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First-episode schizophrenia is associated with a reduction of HERV-K methylation in peripheral blood

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ABSTRACT

Human endogenous retroviruses (HERV) have been widely associated with schizophrenia etiology. Aberrant epigenetic processes may play a role in the etiology of schizophrenia. In this study, we tested whether schizophrenia patients at different stages of illness might present alterations in the levels of HERV-K methylation. We recruited 49 first-episode schizophrenia (FES) patients with 47 age- and sex-matched healthy controls (HCs), and 100 multi-episode schizophrenia (MES) patients with 50 age- and sex-matched HCs. Based on the Schedule for Deficit Schizophrenia, patients with MES were also divided into two subgroups: deficit (D-SCZ) and non-deficit schizophrenia (ND-SCZ). DNA methylation levels of HERV-K sequences were examined in peripheral blood leukocytes. We found significantly lower levels of HERV-K methylation in FES patients compared to HCs. Patients with MES and matched HCs had similar levels of HERV-K methylation. There was a significant positive correlation between chlorpromazine equivalent dosage and HERV-K methylation levels in MES patients, but not in FES individuals. No significant differences in HERV-K methylation levels between D-SCZ and ND-SCZ as well as HCs were found. Our results indicate lower HERV-K methylation levels at early stages of schizophrenia. This difference might normalize with subsequent exacerbations of schizophrenia, likely due to the effects of antipsychotics.

1. Introduction

Schizophrenia represents neurodevelopmental disorders with complex causal mechanisms. The neurodevelopmental hypothesis of schizophrenia states that the disorder develops due to interactions between several genetic factors and environmental insults that impact critical windows of brain development (Marin, 2016; Misiak et al., 2018b). Environmental factors that are believed to play a causal role in the etiology of schizophrenia include i.e. infections in the prenatal period. Their causal role is supported by several studies showing subthreshold inflammatory state in schizophrenia. Indeed, patients with schizophrenia have been found to present distinct cytokine alterations (Miller et al., 2011), abnormal counts of peripheral blood lymphocytes (Miller et al., 2013; Karpinski et al., 2016), elevated levels of several antibodies or indices of central neuro-inflammation (Najjar and Pearlman, 2015; Trepanier et al., 2016). It should be noted that a pro-inflammatory state in schizophrenia has been associated with neurostructural brain abnormalities, cognitive impairment (Misiak et al., 2018a), poor outcome of psychosis (Frydecka et al., 2014) as well as deficit schizophrenia (D-SCZ) features associated with primary and enduring negative symptoms (Kirkpatrick et al., 2001; Garcia-Rizo et al., 2012). Our recent study also revealed that variation in the *CD28* gene, encoding the protein that regulates T-cell activity, might impact the risk of D-SCZ (Mak et al., 2018).

The exact mechanisms underlying subthreshold inflammation in this disorder remain unclear. One of potential explanations might originate from the role of endogenous retroviruses (ERVs). Notably, ERVs have been detected in DNA of several species and represent relics of

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past infections with exogenous retroviruses that occurred about 100 million years ago (Slokar and Hasler, 2015). Human endogenous retroviruses (HERVs) represent almost 8% of the human genome and are distributed across numerous loci (Lander et al., 2001). They are classified based on similarities to exogenous retroviruses, sequence similarities and primer binding sites (Blomberg et al., 2009). These sequences are unable to initiate the development of viral particles or retrotransposition events due to acquired mutations. However, it has been found that about 7% of ERVs might be transcriptionally active (Oja et al., 2007). Interestingly, it has been shown that exogenous viruses and hypoxia, which are believed to serve as schizophrenia risk factors, might reactivate ERVs (Brutting et al., 2017). A recent study by Melbourne et al. (2018) demonstrated that the levels of type W human endogenous retrovirus (HERV-W) transcripts might be associated with a pro-inflammatory phenotype in terms of elevated interleukin-6 and interferon-γ levels in patients with schizophrenia.. Interestingly, elevated levels of HERV-K transcripts have been reported in brain samples of patients with schizophrenia and bipolar disorder (Frank et al., 2005). Furthermore, HERV-K has been found to serve as enhancer of the proline dehydrogenase 1 (*PRODH*) gene that is believed to play a role of in the etiology of schizophrenia (Suntsova et al., 2013).

Several lines of evidence indicate that aberrant epigenetic processes, including DNA methylation, are associated with schizophrenia (Ibi and Gonzalez-Maeso, 2015). Interestingly, a recent study by Gao et al. (2018) provided evidence that aberrant DNA methylation may play a role in the development of D-SCZ. The authors demonstrated higher levels of matrix metalloproteinase-9 (MMP-9) gene expression in peripheral blood mononuclear cells together with its hypomethylation at some CpG sites in exon 4 and exon 5 in patients with D-SCZ. Given that HERV-K sequences might be differentially expressed in patients with schizophrenia, we tested the hypothesis whether there are differences in the levels of DNA methylation at HERV-K sites between patients with schizophrenia at different stages of illness and healthy controls (HCs). To test this hypothesis, DNA methylation levels of HERV-K were assessed in patients with first-episode schizophrenia (FES), D-SCZ and those with non-deficit subtype of illness (ND-SCZ) as well as healthy controls.

2. Methods

2.1. Participants

Patients and controls were recruited in two independent studies. Study protocol was approved by the Ethics Committee of Wroclaw Medical University and Pomeranian Medical University in Szczecin. All participants gave written informed consent for participation in this study. The first group of participants included 49 FES patients, aged 25.9 ± 5.1 years and 47 HCs, aged 26.1 ± 2.8 years. Patients with FES were minimally medicated (chlorpromazine equivalents: 134 ± 112 mg/day and treatment duration: 5.3 ± 4.6 days). They were a convenience sample selected from our previous study that was based on consecutive admissions to Lower Silesian Centre of Mental Health, Wroclaw, Poland (Misiak et al., 2016). The second group consisted of 100 multi-episode schizophrenia (MES) patients (48 males and 52 females), aged 37.5 ± 10.9 years and 50 healthy controls, aged 37.2 ± 17.8 years. These patients were a convenience sample derived from our previous study, investigating genetics of D-SCZ (Mak et al., 2018). In both groups, a diagnosis of schizophrenia was established based on the DSM-IV and ICD-10 criteria. In addition, a diagnosis of schizophrenia was confirmed using the Operational Criteria for Psychotic Illness checklist (OPCRIT) (McGuffin et al., 1991). Patients with MES were divided into two groups – D-SCZ and ND-SCZ patients, using the Schedule for Deficit Schizophrenia (SDS) (Kirkpatrick et al., 1989). According to the SDS, a diagnosis of D-SCZ can be established if at least two negative symptoms are primary or idiopathic to the disease process, persistent and present in the preceding 12 months. The following negative symptoms are captured by the SDS: 1) flat and restricted affect; 2) poverty of speech; 3) reduction in content of speech; 4) attention deficits; 5) curbing of interests; 6) alogy, avolition and apathy and 7) reduced social interaction. Additionally, psychopathological manifestation on the day of recruitment was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

In the study of FES patients, HCs were recruited by the word of mouth among university students and medical staff. They had negative family history of psychotic disorders in first- and second-degree relatives and reported no physical health impairments. In the study of MES patients, HCs had also negative family history of psychotic disorders in first- and second-degree relatives. Additionally, they had no psychiatric disorders based on the Prime MD questionnaire (Spitzer et al., 1999).

2.2. Assessment of HERV-K methylation status

Bisulfite treatment of 1 mg genomic DNA obtained from peripheral blood leukocytes was performed using the EpiTect kit (Qiagen). HERV-K methylation levels were assessed by the Combined Bisulfite Restriction Assay (COBRA), using primer pairs previously described by Jintaridth and Mutirangura (2010). In addition, we applied cubic polynomial regression to correct HERV-K methylation levels for the PCR bias and to reduce technical artefacts between multiple COBRA runs. Detailed procedure of the PCR bias correction by cubic polynomial regression was described by Moskalev et al. (2011).

2.3. Statistics

Between-group differences in the distribution of categorical variables were assessed using the χ^2 test. Normality of data distribution and homogeneity of variances were checked using the Shapiro–Wilk test and the Levene's test. In case of normal distribution and homogeneity of variance, *t*-test and one-way analysis of variance (ANOVA) were used. Otherwise, differences in continuous variables between distinct groups of patients and controls were evaluated using the Kruskal–Walis test or the Mann–Whitney *U* test. Analysis of between-group differences in the levels of HERV-K methylation was performed after removing outliers that were identified by inspection of boxplots. Analysis of co-variance (ANCOVA) was performed to test significance of between-group differences after co-varying for the effects of age, sex, chlorpromazine equivalent dosage and cigarette smoking. Correlations between continuous variables were tested using the Pearson's correlation coefficients. Differences were considered as statistically significant if the p-value was less than 0.05. Statistical analysis was performed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA).

3. Results

General characteristics of patients and controls were presented in Table 1. There were no significant differences in age and sex between patients and HCs in both groups of participants. A number of individuals with higher education level was significantly higher among HCs compared to patients with D-SCZ or ND-SCZ. Patients with D-SCZ had significantly higher PANSS scores of positive, negative and general symptoms.

HERV-K methylation levels in MES and FES patients compared to HCs were shown in Fig. 1. Patients with FES had significantly lower levels of HERV-K methylation compared to HCs ($t = 2.092$, $df = 91$, $p = 0.039$). No significant differences in HERV-K methylation levels between MES patients and HCs were found ($t = 0.036$, $df = 133$, $p = 0.971$). In addition, patients with D-SCZ, those with ND-SCZ and HCs had similar HERV-K methylation levels ($df = 133$, $F = 0.319$, $p = 0.727$) (Fig. 2). Patients with MES had significantly higher HERV-K methylation levels compared to FES patients ($U = 3743$, $p < 0.001$).

Table 1
General characteristics of patients and controls.

	D-SCZ, *n* = 48	ND-SCZ, n = 52	HCs, n = 50	*p*	FES, *n* = 49	HCs, *n* = 47	*p*
Age	38.3 ± 10.9	36.8 ± 10.9	37.2 ± 17.8	0.203	25.9 ± 5.1	26.1 ± 2.8	0.576
Sex, M(%)	24 (50.0)	24 (43.2)	25 (50.0)	0.835	27 (55.1)	23 (48.9)	0.545
Education, higher (%)	9 (18.75)	8 (15.4)	19 (38.0)	0.016	11 (22.4)	10 (21.3)	0.890
BMI, kg/m^2	29.0 ± 0.8	27.9 ± 5.7	–	0.267	22.8 ± 3.3	22.5 ± 2.7	0.965
Cigarette smoker, n(%)	21 (43.75)	26 (50.0)	–	0.532	16 (32.6)	12 (25.5)	0.443
PANSS-P	13.7 ± 4.2	11.9 ± 5.4	–	0.007	22.8 ± 5.4	–	–
-PANSS-N	24.9 ± 7.4	14.0 ± 5.6	–	< 0.001	18.5 ± 6.6	–	–
PANSS-G	36.2 ± 10.1	26.8 ± 9.1	–	< 0.001	42.2 ± 7.3	–	–
CPZeq, mg/day	647 ± 503	626 ± 521	–	0.908	134 ± 112	–	–
Treatment duration, days	–	–	–	–	5.3 ± 4.6	–	–

Data expressed as mean ± SD or the number of cases (%).
p-values calculated using the Mann-Whitney U test (continuous variables) and the χ^2 test (categorical variables).
Abbreviations: BMI – body-mass index, CPZeq – chlorpromazine equivalents, FES – first-episode schizophrenia, HCs – healthy controls, D-SCZ – deficit schizophrenia patients, ND-SCZ – non-deficit schizophrenia patients.

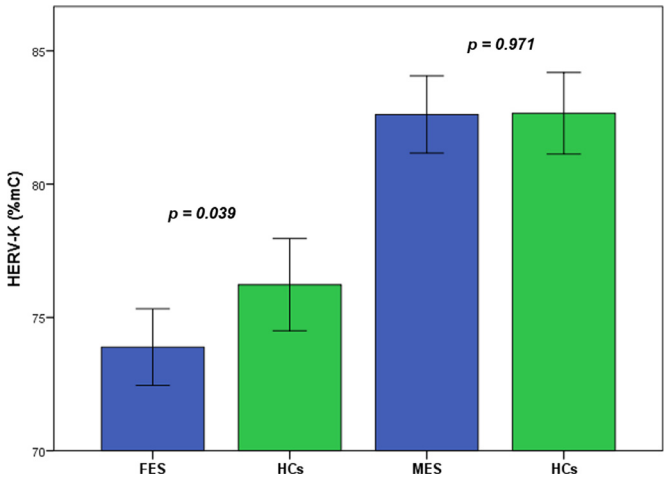

Fig. 1. HERV-K methylation levels in distinct subgroups of patients and controls. Mean levels are presented. Error bars represent 95%CI. *P*-values were calculated using the independent samples *t*-test. Abreviations: FES – first-episode schizophrenia, HCs – healthy controls, MES – multiple-episode schizophrenia.

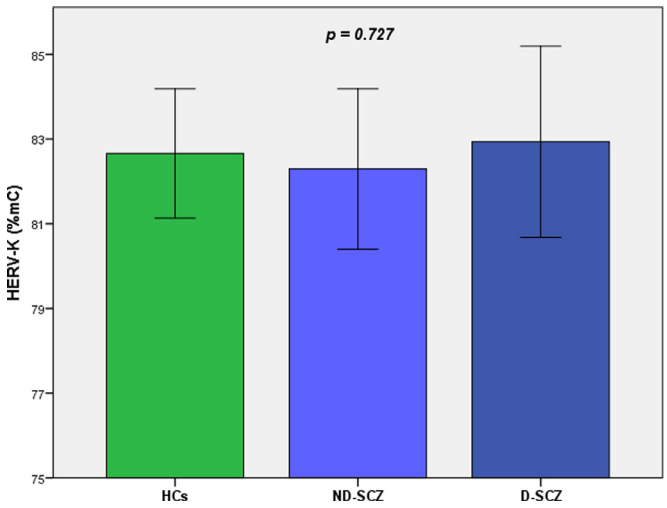

Fig. 2. HERV-K methylation levels with respect to a diagnosis of deficit schizophrenia. Mean levels are presented. Error bars represent 95%CI. *P*-value was calculated using the one-way ANOVA. Abbreviations: D-SCZ – deficit schizophrenia, ND-SCZ – non-deficit schizophrenia, HCs – healthy controls.

Similarly, HCs for the sample of MES patients had significantly higher HERV-K methylation levels in comparison with HCs for the sample of FES patients ($U = 1419$, $p < 0.001$). However, there were also significant differences in age between FES and MES patients ($U = 4084$, $p < 0.001$) as well as between both groups of HCs ($U = 1631$, $p = 0.001$). The difference in HERV-K methylation levels between FES patients and HCs remained significant after co-varying for age, sex, cigarette smoking status and chlorpromazine equivalent dosage (Table 2). In turn, the difference in HERV-K methylation between MES patients and HCs, even after distinction of D-SCZ and ND-SCZ patients, was insignificant after controlling for age, sex and chlorpromazine equivalent dosage.

There was a significant positive correlation between HERV-K methylation level and chlorpromazine equivalent dosage in the group of MES patients ($r = 0.241$, $p = 0.021$) (Fig. 3). However, this correlation was insignificant in FES patients ($r = -0.208$, $p = 0.166$). Similarly, treatment duration was not associated with HERV-K methylation levels in FES patients ($r = -0.062$, $p = 0.681$). Finally, we found no significant correlations between the levels of HERV-K methylation and scores of PANSS subscales neither in FES patients nor in MES individuals (Table 3).

4. Discussion

In this study, we found significantly lower levels of HERV-K methylation in FES patients in comparison with HCs. We did not observe significant differences in HERV-K methylation levels between MES patients and HCs. However, we also found that a dosage of antipsychotics was positively but weakly correlated with the levels of HERV-K methylation in MES patients. In addition, patients with D-SCZ and ND-SCZ as well as HCs had similar levels of HERV-K methylation. These results imply that methylation of HERV-K sequences may not play a role in the pathophysiology of D-SCZ. However, it has recently been show that aberrant epigenetic processes might be involved in the development of D-SCZ (Gao et al., 2018). Negative findings in the group of MES patients might be attributed to the effects of antipsychotic treatment since we found a significant positive correlation between a dosage of antipsychotics and the levels of HERV-K methylation (weak correlation). This correlation was insignificant in FES patients; however, exposure to antipsychotics in this group of patients was relatively low. Therefore, it might be hypothesized that antipsychotic treatment can restore normal methylation levels. Indeed, several studies have found that antipsychotic might impact epigenetic processes, including DNA methylation (Reynolds and Fachim, 2016). In some studies, the dosage of antipsychotics has been found to impact the extent of DNA methylation changes (Ovenden et al., 2018).

Given that DNA hypomethylation is associated with up-regulation of DNA expression, lower levels of HERV-K methylation in FES patients

Table 2
Results of the analysis of co-variance testing for differences in the HERV-K methylation levels between patients and controls after co-varying for age, sex, cigarette smoking status and chlorpromazine equivalent dosage.

	FES patients vs. HCs	MES patients vs. HCs	D-SCZ vs. ND-SCZ vs. HCs
Group (patients vs. HCs)	***F* = 4.29, *p* = 0.041**	$F = 0.66$, $p = 0.417$	$F = 1.20$, $p = 0.306$
Age	$F = 0.27$, $p = 0.604$	$F = 0.44$, $p = 0.510$	$F = 0.500$, $p = 0.481$
Sex	$F = 0.08$, $p = 0.776$	$F = 0.97$, $p = 0.326$	$F = 0.85$, $p = 0.359$
Cigarette smoking (yes/no)	$F = 0.06$, $p = 0.810$	–	–
CPZeq	$F = 1.57$, $p = 0.214$	$F = 1.83$, $p = 0.178$	$F = 1.76$, $p = 0.187$

Abbreviations: CPZeq – chlorpromazine equivalent dosage, D-SCZ – deficit schizophrenia, FES – first-episode schizophrenia, MES – multiple-episode schizophrenia, ND-SCZ – non-deficit schizophrenia.
Significant effects ($p < 0.05$) were marked with bold characters.

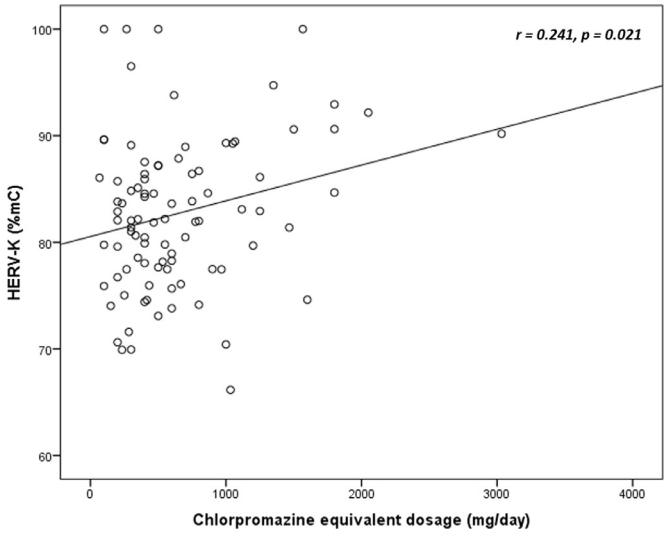

Fig. 3. Correlation between chlorpromazine equivalent dosage and HERV-K methylation in multiple-episode schizophrenia patients.

Table 3
Correlations between HERV-K methylation levels and psychopathological manifestation.

	FES patients	MES patients
PANSS-P	$r = 0.031$, $p = 0.840$	$r = 0.065$, $p = 0.532$
PANSS-N	$r = -0.105$, $p = 0.488$	$r = -0.025$, $p = 0.810$
PANSS-G	$r = 0.066$, $p = 0.662$	$r = -0.094$, $p = 0.364$

Abbreviations: FES – first-episode schizophrenia, MES – multiple-episode schizophrenia, PANSS-G - the Positive and Negative Syndrome Scale – score of general psychopathology, PANSS-N - the Positive and Negative Syndrome Scale – score of negative symptoms, PANSS-P – the Positive and Negative Syndrome Scale – score of positive symptoms.

are in agreement with a recent study showing up-regulated expression of HERV-K10 in brain samples from patients with schizophrenia and bipolar disorder (Frank et al., 2005). Although we analysed DNA methylation in peripheral blood leukocytes, highly concordant patterns of DNA methylation between blood and brain tissues have been reported in patients with schizophrenia (van den Oord et al., 2016). Moreover, one study tested the association between HERV-K115 insertional polymorphism and schizophrenia (Otowa et al., 2006). Authors found no significant difference in the frequency of this polymorphism between patients and controls. However, the HERV-K115 insertional polymorphism was significantly more frequent in patients with early onset of psychosis (< 18 years) compared to those with late onset of psychosis (≥ 18 years). Polymorphisms within the HERV-K18 locus have been also associated with type 2 diabetes in patients with schizophrenia (Dickerson et al., 2008; Nyegaard et al., 2012).

DNA methylation is largely influenced by aging processes. It has been reported that global hypomethylation together with hypermethylation of certain gene promoters appears with aging (Jung and Pfeifer, 2015). Similarly, methylation of endogenous retroelements is subjected to various age-related changes (Cardelli, 2018). Although the majority of studies have reported age-related hypomethylation of endogenous retroelements, there is also some evidence for hypermethylation of these sequences in certain diseases associated with aging e.g. atherosclerosis (Zaina et al., 2014). Only in one study, a negative correlation between age and HERV-K methylation levels was reported (Jintaridth and Mutirangura, 2010). In addition, the authors found that a loss of HERV-K methylation occurs at the age of 40–63 years. Mean age of participants from all subgroups of our study was lower than 40 years. This difference might potentially explain why we did not observe a loss of HERV-K methylation in MES patients and matched HCs. Accelerated aging in terms of indices of inflammation, cytotoxicity, oxidative stress, metabolic homeostasis, gene expression and receptor or synaptic functions has been also observed in patients with schizophrenia (Nguyen et al., 2018). This observation might also potentially explain a lack of differences in HERV-K methylation between MES patients and age-matched HCs. Moreover, a number of environmental factors, including i.e. stress exposure or dietary intake of various nutrients, acting throughout the lifespan, might further impact DNA methylation and might account for a lack of differences between MES patients and HCs (Dauncey, 2014). These factors were not controlled in our study.

Our study has certain limitations that need to be raised. Firstly, we did not assess the levels of HERV-K transcripts and thus it is hard to imply whether observed differences might have a functional impact. Secondly, our subgroups of patients and HCs were not large. Therefore, the risk of type I and type II errors cannot be excluded. Another point is that patients with FES were not drug-naïve; however, we did not find significant correlations between chlorpromazine equivalent dosage or treatment duration and the levels of HERV-K methylation. Another point is that we did not record cigarette smoking status in HCs who were a comparison group for MES patients. Finally, it should be noted that the sample of MES patients, with almost equal numbers of D-SCZ and ND-SCZ patients, was not a representative sample.

In summary, our results indicate hypo-methylation of HERV-K sites in patients with FES. These findings cannot be observed in patients with MES, most likely due to long-term exposure to antipsychotic treatment. Similarly, methylation of HERV-K may not play a role in the pathophysiology of D-SCZ. Future studies should disentangle whether DNA methylation has a functional impact on the levels of HERV-K transcripts. Longitudinal studies are also needed to unveil the mechanisms underlying changes in HERV-K methylation in the course of illness. Finally, investigating the effects of antipsychotics on DNA methylation of HERV-K sequences might provide a broader insight into epigenetic processes involved in their mechanisms of action.

Contributors

M.M. – concept and planning of the study, recruitment and

assessment of MES patients and controls, literature review and manuscript writing (the largest contribution); J.S. – manuscript editing; D.F. – consultation of statistical analysis; J.P.-W. – recruitment and assessment of MES patients; E.S. and P.K. – assessment of DNA methylation; M.M.S. – consultation of molecular techniques used in this study; P.P. – recruitment of FES patients; A.S. – recruitment and assessment of MES patients and controls; B.M. – recruitment and assessment of FES patients and controls, statistical analysis and manuscript writing

Conflict of interest

None to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.012.

References

Blomberg, J., Benachenhou, F., Blikstad, V., Sperber, G., Mayer, J., 2009. Classification and nomenclature of endogenous retroviral sequences (ERVs): problems and recommendations. Gene 448, 115–123.
Brutting, C., Emmer, A., Kornhuber, M.E., Staege, M.S., 2017. Cooccurrences of putative endogenous retrovirus-associated diseases. Biomed. Res. Int. 2017, 7973165.
Cardelli, M., 2018. The epigenetic alterations of endogenous retroelements in aging. Mech. Ageing Dev. 174, 36–40.
Dauncey, M.J., 2014. Nutrition, the brain and cognitive decline: insights from epigenetics. Eur. J. Clin. Nutr. 68, 1179–1185.
Dickerson, F., Rubalcaba, E., Viscidi, R., Yang, S., Stallings, C., Sullens, A., et al., 2008. Polymorphisms in human endogenous retrovirus K-18 and risk of type 2 diabetes in individuals with schizophrenia. Schizophr. Res. 104, 121–126.
Frank, O., Giehl, M., Zheng, C., Hehlmann, R., Leib-Mosch, C., Seifarth, W., 2005. Human endogenous retrovirus expression profiles in samples from brains of patients with schizophrenia and bipolar disorders. J. Virol. 79, 10890–10901.
Frydecka, D., Misiak, B., Pawlak-Adamska, E., Karabon, L., Tomkiewicz, A., Sedlaczek, P., et al., 2014. Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur. Arch. Psychiatry Clin. Neurosci.
Gao, J., Yi, H., Tang, X., Feng, X., Yu, M., Sha, W., et al., 2018. DNA methylation and gene expression of matrix metalloproteinase-9 gene in deficit and non-deficit schizophrenia. Oncotarget.
Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Justicia, A., Bernardo, M., Kirkpatrick, B., 2012. Inflammatory markers in antipsychotic-naïve patients with nonaffective psychosis and deficit vs. nondeficit features. Psychiatry Res. 198, 212–215.
Ibi, D., Gonzalez-Maeso, J., 2015. Epigenetic signaling in schizophrenia. Cell Signal. 27, 2131–2136.
Jintaridth, P., Mutirangura, A., 2010. Distinctive patterns of age-dependent hypomethylation in interspersed repetitive sequences. Physiol. Genom. 41, 194–200.
Jung, M., Pfeifer, G.P., 2015. Aging and DNA methylation. BMC Biol. 13, 7.
Karpinski, P., Frydecka, D., Sasiadek, M.M., Misiak, B., 2016. Reduced number of peripheral natural killer cells in schizophrenia but not in bipolar disorder. Brain Behav. Immun. 54, 194–200.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Kirkpatrick, B., Buchanan, R.W., Mckenney, P.D., Alphs, L.D., Carpenter Jr., W.T., 1989. The schedule for the deficit syndrome: an instrument for research in schizophrenia. Psychiatry Res. 30, 119–123.
Kirkpatrick, B., Buchanan, R.W., Ross, D.E., Carpenter Jr., W.T., 2001. A separate disease within the syndrome of schizophrenia. Arch. Gen. Psychiatry 58, 165–171.
Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., et al., 2001. Initial sequencing and analysis of the human genome. Nature 409, 860–921.
Mak, M., Misiak, B., Frydecka, D., Pelka-Wysiecka, J., Kucharska-Mazur, J., Samochowiec, A., et al., 2018. Polymorphisms in immune-inflammatory response genes and the risk of deficit schizophrenia. Schizophr. Res. 193, 359–363.
Marin, O., 2016. Developmental timing and critical windows for the treatment of psychiatric disorders. Nat. Med. 22, 1229–1238.
Mcguffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch. Gen. Psychiatry 48, 764–770.
Melbourne, J.K., Chase, K.A., Feiner, B., Rosen, C., Sharma, R.P., 2018. Long non-coding and endogenous retroviral RNA levels are associated with proinflammatory cytokine mRNA expression in peripheral blood cells: implications for schizophrenia. Psychiatry Res. 262, 465–468.
Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70, 663–671.
Miller, B.J., Gassama, B., Sebastian, D., Buckley, P., Mellor, A., 2013. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 73, 993–999.
Misiak, B., Łaczmański, Ł., Słoka, N.K., Szmida, E., Piotrowski, P., Loska, O., et al., 2016. Metabolic dysregulation in first-episode schizophrenia patients with respect to genetic variation in one-carbon metabolism. Psychiatry Res. 238, 60–67.
Misiak, B., Stanczykiewicz, B., Kotowicz, K., Rybakowski, J.K., Samochowiec, J., Frydecka, D., 2018a. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: a systematic review. Schizophr. Res. 192, 16–29.
Misiak, B., Stramecki, F., Gaweda, L., Prochwicz, K., Sasiadek, M.M., Moustafa, A.A., et al., 2017b. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. Mol. Neurobiol. 55 (6), 5075–5100.
Moskalev, E.A., Zavgorodnij, M.G., Majorova, S.P., Vorobjev, I.A., Jandaghi, P., Bure, I.V., et al., 2011. Correction of PCR-bias in quantitative DNA methylation studies by means of cubic polynomial regression. Nucleic Acids Res. 39, e77.
Najjar, S., Pearlman, D.M., 2015. Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophr. Res. 161, 102–112.
Nguyen, T.T., Eyler, L.T., Jeste, D.V., 2018. Systemic biomarkers of accelerated aging in schizophrenia: a critical review and future directions. Schizophr. Bull. 44, 398–408.
Nyegaard, M., Demontis, D., Thestrup, B.B., Hedemand, A., Sorensen, K.M., Hansen, T., et al., 2012. No association of polymorphisms in human endogenous retrovirus K18 and CD48 with schizophrenia. Psychiatr. Genet. 22, 146–148.
Oja, M., Peltonen, J., Blomberg, J., Kaski, S., 2007. Methods for estimating human endogenous retrovirus activities from EST databases. BMC Bioinform. 8 (Suppl 2), S11.
Otowa, T., Tochigi, M., Rogers, M., Umekage, T., Kato, N., Sasaki, T., 2006. Insertional polymorphism of endogenous retrovirus HERV-K115 in schizophrenia. Neurosci. Lett. 408, 226–229.
Ovenden, E.S., McGregor, N.W., Emsley, R.A., Warnich, L., 2018. DNA methylation and antipsychotic treatment mechanisms in schizophrenia: Progress and future directions. Prog. Neuropsychopharmacol. Biol. Psychiatry 81, 38–49.
Reynolds, G.P., Fachim, H.A., 2016. Does DNA methylation influence the effects of psychiatric drugs? Epigenomics 8, 309–312.
Slokar, G., Hasler, G., 2015. Human endogenous retroviruses as pathogenic factors in the development of schizophrenia. Front Psychiatry 6, 183.
Spitzer, R.L., Kroenke, K., Williams, J.B., 1999. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. JAMA 282, 1737–1744.
Suntsova, M., Gogvadze, E.V., Salozhin, S., Gaifullin, N., Eroshkin, F., Dmitriev, S.E., et al., 2013. Human-specific endogenous retroviral insert serves as an enhancer for the schizophrenia-linked gene PRODH. Proc. Natl. Acad. Sci. USA 110, 19472–19477.
Trepanier, M.O., Hopperton, K.E., Mizrahi, R., Mechawar, N., Bazinet, R.P., 2016. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol. Psychiatry 21, 1009–1026.
Van Den Oord, E.J., Clark, S.L., Xie, L.Y., Shabalin, A.A., Dozmorov, M.G., Kumar, G., et al., 2016. A whole methylome CpG-SNP association study of psychosis in blood and brain tissue. Schizophr. Bull. 42, 1018–1026.
Zaina, S., Heyn, H., Carmona, F.J., Varol, N., Sayols, S., Condom, E., et al., 2014. DNA methylation map of human atherosclerosis. Circ. Cardiovasc. Genet. 7, 692–700.