: 645 (273/372); 250 (190/60) [RC]	37.65 – 34.96 –	39.53 – 35.1 –	DSM-IV	–	*M* ≈ 92%	Whole blood	GWDMP 450K array	Illumina Infinium HumanMethylation 450K BeadChip	SZ-associated differences at 923 CpG sites (discovery cohort) (FDR < 0.2) SZ-associated differences at 625 CpG sites in the replication set (yielding the same direction of effects); 172 with $p < .05$ corrected for cell type heterogeneity and other confounding factors • Genes (examples): *NCOR2*, *SULT4A1*, *HES1* (neuronal functions), *RPS6KA1*, *MAD1L1*, DDR1 (previously related to SZ), *ZC3H12D*, *TCF3*, *IKZF4* (T-cell development), *SORL1*, *HES1*, *MARK4*, *SCAP*, *DHCR24*, *GAS7*, *CARD10*, *CDC37*, *CUTA*, *IRS1*, *FOXO1* (Alzheimer's disease)	Energy metabolism, amino acid metabolism, post-translational modification, hereditary disorder, neurological disease, organismal injury/abnormalities, embryonic development
Nishioka et al. [38]	SZ(FE): 18 (11/7)	HC: 15 (10/5)	22.8 ± 4.5	23.3 ± 4.0	DSM-IV (SIPS)	Asian (Japan)	*M*	Whole blood	GWDMP 27K array	Illumina Infinium HumanMethylation 27K BeadChip	603 differentially methylated CpG sites; top ten: *CLDN12*, *KCNF1*, *RANBP2*, *PSD2*, *RAF1*, *PKNOX1*, *MSH6*, *DEXI*, *KPNA6*, *LIMK2*; *HTR1E*, *COMTD1*, *SLC6A3*, *NEUROD4*, *HDAC11*, *ADAMTS3* All the top-ranked CpG sites showed hypomethylation Beta-value correlation with clinical indicators: *ANKS3* and *TRA2A* with PANSS (negative), GAF and PANSS (positive); *TRA2A* with age at disease onset (positive); *CLDN12* and duration of unmedicated psychosis (negative) 1352 genes (1429 CpG sites) and 172 genes (173 CpG sites) differentially methylated in males, and females, respectively	Nuclear lumen and nucleotide and transcription factor binding
Rukova et al. [88]	SZ: 220 (110/110)	HC: 220 (110/110)	*m*: 42 ± 11 *f*: 45 ± 11	*m*: 50 ± 14 *f*: 51 ± 14	DSM-IV	Caucasian (Bulgaria)	NR	Whole blood	GWDMP MeDIP (oligonucleotide microarray 27K CpGs)	Agilent Human DNA Methylation Microarray	394 differentially methylated regions, top ten genes: *HRH1*, *GABRA2*, *LIN7B*, *MYLIP*, *NXPH3*, *HMOX1*, *CRMP1*, *FGFR1*, *CASP3*, *MACF1* • 170 differentially methylated regions for male SZ-HC contrast, top ten genes: *GABRA2*, *LIN7B*, *MIR193B*, *MIR181C*, *DNMT3A*, *CASP3*, *DHX37*, *GIPC1*, *MAP2K2*, *FNDC4* • 162 differentially methylated regions for female SZ-HC contrast, top ten genes; *GABRD*, *GNAQ*, *PTK2*, *XIAP*, *PRKACA*, *CASP3*, *OXT*, *MACF1*, *PPP2R2A*, *KRT7*	Apoptosis, synaptic transmission, and nervous system development
van Eijk et al. [168]	SZ: 260 (–/–)	HC: 250 (–/–)	–	–	NR	NR (Netherlands)	NR	Whole blood	GWDMP 27K array	Illumina Infinium HumanMethylation 27K BeadChip	11,320 differentially methylated CpGs (0.05 FDR correction); 432 CpG sites with differential methylation levels and associated with differential gene expression; Examples: *CNNM2*, *CALHM1*, *PRRT1*, *HLA-C*, *MRPL41*	–
van den Oord et al. [80]	SZ: 712 (395/317) [DC]; 370 (231/139) [VC]	HC: 696 (377/319) [DC]; 377 (233/144) [VC]	53.17 ± 11.50 54.70 ± 10.97	55.27 ± 11.75 58.39 ± 10.43	Hospital discharge register	NR (Sweden)	NR	Whole blood Buffy coat	MWAS CpG-SNP MBD-seq BPS	MethylMiner™, SOLiD platform	7 CpG-SNPs (FDR, *q* -values < 0.1); 97 additional CpG-SNPs (*q* -value < 0.25); Top findings: *FOXP1*, *IL1RAP*, *AKAP13*, *SLC39A11*. Top replication IL1RAP	Findings enriched for sites binding transcription factor *CEBPB* (CCAAT/enhancer-binding protein beta); immune and inflammatory responses

Table 1 (continued)

Genome-wide dna methylation

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsych. medication	Tissue source (database)	Method	Assay/Platform	Findings	Enrichment/pathway/network analysis
	Cases	CTRLS	Cases	CTRLS								
Walton et al. [85]	SZ: 110 (82/28)	HC: 118 (75/43)	34.7 ± 10.59	32.53 ± 11.11	DSM-IV	NR (USA)	*M*	Whole blood	GWDMP 450K array	Illumina Infinium HumanMethylation 450K BeadChip	Genes (examples): *NC6F4*, *AVPR1A*, *OGDH*, *MCHR1*, *WFS1*, *AVP*	Generation of precursor metabolites and energy

Candidate genes in bold appeared at least four times across the studies.

↑ hypermethylation, ↓ hypomethylation, *X* no difference, *27K* array covering ≈ 27,000 CpG sites, *450K* array covering ≈ 485,000 CpG sites, *5hmC* 5-hydroxymethylcytosine, *5mC* 5-methylcytosine, *AC* anterior cingulate, *ARC* activity-regulated cytoskeleton-associated protein, *BA* Brodmann area, *BAIAP2* BAI1 Associated Protein 2, *BDNF* brain-derived neurotrophic factor, *BMI* body mass index, *BPD* brief psychotic disorder, *BPS* bisulfite pyrosequencing, *BS* bisulfite sequencing, *BS-OLE* bisulfite conversion specific one-label extension method, *CASH* Comprehensive Assessment of Systems and History, *CBL* cerebellum, *CDK4* cyclin-dependent kinase 4, *CG* cingulate gyrus, *CHRM1* cholinergic receptor muscarinic 1, *CNR1* cannabinoid receptor 1, *COBRA* combined bisulfite restriction assay, *COMT* catechol-*O*-methyltransferase, *CRE* cyclic AMP response element, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *CTRLS* controls, *CXCL1* chemokine ligand 1, *DBCBB* Douglas-Bell Canada Brain Bank (Montreal, Canada), *DC* discovery cohort, *DIBS* Diagnostic Instrument for Brain Studies, *DIGS* Diagnostic Interview for Genetic Studies, *DLG1* disks large homolog 1, *DLGAP2* DLG associated protein 2, *DLPFC* dorso-lateral prefrontal cortex, *DMR* differentially methylated regions, *DRD*(1) dopamine receptor D(1), *DSM* Diagnostic and Statistical Manual of Mental Disorders, *DTNBP1* dystrobrevin binding protein 1 (dysbindin), *DUSP22* dual specificity phosphatase 22, *E* exon, *f* female, *FEP* first-episode psychosis, *FPDM* fluorescence polarization-based DNA modification measurement, *GABA* gamma-aminobutyric acid, *GABRB2* gamma-aminobutyric acid A receptor beta 2, *GAD1* glutamate decarboxylase 1, *GCH1* GTP cyclohydrolase 1, *GEO* Gene Expression Omnibus, *GHSR* growth hormone secretagogue receptor, *GRIA1* glutamate ionotropic receptor AMPA type subunit 1, *GRM* glutamate metabotropic receptor, *GSTP1* glutathione S-transferase P, *GSTT1* glutathione S-transferase (GST) theta 1, GWDMP genome-wide DNA methylation profiling, *HBSFRC* Human Brain and Spinal Fluid Resource Center (Los Angeles, CA, USA), *HBTRC* Human Brain Tissue Resource Center (Belmont, MA, USA), *HC* healthy controls, *HIPP* hippocampus, *HPLC* high performance liquid chromatography, *HRM-PCR* high-resolution-melt PCR (polymerase chain reaction), *I* intron, *ICD-10* International Classification of Diseases 10th Edition, *IL6* interleukin 6, *LI* Lieber Institute (Baltimore, USA), *LINE-1* long interspersed nuclear element, *LNDBB* London Neurodegenerative Diseases Brain Bank (London, UK), *m* male, *M* medicated, *MAOA* monoamine oxidase A, *MB-COMT* membrane-bound catechol-*O*-methyltransferase, *MBD-seq* methyl-CpG binding domain protein-enriched genome sequencing, *MBOAT4* membrane bound *O*-acyltransferase 4, *mC* methylated deoxycytidine, *md* missing data, *MCM7* minichromosome maintenance complex component 7, *MeDIP-seq* methylated DNA immunoprecipitation followed by sequencing, *MMP9* Matrix metalloproteinase 9, *MSP* methylation-specific PCR (polymerase chain reaction), *MSREs* methylation-sensitive restriction enzymes, *MWAS* methylation-wide association study, *N* sample number, *NIMH BTC* National Institute of Mental Health Brain Tissue Collection, *NR* not reported, *OC* occipital cortex, *OPCRIT* Operational Criteria for Psychotic Illness, *OPD* other psychotic disorder, *OXTR* oxytocin receptor gene, *P* promoter, *PANSS* Positive and Negative Syndrome Scale, *PBMCs* peripheral blood mononuclear cells, *PFC* prefrontal cortex, *PGC* Psychiatric Genomics Consortium, *PHG* parahippocampus gyrus, *PLA2G4C* cytosolic phospholipase A2 gamma, *POLD4* DNA Polymerase Delta 4, *PVALB* parvalbumin gene, *qMSP* quantitative methylation-specific PCR (polymerase chain reaction), *qPCR* quantitative polymerase chain reaction, *RC* replication cohort, *RDC* Research Diagnostic Criteria, *RELN* reelin, *ROC* receiver operating characteristic, *S-COMT* soluble catechol-*O*-methyltransferase, *SD* standard deviation, *SEM* standard error of the mean, *SFBC* Stanley Foundation Brain Collection, *SFNC* Stanley Foundation Neuropathology Consortium, *SHP-1* a protein tyrosine phosphatase, *SIPS* Structured Interview for Psychosis-Risk Syndromes, *SLC6A3*(4) solute carrier family 6 member 3(4), *SMRI* Stanley Medical Research Institute (Bethesda, MD, USA), *SMRT-BS* single-molecule real-time bisulfate sequencing, *SNP* single-nucleotide polymorphism, *SOX10* SRY-Box 10, *SP-1* stimulating protein 1, *STD* schizotypal disorder, *STG* superior temporal gyrus, *STR* striatum, *SWBB* Southwest Brain Bank (El Paso, TX, USA), *SVA* surrogate variable analysis, *SYN III*: synapsin III, *SZ* schizophrenia, *SZAD* schizoaffective disorder, *SZ(A)* acute schizophrenia, *SZ(C)* chronic schizophrenia, *SZ(sci)* schizophrenia with severe cognitive impairment, *SZ(D)* deficit schizophrenia, *SZ(Def)* [^{3}H]pirenzepine binding deficient schizophrenia, *SZ(FamE)* schizophrenia with famine exposure, *SZFD* schizophreniform disorder, *SZ(FE)* first-episode schizophrenia, *SZ(H)* schizophrenia with homicidal behavior, *SZ(NFamE)* schizophrenia without famine exposure, *SZ(smci)* schizophrenia with severe and mild cognitive impairment, *SZ(ND)* non-deficit schizophrenia, SZ(NDef) schizophrenia without deficits in [^{3}H]pirenzepine binding, *SZ(NTD)* schizophrenia without tardive dyskinesia, *SZ(P)* paranoid schizophrenia, *SZ(sci)* schizophrenia with severe cognitive impairment, *SZ(TD)* schizophrenia with tardive dyskinesia, *SZ(U)* schizophrenia undifferentiated, *TR* technical replicates, *TREM2* triggering receptor expressed on myeloid cells 2, *TSS* transcriptional start site, *U* unmedicated, *VC* validation cohort.

Table 2 Details of studies reporting histone modifications associated with schizophrenia and other psychotic disorders.

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Histone residue	Epigenetic mechanism	Method	↑ ↓ X	Findings	Additional information Association with gene expression
	Cases	CTRLS	Cases	CTRLS										
Brain postmortem tissue														
Akbarian et al. [169]	SZ: 41 (28/13)	HC: 41 (29/12)	50.7 ± 2.8 (SEM)	51.1 ± 2.8 (SEM)	DSM-IV	NR (USA)	*M* 85%	PFC (UC, MPRC)	H3R17, H3S10-K14, H3K9/14, H3K4, H4K8, H4K12	Methylation Acetylation Phosporylation	Immunoblotting and IHC	X ↑#	No significant differences in the whole-group contrast; Increased methylation for a subgroup of 8 SZ cases#	H3R17 methylation associated with decreased expression of metabolic transcripts of *CRYM*, *CYTOC/CYC1*, *MDH*, and *OAT*
Chase et al. [46]	SZ: 13 (8/5)	HC: 13 (8/5)	44.5 ± 13.1	48.1 ± 10.7	DSM-IV	NR (USA)	*M* 85%	Parietal cortex (SFNC)	H3K9	Di-methylation	Immunoblotting	↑	SZ-associated increased H3K9me2	SZ-associated increased *GLP* and SETDB1 mRNA expression
Huang et al. [97]	SZ: 36 (24/12) + 9 (5/4)	HC: 36 (24/12)	52.1 ± 2.1 (SEM) 41.11 ± 11.25	51.4 ± 2.8 (SEM)	NR	NR (USA)	M 87%	PFC [BA10] (UC, MPRC, BVARC)	H3K4 H3K27	Tri-methylation	NChIP qPCR	X ↓#	No significant differences in *GAD2* histone methylation; Decreased *GAD1* H3K4me3 levels for female SZ# Significant difference in *GAD1* H3K4me3 levels with clozapine-treated SZ (versus other antipsychotics), but no differences in *GAD1* H3K27me3	No significant differences in *GAD2* mRNA levels; Decreased expression of *GAD1* mRNA for female SZ
Tang et al. [98]	SZ (16 + 8 + 8): (11/5) + (–/–) + (7/1)	HC (18 + 8 + 8): (11/7) + (–/–) + (6/2)	range: 11–80, 18–36, 55–92	range: 11–80, 18–36, 55–92	DSM-IV (DIBB)	NR (USA)	NR	PFC [BA10, BA46] (HBTRC, VBBN)	H3K9 H3K14	Acetylation	ChIP-PCR	↓#	Significant hypoacetylation of H3K9K14 in young SZ cases#	Promoter-associated ac-H3K9K14 levels correlated with gene expression of *GAD1*, *HTR2C*, *TOMM70A*, and *PPM1E*
Biofluid														
Chase et al. [46]	SZ: 25 (16/9)	HC: 19 (14/5)	30.5 ± 11.1	31.5 ± 8.7	NR (PANSS)	NR (USA)	*M* 72%	PBMCs (Lymphocytes)	H3K9	Di-methylation	Immunoblotting	↑	SZ-associated increased H3K9me2	SZ-associated increased GLP, SETDB1, and G9a mRNA expression; Increased histone methyltransferase mRNA expression associated with symptom severity, illness duration, and family history of SZ
Chase et al. [127]	SZ: 40 (21/19)	HC: 34 (15/19)	*m*: 35.4 ± 12.18 *f*: 40.1 ± 13.51	*m*: 33.9 ± 9.65 *f*: 35.1 ± 11.03	DSM-IV-TR	Caucasian ≈ 18%, Asian ≈ 8%, Other ≈ 74% (USA)	*M* ≈ 95%	PBMCs (Lymphocytes)	H3K9	Di-methylation	ELISA	↑#	SZ-associated elevation of H3K9me2 levels for males (compared to HC and SZ females)#	Histone methyltransferase mRNA levels (G9α, SETDB1) increased for SZ males Increased H3K9me2, G9α, and SETDB1 levels correlated with severity of symptoms in a sex-dependent manner
Sharma et al. [47]	SZ: 37	HC: 42	NR	NR	NR	NR (USA)	*M*	PBMCs (Lymphocytes)	H3S10	Phosphorylation	ELISA	↑	SZ-associated elevation of H3K10phos levels	Correlation between H3S10phos and clinical symptomology measured by PANSS

↓ decrease, ↑ increase, *X* no difference, # effects are significant for subgroups, *BA* Brodmann area, *BE II* BrainNet Europe II (Munich, Germany), *BS* bisulfite sequencing, *BVARC* Bronx Veterans Affairs Research Center (Bronx, NY, USA), *C* Cases, *ChiP-PCR* chromatin immunoprecipitation PCR, *CTRL* controls, *DIBB* Diagnostic Instrument for Brain Studies, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *f* female, *GAD1* glutamate decarboxylase 1, *GLP* Eu-HMTase1, *G9α* Eu-HMTase2, *H* histone, *HBTRC* Harvard Brain Tissue Resource Center (Boston, MA, USA), *HC* healthy controls, *HMT* histone methyltransferases, *IHC* immunohistochemistry, *K* lysine, *m* male, *MPRC* Brain Bank of Maryland Psychiatric Research Center (Baltimore, MD, USA), *N* sample number, *NChIP* native chromatin immunoprecipitation, *NR* not reported, *PANSS* Positive and Negative Syndrome Scale, *PBMCs* peripheral blood mononuclear cells, *PFC* prefrontal cortex, *qPCR* quantitative polymerase chain reaction, *R* arginine, *SD* standard deviation, *SEM* standard error of the mean, *SETDB1* SET domain bifurcated histone lysine methyltransferase 1, *SFNC* Stanley Foundation Neuropathology Consortium (Bethesda, MD, USA), *SZ* schizophrenia, *UC* University of California Brain Bank (Davis, CA, USA), *UIC* University of Illinois at Chicago Medical Center (Chicago, IL, USA), *VBBN* Victorian Brain Bank Network (Melbourne, Australia).

mmunoblotting, and chromatin immunoprecipitation PCR served as quantification methods. There were two reports of disease-specific findings [46, 47], while the other studies yielded no differences or effects that were significant only in relation to sex or a population subgroup.

MicroRNA

Table 3 presents the details of 42 articles investigating miRNAs (22 in brain tissue, 20 in the blood). They differed in the number of tested miRNAs (from a single miRNA to several hundred), quantification method (i.e., custom or commercial microarray assays, quantitative reverse transcription PCR, RNA-seq, Taqman Low-Density Array), and the use of qPCR validation (10 studies). A mixed expression pattern emerged: 16 studies found only upregulations (↑), 6 only downregulations (↓), 15 identified a mixed pattern (↑↓), while 7 revealed no difference (x) in miRNA expression. Altogether, 241 and 164 miRNAs were found to be upregulated and downregulated, respectively. The following nine miRNAs were most frequently identified as having significant effects across all studies in this category: miR-34a (×8: 8↑), miR-30e (×7: 5↑, 2↓), miR-7 (×7: 6↑, 1↓), miR-181b (×6: 6↑), miR-132 (×5: 2↑, 3↓), miR-195 (×5: 3↑, 2↓), miR-212 (×5: 2↑, 3↓), miR-432 (×4: 3↓, 1↑), and miR-107 (×4: 2↓, 2↑). Upregulations of miR-34a, miR-7, and miR-181b were the most consistent findings.

Discussion

This systematic review was motivated by the exponential rise in studies of psychiatric epigenetics over the last decade (see Supplementary Material Fig. S2), coupled with the lack of recent systematic reviews of psychosis in particular and the putative role of epigenetic signaling in its etiology. Following a discussion of key findings, we delineate some major limitations and future prospects.

Global methylation

Overall, global methylation studies have delivered ambiguous results. Specifically, schizophrenia-related hypermethylation was found in both brain tissue [36, 41] and leukocytes [43]. Conversely, a lower level of methylation was detected in blood cells [38, 39, 42], while four studies, one in brain tissue [37] and three in leukocytes [40, 44, 45] pointed to no differences. Notably, secondary findings have shed some light on the missing primary effects, which may be better explained as sex- or age-dependent [44, 45], in association with childhood trauma [40] or smoking status [45]. Confounding factors might have blurred observable effects. Perhaps global methylation is an insufficiently sensitive measure to detect disease-related epigenetic signatures. Moreover, this marker may be more related to sex, age, and/or cellular composition than the psychotic disorders themselves. Nevertheless, this does not preclude this process being involved in the disease. Notably, alterations in global DNA methylation have been linked to genomic instability [48], and in one previous study, haloperidol treatment was found to reduce global hypermethylation in schizophrenia patients towards a more "control-like" state [42].

Candidate genes

Studies using a priori selected genes comprised the largest group ($n = 64$). They historically precede more recent genome-wide techniques, with more than half exploring genes related to common neurotransmitter pathways (grouped into neurotransmitter- and other-system-related categories). In conformity with the dopamine hypothesis of schizophrenia [49], several studies have examined genes related to dopaminergic regulation, with some of them being of primary relevance, i.e., *DRD1*-5 and *COMT*, which encode dopamine-degrading enzymes. Notably, Cheng et al. [50] found schizophrenia-associated hypermethylation at the *DRD4* promoter in peripheral blood; a very similar effect was identified by Dai et al. [51] for *DRD3* in the same tissue, while other authors reported hypomethylation of *DRD2*, *DRD4*, and *DRD6* [52]. In addition, two isoforms of a dopamine-metabolizing system, namely *MB-COMT* and *S-COMT*, were also differentially methylated. Specifically, *MB-COMT* hypomethylation [53–55] and *S-COMT* hypermethylation [42] were identified, but the latter was not confirmed independently [56]. The GABAergic system is another primary mammalian (inhibitory) neuro-signaling system, with *RELN* and *GAD1* being the most representative genes. Disease-specific hypermethylation at the promoter region was found for *RELN* in the brain [57, 58] as well as in the whole blood [59]. However, three independent reports found no difference between cases and controls [60–62]. For *GAD1*, decreased methylation levels were evident in the prefrontal cortex for cases [63]. Additionally, genes regulating serotonergic signaling (1A and 2A receptors and serotonin transporter) were typically found to be hypermethylated in association with schizophrenia [64–66].

Outside the neurotransmitter-related category, brain-derived neurotrophic factor deserves special attention for its role in neuroplasticity [67]. While *BDNF* I promoter hypermethylation has been linked to schizophrenia [68], IV promoter hypomethylation has been found [69], but could not be confirmed elsewhere [68]. Furthermore, other authors were unable to find any effects [13, 70]. Differential methylation of a few other loci was detected for *SOX10* (↑ brain) [71], which regulates embryonic development and

Table 3 Details of studies reporting changes in miRNA expression associated with schizophrenia and other psychotic disorders.

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Method	miRNAs	Expression	Target genes/pathways/function
	Cases	CTRLS	Cases	CTRLS								
Postmortem brain tissue												
Banigan et al. [170]	SZ: 8 (8/0)	HC: 13 (9/4)	69.88 ± 15.97	64.15 ± 18.11	NR	NR (Europe, USA)	*M* ≈ 88%	PFC exosomes [BA9] (HBTRC, BNE II, BMC)	Luminex FlexMap 3D microarray assay, qRT-PCR	↑ miR-31, miR-33, miR-96, miR-28, miR-30e-5p, miR-199a*, miR-15b, miR-455, miR-323, miR-93, miR-32, miR-20b, miR-92, miR-30a-3p; ↓ miR-501, miR-504, miR-29c, miR-380-3p, mIr-527, miR-516-5p, miR-497; ↑ miR-497	Upregulation (14) Downregulation (7) (RT-PCR validation underlined)	Pathways: cortical gene expression, regulation of anti-apoptotic proteins, neuronal K(+) Cl(−) co-transporter 2, neuronal death
Beveridge et al. [102]	SZ: 21 (14/7)	HC: 21 (15/6)	52.7 ± 11.7	53.2 ± 11.4	DSM-IV (IGC-SCAN, DIBS)	Caucasian (Australia)	*M*	STG [BA22] (NSW BTRC)	Custom miRNA microarray assay, qRT-PCR	↑ **miR-181b**	Upregulation (1)	Related functions: regulation of numerous target genes, e.g., *VSNL1*, *GRIA2*
Beveridge et al. [103]	SZ: 21 (14/7)	HC: 21 (15/6)	52.7 ± 11.7	53.2 ± 11.4	DSM-IV (IGC-SCAN, DIBS)	Caucasian (Australia)	*M*	STG [BA22] (NSW BTRC)	Custom miRNA microarray assay, qRT-PCR	↑ let-7e, miR-9*, miR-15a, miR-15b, miR-16, miR-17-3p, miR-17-5p, miR-19a, miR-20a, miR-23a, miR-24, miR-26b, miR-27b, miR-28, miR-99a **miR-107**, miR-125b, miR-128a, miR-128b, miR-129, miR-130a, miR-133b, miR-138, miR-146b, miR-148a, miR-150, miR-152, miR-155, **miR-181b**, **miR-195**, miR-197, miR-199a*, miR-222, miR-296, miR-328, miR-330, miR-335, miR-338, miR-339, miR-340, miR-373*, miR-381, miR-409-5p, **miR-432***, miR-452*, miR-455, miR-484, miR-485-5p, miR-486, miR-487a, miR-489, miR-494, miR-499, miR-502, miR-517a, miR-517c, miR-518b, miR-519d, miR-520a*, miR-520g	Upregulation (59) (qRT-PCR validation underlined)	Pawthways: miR-107 and miR-15 family: Wnt signaling, MAPK signaling, focal adhesion, regulation of actin cytoskeleton, axon guidance; Examples of predicted genes: *RGS4*, *GRM7*, *GRIN3A*, *HTR2A*, *RELN*, *VSNL1*, *DLG4*, *DRD1*, *PLXNA2*
	SZ: 15 (11/4)	HC: 15 (10/5)	50.5 (12.7)	52.4 (12.2)	DSM-IV (IGC-SCAN, DIBS)	Caucasian (Australia)	*M*	DLPCF [BA9] (NSW BTRC)	Custom miRNA microarray assay, qRT-PCR	↑ let-7d, **miR-7**, miR-16, miR-20a, miR-27a, miR-29c, miR-31, miR-33, miR-101, miR-105, miR-126*, miR-128a, miR-153, miR-181a, **miR-181b**, miR-181d, miR-184, miR-199a, miR-219, miR-223, miR-302a*, miR-302b*, miR-338, miR-409-3p, miR-512-3p, miR-519b	Upregulation (26) (qRT-PCR validation underlined)	–
Burmistrova et al. [171]	SZ: 12 (–/–)	HC: 12 (–/–)	–	–	ICD-10	NR (USA)	NR	Parietal cortex [BA7] (SMRI)	miRNA microarray assay, qRT-PCR	X miR-130b	No differences	–
Guella et al. [172]	SZ (7 + 35): (4/3) + (25/10)	HC (10 + 33): (7/3) + (25/8)	46.1 ± 10.0 42.6 ± 8.5	48.0 ± 13.0 43.6 ± 7.6	NR	NR (USA)	NR	AC, AMY, CAUN, CBL, DLPFC, HIPP, NACC, OFC, PUT, THAL (UC IBB, SMRI)	qRT-PCR	X **miR-137**	No differences (but decreased miR-137 expression associated with the SZ risk allele rs1625579)	Genes: *TCF4* (transcription factor)
Kim et al. [173]	SZ: 35 (26/9)	HC: 35 (26/9)	42.57 ± 8.47	44.20 ± 7.58	DSM-IV	Caucasian (USA)	*M* ≈ 91%	DLPFC [BA46] (SMRI)	qRT-PCR	↑ **miR-132**, miR-132*, miR-154*, **miR-212**, **miR-34a**, miR-544, **miR-7**	Upregulation (7)	Targets in brain-specific genes contained within networks overrepresented for neurodevelopment, behavior, and SZ neurodevelopment. *GRM3*, *PGD*, tyrosine hydroxylase
Kimoto et al. [174]	SZ + SZAD (39 + 23): 62 (47/15)	HC: 62 (47/15)	47.7 ± 12.7	48.7 ± 13.8	DSM-IV	Caucasian ≈ 87%, Other ≈ 13% (USA)	*M* ≈ 76%	DLPFC [BA9]	qRT-PCR	↑ miR16	Upregulation (1) (matched comparison subject analysis)	*RGS4* (Regulator of G protein Signaling 4); NMDAR signaling
Lai et al. [175]	SZ: 25 (21/4)	HC: 27 (22/5)	43.4 ± 18.3	43.3 ± 18.1	DSM-IV DIBS	NR (Australia)	*M*	DLPFC [BA46], PUT (ABBN)	qRT–PCR	X **miR-34a**	No differences (miR-34a higher in BA46 for SZ with long duration of illness (DOI))	–
Liu et al. [176]	SZ: 14 (–/–)	HC: 13 (–/–)	–	–	NR	Caucasian (USA)	NR	AMY (LIBD)	RNA-seq	↑ miR-196a-2, miR-1975, miR-34c, miR-451, **miR-34a**, miR-375, miR-144; ↓ miR-663, miR-639, **miR-132**, miR-124-2, **miR-212**, miR-483, miR-886, miR-585, miR-424, miR-520d	Upregulation (7) Downregulation (10)	Expression of neurogenesis genes, glucocorticoid signaling, neural differentiation

Table 3 (continued)

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Method	miRNAs	Expression	Target genes/pathways/function
	Cases	CTRLS	Cases	CTRLS								
Mellios et al. [177]	SZ: 20 (13/7)	HC: 20 (13/7)	57.55 ± 15.48	57.25 ± 15.62	DSM-IV-R	NR (USA)	*M* 90%	PFC [BA10]	qRT-PCR	X **miR-195**, miR-30a-5p ↓[#]	No differences Downregulation for mature miR-195[#]	miR-195: related to BDNF pathway and NPY (neuropeptide Y) and SST (somatostatin)
Mellios et al. [178]	SZ: 20 + 10 (PFC) + 11 (PC): (13/7 + 5/5 + 9/2)	HC: 20 + 10 (PFC) + 12 (PC): (13/7 + 5/5 + 7/5)	57.6 ± 3.5; 43.7 ± 3.2; 41.6 ± 3.5 (SEM)	57.3 ± 3.5; 42.4 ± 3.5; 47.1 ± 2.7 (SEM)	DSM-IV	NR (USA)	*M* (mostly)	PFC [BA9, BA10]; PC [BA7]	qRT-PCR	X miR-30b ↓ miR-30b[#]	No difference Down-regulation (only in SZ females in PFC[#])	Predicted miR-30b SZ-related target genes: *ATXN1*, *GRM5*, *SLC1A2*, *SLC25A14*, *TNXB*, *NR4A2*, *FRK*, *HSPA5*, *JARID2*, *ST8SIA4*, *BDNF*, *CNR1*, *CLOCK*, *JAG2*, *GRM3*, *PIP4K2A*, *KPNA3*, *DPYSL2*, *MECP2*, *CHL1*
Miller et al. [100]	SZ: 35 (26/9)	HC: 34 (25/9)	42.6 ± 8.5	43.8 ± 7.4	DSM-IV	Caucasian (USA)	*M* ≈ 91%	DLPFC [BA46] (SMRI)	Custom miRNA microarray assay, qRT-PCR	↓ **miR-132**	Downregulation (1)	Target genes (among others): *GATA2*, *PDE7B*, *ANKRD11*, *P250GAP*, *FKBP2* Long-term potentiation and long-term depression pathways, CREB signaling, synaptic outgrowth, postmitotic neuronal differentiation
Moreau et al. [179]	SZ: 35 (26/9)	HC: 35 (26/9)	42.57 ± 8.47	44.20 ± 7.58	DSM-IV	Caucasian (USA)	*M* ≈ 91%	PFC [BA9] (SMRI)	qRT-PCR, FlexmiR v2 assay (Luminex)	↑ miR-193b, miR-545, miR-301, miR-27b, miR-148b, miR-639, miR-186, miR-99a, miR-190; ↓ miR-33, miR-138, miR-151, miR-210, miR-324-3p, miR-22, miR-425, miR-106b, miR-338, miR-339; X miR-330, miR-181a, miR-193a, miR-192, miR-15a	Upregulation (9) Downregulation (10) No differences (5)	Host genes: *EML2*, *SREBF2*, *PTK2*, *ACADVL*, *C17orf91*, *DALDR3*, *NR6A1*, *MCM7*, *FAM33A*, *C9orf3*, *COPZ1*, *AATK*, *GPSN2*, *DLEU2*, *ZRANB2*, *C21orf34*, *TLN2*, *C7orf50*
Perkins et al. [180]	SZ + SZAD (13 + 2): 15 (10/5)	HC: 21 (16/5)	–	–	NR	NR (USA)	*M*	PFC [BA9] (HBTRC)	Custom miRNA microarray assay, qRT-PCR	↓ **miR-7**, miR-9-3p, miR-20b, miR-24, miR-26b, miR-29a, miR-29b, miR-29c, miR-30a-5p, miR-30b, miR-30d, **miR-30e**, miR-92, **miR-195**, **miR-212**; ↑ miR-106b	Downregulation (15) Upregulation (1) (qRT-PCR validation underlined)	Regulation of actin cytoskeleton, focal adhesion, MAPK/ phosphatidylinositol/calcium/ insulin/ JAK-STAT signaling pathways, ECM-receptor interaction, methionine metabolism, gab junction, tight junction, circadian rhythm
Pietersen et al. [181]	SZ: 9 (4/5)	HC: 9 (4/5)	68.11 ± 6.60 (SEM)	69.11 ± 6.85 (SEM)	NR	NR (USA)	*M*	STG [BA42] (HBTRC) laser-captured pyramidal neurons from layer 3	Megaplex miRNA TaqMan arrays, qRT-PCR	↑ miR-328, miR-30b, miR-99b, miR-126, miR-520d-3p; ↓ miR-628-5p, miR-150, miR-1243, miR-875-5p, miR-378	Upregulation (5) Downregulation (5)	TGF-β signaling, regulation of actin cytoskeleton, ECM-receptor interaction, apoptosis, mitogen-activated protein kinase (MAPK) signaling, neurotrophin signaling, axon guidance, WNT signaling
Pietersen et al. [182]	SZ: 8 (4/4)	HC: 8 (4/4)	67.1 ± 21.2	67.0 ± 20.9	NR	NR (USA)	*M*	STG [BA42] (HBTRC) parvalbumin-immunoreactive neurons from layer 3	Megaplex miRNA TaqMan arrays	↓ miR-106a, miR-218, miR-342-3p; ↑ miR-151-3p, miR-338-5p, miR-197, miR-342-3p, miR-518f, miR-1274b, miR-151-3p, **miR-195**, miR-197, **miR-34a**, miR-361-5p, miR-520c-3p	Downregulation (3) Upregulation (12)	WNT and NOTCH signaling, DNA damage, apoptosis, cell cycle and actin cytoskeleton regulation pathways
Ragan et al. [183]	SZ: 22 (11/11)	HC: 22 (11/11)	52 ± 13.9	53 ± 15.0	NR	NR (Australia)	*M* ≈ 82%	ACC (UQBB, ABBN)	RNA-seq using Illumina HiSeq 2000 platform	X	No differences (18 miRNAs differentially expressed between male and females, 11 between female SZ and HC)	–
Santarelli et al. [184]	SZ + SZAD (30 + 7): 37 (24/13)	HC: 37 (30/7)	51.3 ± 14.1	51.1 ± 14.6	DSM-IV	Caucasian (Australia)	*M*	DLPFC [BA9] (NSW BTRC)	miRNA microarray assay, qRT-PCR	↑ miR-17, **miR-107**, miR-134, miR-328, miR-382, miR-652	Upregulation (6) qRT-PCR validation (based on initial 28 differentially expressed miRNAs, 25 upregulated, 3 downregulated)	299 schizophrenia candidate genes, including *GRIN1*, *GRIN2*, *GRIN3*, *EGR3;* Synaptic plasticity, axon guidance, long-term potentiation
Scarr et el. [123]	SZ: 27 (21/6) (14 SZ(Def) + 13 SZ (Ndef))	HC: 15 (12/3)	45 ± 3	45 ± 4	DSM-IV (DIBS)	NR (Australia)	*M*	PFC [BA9]	qRT-PCR	↓ **miR-107**[#]	Downregulation (for contrast SZ(Def) vs. HC)[#]	CHRM1 expression

Table 3 (continued)

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Method	miRNAs	Expression	Target genes/pathways/function
	Cases	CTRLS	Cases	CTRLS								
Smalheiser et al. [185]	SZ: 15 (9/6)	HC: 15 (9/6)	44.2	48.1	DSM-IV	Caucasian 90%, Asian ≈7%, Other ≈3% (USA)	*M* ≈ 93%	PFC [BA10] (SFBC NC)	TLDA, RNA-seq, qRT-PCR	↑ miR-17-5p, miR-331-5p, miR-16-5p, miR-106b-5p, miR-454-3p, miR-185-5p, miR-429-3p, miR-18a-5p, miR-590-5p, miR-106a-5p, miR-642a-5p, miR-625-5p, miR-219-2-3p ↓ miR-187-3p, miR-485-5p, miR-129-2-3p, miR-511, miR-145-5p, miR-508-3p	Upregulation (13) Downregulation (6)	Synaptic signaling, NMDAR
Wong et al. [186]	SZ + SZAD (30 + 7): 37 (24/13)	HC: 37 (30/7)	51.3 ± 2.32 (SEM)	51 ± 2.40 (SEM)	DSM-IV	Caucasian ≈ 97%, Asian ≈ 3% (Australia)	*M*	DLPFC [BA9] (NSW BTRC)	miRNA microarray assay, qRT-PCR	↑ miR-17	Upregulation	*NPAS3* (transcription factor)
Zhu et al. [187]	SZ: 35 (29/6)	HC: 34 (–/–)	42.57 ± 8.47	–	DSM-IV	Caucasian (USA)	*M* ≈ 91%	DLPFC [BA46] (SMRI)	qRT-PCR	↓ **miR-346**	Downregulation	*MiR-346* gene, located in intron of *GRID1* Targeted SZ-related genes: *CSF2RA*, *DGCR6L*, *GRIN2C*, *HTR1D*, *IL4R*, *LST1*, *OPRS1*, *PTGDS*, *RTN4R*, *SLC44A4*, *ZNF471*, *ARVCF*, *L1CAM*
Biofluid												
Alacam et al. [188]	SZ(TResp): 19 (13/6) SZ(TRes): 18 (14/4)	HC: 10 (6/4)	39.05 ± 12.14 41.61 ± 9.63	31.50 ± 7.98	DSM-IV	NR (Turkey)	*M*	Plasma	qRT-PCR	SZ(TResp) vs. HC: ↓ miR-181b-3p, miR-195-5p, miR-301a-3p; SZ(TRes) vs. HC: ↑ miR-181b-3p, miR-195-5p, miR-301a-3p	Downregulation Upregulation	Target genes: *GRIA2*, *VSNL1*, *HTR2A*, *DRD1*, *BDNF*, *GRID2*
Cattane et al. [189]	SZ: 32 (18/14)	HC: 17 (9/8)	48.1 ± 1.1 (SEM)	46.5 ± 2.3 (SEM)	DSM-IV	NR (Italy)	*M*	Whole blood	miRNA microarray assay, qRT-PCR	X (numerous, hypothesis-free)	No differences (but downregulation of miR-125b-1-3p in a subgroup with history of childhood trauma)	Stress vulnerability Immune response
Fan et al. [190]	SZ: 55 (32/23)	HC: 28 (15/13)	33.28 ± 14.96	33.35 ± 15.43	DSM-IV	Asian (China)	*U*	PBMCs	miRNA microarray assay, qRT-PCR	↑ miR-1228, miR-12246, miR-1273d, miR-1303, miR-1908, miR-1910, miR-21, miR-3064-5p, miR-3131, miR-3156-5p, miR-3188_st, miR-3617, miR-3687, miR-3916, miR-3937, miR-4271, miR-4428, miR-4436b-5p, miR-4467, miR-4486, miR-4488, miR-4492, miR-4506, miR-4508, miR-4646-5p, miR-4708-5p, miR-4725-3p, miR-4753-5p, miR-5096, miR-885-3p, miR-885-5p, miR-92b; ↓ miR-4701-3p	Upregulation (32) Downregulation (1) qRT-PCR validation underlined	Target genes: *EIF2C1*, *CLIC6*, *DCAF7*, *DGKB*, *DSEL*, *ESRRG*, *GLDN*, *KCNA1*, *LPP*, *PCGF5*, *RAB22A*, *ZNF445* Synaptic transmission, axon guidance, regulation of long-term neuronal synaptic plasticity, nerve growth factor receptor/ErbB/ Chemokine/TGF-beta/Notch/Wnt/ JAK-STAT signaling pathways
Gardiner et al. [191]	SZ: 112 (69/43)	HC: 76 (34/39) 3 *NR*	40.71 ± 12.35	37.83 ± 15.58	DIP	Caucasian (mostly) (Australia)	*U* ≈ 80%	PBMCs (ASRB, HDB)	miRNA microarray assay, qRT-PCR	↓ miR-329, miR-31, miR-409-3p, miR-224, **miR-432**, miR-487b, miR-134, miR-431, miR-150*, miR-99b, miR-1275, miR-335*, miR-200c, miR-486-3p, miR-29b-1*, miR-16-2*, miR-877, **miR-107**, miR-130b, miR-544, miR-342-5p, miR-148b, miR-625*, miR-28-3p, mIR-576-5p, miR-151-3p, miR-28-5p, miR-664, miR-128, miR-584, miR-574-3p, miR-181a, **miR-30e***, miR-433	Downregulation (33) Q-PCR validation underlined	Pathways: axon guidance, long-term potentiation, focal adhesion, neurotrophin, ErbB, calcium and mitogen-activated protein kinase signaling, neurological, and immune system pahtways
Lai et al. [192]	SZ: 30 (12/18) [LC] SZ: 30 (13/17) [TC]	HC: 30 (12/18) [LC] HC: 60 (28/32) [TC]	– range: 20–65	– range: 20–65	DSM-IV DIGS	Asian (Taiwan)	*M*	Leukocytes	TLDA genome-wide profiling for a subset of cases and controls, qRT-PCR	↑ **miR-34a**, miR-449a, miR-564, miR-548d, miR-572, miR-652; ↓ **miR-432**	Upregulation (6) Downregulation (1) (RT-PCR validation underlined)	Multiple target genes, e.g., *DLL1*, *JAG1*, *BCL1*, *MAP2K1*; Cyclin-dependent kinase 5 (Cdk5), Notch signaling
Lai et al. [175]	SZ: 48 (25/23)	HC: 37 (14/23)	40.2 ± 10.7	38.0 ± 10.8	DSM-IV	Asian (Taiwan)	*M*	PBMCs	qRT-PCR	↑ **miR-34a**, miR449a, miR-564, miR-548d	Upregulation (4)	SZ-associated and age-dependent increases in miR-34a expression miR-34a targets: *GREM2*, *CAMSAP1*, *TANC2*, *6CALN1*, *RGMB*, *FKBP1B*, and *RTN4RL1* (related to neural development and function)

Table 3 (continued)

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Method	miRNAs	Expression	Target genes/pathways/function
	Cases	CTRLS	Cases	CTRLS								
Liu et al. [193]	SZ: 38 (15/23)	HC: 50 (18/32)	36.8 ± 10.7	37.0 ± 7.3	DSM-IV	Asian (China)	*M*	PBMCs	qRT–PCR	↓ miR-30a-5p, miR-30e-5p X miR-30c-5p	Downregulation (2) No differences	*EGR1-miR-30a-5p-NEUROD1* axis
Ma et al. [194]	SZ(FO): 10 (5/5)	HC: 10 (5/5)	*m*: 27.70 ± 1.71 *f*: 28.10 ± 1.69	*m*: 29.22 ± 2.22 *f*: 29.06 ± 1.93	DSM-IV	Asian (China)	NR	Whole blood	RNA-seq qRT-PCR	↑ miR-22-3p, miR-30d-5p, miR-30e-5p, miR-92a-3p, **miR-137**, miR-148b-5p, miR-181a-3p, miR-181a-5p, miR-181b-5p, miR-195-5p, miR-199b-5p, and miR-497-5p	Upregulation (12) (qRT-PCR validation underlined)	Gene ontology enrichment: PSD, synapse, and synaptic transmission
Shi et al. [195]	SZ: 115 (78/37)	HC: 40 (25/15)	35.7 ± 12.7	32.5 ± 10.7	ICD-10	Asian (China)	*M*	Serum	qRT–PCR	↑ **miR-181b**, miR-219-2-3p, miR-1308, let-7g, **miR-346**, miR-92a; ↓ **miR-195**, miR-17; X miR-103	Upregulation (6) Downregulation (2) No difference (1)	Expression regardless of family history subtypes, age, and gender Target genes associated with NMDA-R signaling, *BDNF* expression, and neuronal differentiation
Song et al. [196]	SZ: 20 (11/9)	HC: 20 (12/8)	30.90 ± 11.94	30.85 ± 12.10	DSM-IV	Asian (China)	*U*	Plasma	qRT-PCR	↑ **miR-181b**, **miR-30e**, **miR-34a**, **miR-7;** X **miR-132**, **miR-195**, **miR-212**, **miR-346**, **miR-432**	Upregulation (4) No differences (5)	Related functions: synaptic transmission, nervous system, developmental disorders
Sun et al. [197]	SZ: 61 (39/22)	HC: 62 (40/22)	27.84 ± 10.64	28.08 ± 10.98	DSM-IV	Asian (China)	*U*	Plasma	qRT–PCR	↑ **miR-181b**, **miR-30e**, **miR-346**, **miR-34a**, **miR-7;** X **miR-132**, **miR-195**, **miR-212**, miR-432, **miR-137**	Upregulation (5) X no differences (5)	Related functions: *GRM7*, *GRID1*
Sun et al. [198]	SZ: 25 (17/8)	SZ: 13 (7/6)	27.84 ± 10.64	28.08 ± 10.98	DSM-IV	Asian (China)	*U*	PBMC ---------- Plasma	qRT–PCR	↑ **miR-212**, **miR-34a**, **miR-30e;** ---------- ↑ **miR-132**, **miR-195**, **miR-30e**, **miR-7**	Upregulation	Regulation of *Ubc9* expression Regulator of prefrontal *BDNF* expression
Wei et al. [199]	SZ: 164 (81/83) [TC] SZ: 400 (189/211) [VC]	HC: 187 (88/99) [TC] HC: 213 (105/108) [VC]	29.2 ± 9.8 25.0 ± 7.5	28.7 ± 9.5 26.2 ± 56	DSM-IV	Asian (China)	*U*	Plasma	RNA-seq TLDA qRT-PCR	↑ **miR-122**, miR-130a, miR-130b, miR-193a-3p, miR-193b, miR-502-3p, miR-652, miR- 886-5p	Upregulation (8) (from both methods) (RT-PCR validation underlined)	*PDGFRA*, *PPARG*, *ErbB4* (SZ susceptibility genes), *RUNX3*, *ITGB1*, *FMR1*, *STAT3* (neurodevelopment-related genes), *S6K2*, *MCL1* (neuroprotective genes)
Weigelt et al. [200]	PP: 8 [TC] PP: 20 [VC]	HCP: 8 HCNP: 8 [TC] HCP: 20 HCNP: 20 [VC]	34 range: 25–41 33 range: 25–41	37 range: 33–42 31 range: 25–44 32 range: 25–36 32 range: 22–41	DSM-IV-TR (SCID–I/P)	Caucasian (Netherlands)	*M* ≈ 60%	PBMCs	miRNA microarray assay, qRT-PCR	↓ miR-146a (PP vs. HCP and HCNP) ↓ **miR-212**, miR-92a (PP vs. HCNP, but not HCP) ↑ miR-296-5p (HCP vs. HCNP)	Downregulation Upregulation	miR-146a: *ADAM17*, *EGR3*, *IRAK3*, *PTGS2* miR-212*: CXCL2*, *PTGS2* Inflammation
Wu et al. [201]	SZ: 44 (22/22)	HC: 44 (22/22)	*m*: 28.45 ± 6.79 *f*: 30.73 ± 7.67	*m*: 30.22 ± 4.22 *f*: 30.36 ± 7.59	DSM-IV	Asian (China)	*U*	Whole blood	qRT-PCR	↑ **miR-137**	Upregulation	*EFNB2 gene*
Xu et al. [202]	SZ: 43	HC: 40	(–/–)	(–/–)	DSM-IV	Asian (China)	NR	Leukocytes	qRT-PCR	↑ **mir-30e**	Upregulation	–
Xu et al. [203]	SZ: 38 (15/23)	HC: 48 (17/31)	34.3 ± 10.6	31.6 ± 6.88	DSM-IV	Asian (China)	*U*	PBMCs	qTR-PCR	↑ miR-124-3p	Upregulation	*EGR1*, *SKIL* Regulation of differentiation and maturation in the CNS
Yu et al. [204]	SZ: 105 (50/55)	HC: 130 (60/70)	25.03 ± 8.34	22.73 ± 6.79	DSM-IV	Asian (China)	*U*	PBMCs	miRNA microarray assay, qRT-PCR	↓ **miR-132**, miR-134, miR-1271, miR-664*, miR-200c, **miR-432**	Downregulation (6) (underlined qPCR results, based on initial 41 differentially expressed miRNAs)	–

Table 3 (continued)

Reference	*N* (m/f)		Mean age ± SD		Diagnosis	Ancestry (country)	Antipsychotic medication	Tissue source (database)	Method	miRNAs	Expression	Target genes/pathways/function
	Cases	CTRLS	Cases	CTRLS								
Zhang et al. [205]	SZ(FO): 15 (8/7)	HC: 15 (7/8)	13.80 ± 1.93	14.07 ± 1.82	DSM-IV	Asian (China)	*U*	Whole blood	miRNA microarray assay	↓ miR-3174, miR-4259, miR-574-5p, miR-3148, miR-505-5p, miR-3149, miR-664-5p, miR-208a, miR-4538, miR-4653-3p, miR-1299, miR-H7-5p, miR-4297, miR-4742-3p, miR-376a-5p, miR-4303, miR-4540, miR-513b, miR-BART1-5p, miR-3924, miR-4723-5p, miR-4270, miR-4529-3p, miR-4429, miR-34a-5p, miR-BHRF1-3, miR-4251, miR-M1-3p, miR-1827, miR-409-3p, miR-937, miR-4686, miR-202-3p, miR-4458, miR-BART4, miR-3935, miR-K12-4-3p, miR-154-5p, miR-32-3p, miR-635, miR-297, miR-1204, miR-892a, miR-4307, miR-1972, miR-127-5p, miR-92a-2-5p, miR-3191-5p, miR-193b-3p, miR-4539, miR-208b, miR-432-3p, miR-3649, miR-183-3p, miR-BART2-3p, miR-5001-3p, miR-337-3p, miR-451b, miR-325, miR-124-3p, miR-H1, miR-4329, miR-520g/miR-520h	Downregulation (63)	107 miRNA target pairs involving 15 miRNAs and 48 genes Overall dysregulation of transcription
Zhang et al. [206]	SZ: 50 (32/18)	HC: 50 (32/18)	27.22 ± 10.22	26.82 ± 10.00	DSM-IV	Asian (China)	*U*	Plasma	miRNA microarray assay, qRT-PCR	↑ **miR-7**	Upregulation	*SHANK3* expression

miRNAs in bold appeared at least four times across the surveyed studies. Underlined miRNAs were additionally validated within a specific study.

↓ decrease, ↑ increase, *X* no difference, # effects are significant for subgroups, *ABBN* Australian Brain Bank Network, *AC* anterior cingulum, *AMY* amygdala, *ASRB* Australian Schizophrenia Research Bank, *BA* Brodmann area, *BMC* Boston Medical Center (Boston, USA), *BNE* BrainNet Europe II (Munich, Germany), *CAUN* caudate nucleus, *CBL* cerebellum, *CTRL* controls, *DIBS* Diagnostic Instrument for Brain Studies, *DIGS* Diagnostic Interview for Genetic Studies, *DIP* Diagnostic Interview for Psychosis, *DLPFC* dorsolateral prefrontal cortex, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *f* female, *HBTRC* Harvard Brain Tissue Resource Center, *HC* healthy controls, *HCNP* healthy controls non-postpartum, *HCP* healthy controls postpartum, *HDB* Hunter DNA Bank, *HIPP* hippocampus, *ICD-10* International Classification of Diseases, 10th Edition, *IGC-SCAN* Item Group Checklist of the Schedules for Clinical Assessment in Neuropsychiatry, *LC* learning cohort, *LIBD* Lieber Institute Brain Depository, *M* medicated, *m* male, *N* sample number, *NACC* nucleus accumbens, *NR* not reported, *NSW BTRC* The New South Wales Brain Tissue Resource Center (University of Sydney, Australia), *OFC* orbitofrontal cortex, *PBMCs* peripheral blood mononuclear cells, *PC* parietal cortex, *PFC* prefrontal cortex, *PP* postpartum psychosis, *PUT* putamen, *qRT-PCR* quantitative reverse transcription polymerase chain reaction, *SD* standard deviation, *SEM* standard error of the mean, *SFBC NC* Stanley Foundation Brain Collection Neuropathology Consortium, *SMRI* Stanley Medical Research Institute collection, *SNC* Stanley Neuropathology Consortium, *STG* superior temporal gyrus, *SZ* schizophrenia, *SZAD* schizoaffective disorder, *SZ(Def)* [^{3}H]pirenzepine binding deficient schizophrenia, *SZ(FO)* first-onset schizophrenia, *SZ(NDef)* schizophrenia without deficits in [^{3}H]pirenzepine binding, *SZ (TRep)* treatment-responsive schizophrenia, *SZ(TRes)* treatment-resistant schizophrenia, *TC* testing cohort, *THAL* thalamus, *TLDA* Taqman Low Density Array, *U* unmedicated, *UC IBB* University of California Irvine Brain Bank, *UQBB* University of Queensland Brain Bank, *VC* validation cohort.

cell fate, *BAIAP2* (↓ brain) [72], which is responsible for dendritic spine density abnormalities, *CTLA4* (↑ blood) [73], known for its involvement in immune function, and *OXTR* (↑ blood) [74]. *OXTR* is particularly notable for encoding the oxytocin receptor, a key element of the oxytocin system, which was previously linked to schizophrenia-related deficits in social cognition [75]. Overall, these findings indicate varying levels of evidence for the altered DNA methylation status of genes regulating dopamine, serotonin, γ-aminobutyric acid, and neurotrophin availability, as well as for a few genes with less understood functions.

Genome-wide methylation

This group of studies revealed numerous differentially methylated sites between cases and controls. As genome-wide methylation profiling typically tests a large number of markers, which complicates replications, unsurprisingly, the overlap was small, with only one gene appearing twice across top hits, *GRIA1* [13, 76]. *GRIA1* encodes one of the four ionotropic AMPA receptor subunits and is primarily involved in synaptic plasticity. It was described earlier as a key element in the genetic architecture of schizophrenia [15]. Interestingly, some of the data-driven findings have overlapped with those from candidate genes, i.e., *RELN* [77, 78], *COMT* [78], *DTNBP1* [79], and *SOX10* [79]. This is noteworthy because most common high-throughput arrays investigate around 27,000 or 485,000 sites, and undergo conservative corrections for multiple testing to assess statistical significance.

Functional annotation approaches that identify biological attributes of discovered effects are particularly helpful in interpreting the many findings of genome-wide association studies, with a few being especially worthy of consideration. Neuroinflammation/immune function was a recurrent finding across studies of both brain [36, 78, 80] and blood tissues [77, 80–82]. The repeatedly postulated link between schizophrenia and dysregulated immune systems is based on markers of elevated cerebral inflammation in post-mortem brain tissue and microglial activation [83]. Significantly, this agrees with conclusions from a large epidemiological study suggesting severe infections and autoimmune disorders are schizophrenia risk factors [84]. Similar conclusions have been reached for mitochondrial dysfunction and energy metabolism processes [13, 85]. Notably, substantial links between mitochondrial deficits and schizophrenia come from genomics, proteomics, and anatomical studies [86]. Furthermore, gene annotation referring to synaptic transmission [78, 87, 88] is consistent with research on aberrant brain neurotransmitter signaling [89], largely reflected in the aforementioned candidate gene studies. Further associated terms were neurogenesis and neurodevelopment [78, 87, 90–92], highlighting the progressive characteristics and early molecular origins of schizophrenia [93]. Accordingly, one recent study found enrichment of methylation in fetal brain tissue for schizophrenia susceptibility loci identified from a large genome-wide association study [94]. These biological processes present a series of hypotheses awaiting evaluation, but they may also be interrelated. For example, as ATP synthase and calcium homeostasis are crucial for preserving synaptic strength, their impairment can cause metabolic and synaptic signaling deficiencies [95]. Mitochondrial dysfunction may cause oxidative stress and inflammation, subsequently initiating neuroprogressive changes [96] that produce disease symptoms.

Histone modification

Chase et al. [46] and Sharma et al. [47] uncovered schizophrenia-related increases in H3K9 di-methylation in brain and blood tissues and higher H3K10 phosphorylation in blood, respectively. The same pattern in blood and brain positions the H3K9 di-methylation as a putative epigenetic hallmark that may underlie schizophrenia pathogenesis. Notably, this effect was accompanied by elevated histone methyltransferase enzymes (GLP, SETDB1, G9α) [46]. While histone modification results lack an exact consensus, they are indicative of a restrictive chromatin environment and reduced expression of gene groups such as *GAD1* [97, 98].

MicroRNAs

The existing data generally support the hypothesis that miRNA is dysregulated in schizophrenia and other psychotic disorders. As it would be outside the scope of this review to comment on each miRNA, especially since the exact roles for many are still unclear, we list and refer to the most recurrent and representative differentially expressed miRNAs, which may also be potential schizophrenia biomarkers: miR-7, miR-16, miR-30e, miR-31, miR-34a, miR-92, miR-107, miR-130, miR-132, miR-137, miR-181b, miR-195, miR-212, miR-346, and miR-432. Some of these miRNAs have been discussed previously in the context of schizophrenia. For example, miR-137 overexpression influences synaptogenesis, pre-synaptic micro-structure, and function, thus reducing synapse density and compromising synapse performance [99], a potential central disruption hypothesized in schizophrenia. Downregulated miR-132 regulates genes involved in neurodevelopment, including *DNMT3A*, *DPYSL3*, and *GATA2* [100]. Moreover, the miR-132/miR-212 family influences genes relevant for circadian clock entrainment [101], consistent with the defective circadian synchronization that has been

observed in schizophrenia. The upregulation of miR-181b [102] was associated with downregulated schizophrenia-related genes, including *VSNL1* and *GRIA2*. In addition, miR-195 might act as a "fine-tuner" of the BDNF protein, an effect that can extend to prefrontal abnormalities of GABAergic mRNAs [103]. The multitude of non-coding RNAs actively respond to environmental and bodily molecular signals, and ~70% of human miRNAs are expressed in the nervous system [104] and regulate approximately 60% of human genes [105], adding complexity to transcriptional regulation mechanisms. Our findings are consistent with previous conclusions on dysregulated miRNAs within a broader spectrum of major psychiatric disorders [106]. As evident from proteomic studies, a single miRNA may shape the molecular identity of individual cells, with continuous widespread influences during neurodevelopmental stages and adulthood [106]. The reported studies are limited in their conclusions regarding causality and the exact contribution of miRNAs in coordinating the gene regulatory network and gene expression. This challenge has been undertaken by systems biologists [107] and has started revealing important insights into the mechanics of this subject.

Secondary findings

As methylation is relevant not only as a local molecular occurrence, but also through its impact on gene expression, we were particularly interested in the methylation–expression link. From the pool of candidate gene studies reviewed, a majority of those that reported both significant methylation effects and methylation–expression status revealed an inverse relationship. This was the case for *RELN* [57], *MB-COMT*, and *DRD1* expression [53], *HTR2A* and its -1438/G (rs6311) polymorphism [108], *SLC6A4* [64], *HTR2A* [65] *SOX10* [71], *GAD1* regulatory genes [109], *GCH1* [110], *BDNF* [69], *GRM2*, *GRM5* [111], *DRD2*, *DRD4*, *DRD5* [52], *SHP-1* [112], *TREM2* [113], and *CXCL1* [114]. Three studies have identified inverse associations among subgroups of cases for *RELN* [59], *MMP9* [115], and *CNR1* [116]. These findings align well with gene silencing as the relevant mechanism, where the methylation of CpGs localized in the proximity of transcription start sites typically represses this process. This may happen through either blocking access to transcription factors or recruiting other repressive methyl-binding proteins [117]. There were also instances in which no relationship was evident: *DUSP22* [118], *BDNF* [119], *FOXP2* [120], *SLC6A3* [69], and *COMT* [121]. Moreover, positive associations between methylation and mRNA expression were detected for *BDNF* [122], *GAD1* [63], *CTLA4* [73], *CHRM1* [123], *HTR2A*, and its T102C (rs6313) polymorphism [108], and *GAD1* regulatory genes [109]. Such conflicting results have been described in recent epigenetic studies [124], suggesting indirect effects, but also an insufficient understanding of the underlying mechanisms, but not precluding methylation as an important modulator.

Some additional variables were also associated with epigenetic mechanisms, primarily sex [13, 38, 44, 45, 51, 54, 68, 88, 97, 121, 125–127] age [43, 44, 54, 98, 113, 116, 128, 129], and antipsychotic medication [42, 64, 82, 97, 121, 130, 131], but also genotype [13, 128, 130, 132], disease onset (early/late) [38, 42, 82, 108, 131], symptoms [38, 47, 82], illness duration [70, 82], brain anatomy or function [55, 74], cognition [133], tobacco use [45], alcohol use [53], body mass index [121], and family history of psychiatric illness [130]. This suggests that numerous disease-related, unspecific, and environmental conditions influence the epigenetic landscape.

Limitations

Although the considered literature generally confirms a moderate effect for epigenetic dysregulation underlying schizophrenia and psychosis, some limitations bear mentioning. First, the effect of tissue source and reliability of extrapolations made across tissues are unclear. Studies explicitly addressing this question indicate a relatively low proportion of correlated CpGs between the brain (in vivo) and peripheral tissues, which increases with the consideration of specific markers [85], being highest for blood (which was also the primary bio-fluid type surveyed) followed by buccal tissue and saliva samples [134]. Among the evaluated studies, several found a cross-tissue correspondence of effects, i.e., *RELN* (↑) [57–59], *MB-COMT* (↓) [53–55, 132], *BDNF* (↓) [69, 122], *SLC6A4* (↑) [64], *HTR2A* (↑) [65, 108, 128], *IL1RAP* [80], and *DUSP22* (↑) [118]. Nevertheless, postmortem tissue analyses are more subject to spurious findings under pH dependency, terminal conditions, time lapsed before sample preparation, and death-related acidosis, each of which may interfere with DNA integrity [135]. Despite these caveats, different tissues are important sources of information in psychiatric epigenetics, but the field would highly benefit from more rigorous study designs and validation of blood and saliva as surrogate tissues. An important contribution to this debate was made by confirming the postulated "signature model" and the "mirror-site model," which assume that changes within the brain leave a signature in the blood and that those in the blood mirror the brain [136]. Additionally, several online tools for examining the concordance of brain–blood data are available [137].

Another unresolved issue is the precise disentanglement of disorder-specific effects from confounding factors. Studies were heterogeneous in how they controlled for these variables. As antipsychotic medication influences epigenetic

events [22], most studies investigated medicated patients (only 14% of studies included antipsychotic drug-free cases), and not all analyses controlled for drug use, caution is warranted in interpreting the findings. Additionally, given that ancestry is detectable based on DNA methylation [138], undeclared population origin, or mixed ancestry, which characterized individuals in a portion of these studies, may be another largely neglected source of artefacts. Moreover, the inclusion of a broader phenotype of psychotic disorders (e.g., schizoaffective disorder) might have increased the number of genetic associations.

A potential bias and related replicability issue across the findings may arise from the heterogeneity of the techniques and methods used, with a range in sensitivity for detecting effects. For example, bisulfite sequencing is susceptible to a PCR amplification bias, and so the method itself may hinder the identification of highly polymorphic sites [139]. Among the so-called genome-wide methods, MeDIP provides better genome coverage compared to other methods, including some types of microarrays [140]. Moreover, translating gene ontology approaches into epigenetic findings may lead to unsubstantiated interpretations [141]. Some technical and methodical differences may also affect miRNA profiling, with qRT-PCR having the widest dynamic range and highest accuracy, and providing absolute quantification measures [142], while enzymatic miRNA-labelling is vulnerable to substrate sequence bias [143]. Finally, if analyses do not account for cell count, cell type, and/or cell proportions in whole blood analyses, they may mirror cellular composition in general, rather than be disease-specific markers. Studies by Kinoshita et al. [144] and Montano et al. [145] are positive examples of integrating this aspect and adjusting the genome-wide results to account for cell specificity.

Future prospects

This review juxtaposes several epigenetic mechanisms that may operate together to regulate the same genes or gene complexes. Recent research has delivered valuable insights into miRNA-epigenetic feedback loops involving DNA methylation, as well as RNA and histone modifications, which may exert far-reaching influences on gene expression [30]. Technical advances, new bioinformatic tools, and access to multiple cost-effective "omics" methods may pave the way for new discoveries of possible interacting regulatory pathways. Future research may particularly benefit from joint genetic and epigenetic analyses within the framework of integrated functional genomics. There are compelling arguments for epigenetic marks being regulated genetically [18, 146]. For example, Hannon et al. [81] interrogated genetic and epigenetic variation associated with schizophrenia as part of a methylation quantitative trait loci (mQTL) analysis (i.e., assessing the influence of SNPs on CpG methylation state), demonstrating that schizophrenia-associated loci identified by genome-wide associated studies co-localized with mQTLs. The polygenic burden indexed by schizophrenia polygenic risk scores was associated with epigenetic variation [81]. Additionally, haplotype-dependent allele-specific DNA methylation, particularly of variants in CCCTC-binding factor and transcription factor binding sites, may reveal transcriptional pathways associated with psychiatric disorders [147]. Genetically driven and schizophrenia-associated DNA methylation effects have also been identified throughout development in the frontal cortex, particularly for the prenatal-postnatal transition [90]. Similarly, other studies have observed various roles of miRNAs in the neurodevelopment of schizophrenia [148]. Therefore, future studies might productively investigate genetic–epigenetic interactions and integrate a longitudinal perspective, as exemplified by one recent study that identified specific methylomic changes after a conversion to psychosis [149]. Another point to consider is diagnosis. The majority of the herein examined research included patients that met the standard diagnostic criteria (mostly based on DSM), which provides a common basis for differentiated case–control comparisons. Nevertheless, given a general dissatisfaction with psychiatric nosology, future research may consider other classifications, such as the Research Domain Criteria or more clinical spectrum-based approaches. A final note accommodates a possible transition of drugs modulating epigenetic signaling into therapeutics. At this very preliminary stage, at least three classes of molecules, i.e., histone demethylase inhibitors (HMT), histone deacetylase inhibitors (HDAC), and DNMT inhibitors acting on DNA methylation, show some potential as a new class of medication "epidrugs" targeting epigenetic mechanisms [21, 150].

Conclusion

Despite the variability of results examined, this systematic review provides support for the view that epigenetic mechanisms differentiate healthy controls from cases with schizophrenia and related psychotic disorders. Bipolar disorder was not considered in this work.

Compliance with ethical standards

Conflict of interest SW has received royalties from Thieme Hogrefe, Kohlhammer, Springer, and Beltz and lecture honoraria from Opopharma in the last 5 years. Her research has been supported by the Swiss National Science Foundation (SNSF), several EU FP7s, HSM High Specialized Medicine of the Canton Zurich, Switzerland, Bfarm Germany, the Hartmann Müller Foundation, Olga Mayenfisch

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