IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Research Article
October 2018 Vol.:10, Issue:4
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Disturbance of RELN Gene Methylation in Patients with the Paranoid Syndrome

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
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Arkhipov Andrei Yu.[1]*., Rodionov Georgy I.[1], Nurbekov Malik K.[2,6], Kostyuk Georgiy P.[4], Morozva Anna[5], Reznik Alexander M.[6], Zaharova Natalia V.[4], Strelets Valeria B.[1]

1 Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Science

2 Institute of General Pathology and Pathophysiology.

3 Moscow State Pedagogical University.

4 Psychiatric Clinical Hospital 1 n. a. N.A. Alekseev of Healthcare Department of Moscow.

5 V. Serbsky National Medical Research Center for Psychiatry and Narcology, Moscow.

6 Institute of Medico Social Technology of the Moscow State University of Food Production.

Submission: 22 September 2018
Accepted: 30 September 2018
Published: 30 October 2018

HUMAN JOURNALS
www.ijsrm.humanjournals.com

Keywords: schizophrenia, hallucinatory-paranoid syndrome, RELN, methylation.

ABSTRACT

Alterations of RELN gene functioning are considered to have an important role in paranoid syndrome in schizophrenia. RELN functions take part in neurotransmitter systems development, particularly in dopaminergic, glutamatergic and GABA-ergic systems. Arguments linking RELN methylation level and the onset of schizophrenia are still unconvincing because the studies dispose of limited postmortem brain tissue samples. Methylation level in peripheral blood flow may reflex alterations taking place in the brain, thus methylation of peripheral blood can be used as a biological marker of these alterations. Disturbance of different DNA loci methylation is one of the most pathological factors of schizophrenia pathogenesis. The current investigation is aimed at the study of RELN promoter methylation and it's role in paranoid syndrome pathogenesis using genome DNA obtained in peripheral blood of acute psychosis schizophrenia patients. After bisulfite transformation of Cq computation base levels of DNA methylation were evaluated and estimated with highly sensitive real-time TaqMan procedure. Patients in contrast to controls appeared to have demethylation in -415 to -530 promoter area. Information concerning relations between methylation changes in brain and peripheral blood is important for the study of the pathogenesis of paranoid schizophrenia. DTI and fMRI experiments have been done on the similar group of patients revealing alterations in neural networks and in connections between brain structures. In the study of ERPs, there have been revealed deviations pointing to cortical activation impairment while processing significant stimuli. Alterations of different-level brain activity may be caused by microstructure pathology, this pathology being evolved during ontogenesis from RELN aberrations and reelin malfunction.

INTRODUCTION

Despite multiple genetic alterations seen in schizophrenia, such as gene mutations, translocation, duplication [1], and polymorphisms, etiology and pathogenesis of this disease remain unclear [2-3]. Case studies [4] and twin observations [5] cannot provide a definite evidence for the genetic origin of schizophrenia. Genetic factors themselves cannot explain the absence of 100% concordance found in unioval twins of schizophrenia patients. There is no convincing evidence regarding human DNA promotor methylation inheritance. Part of researchers supposes that DNA methylation processes can be explained only by gene structure variations, without the engagement of conditions [6]. Yet there exist many viewpoints that epigenetic mechanisms play an important role in schizophrenia pathogenesis, thus it is particularly necessary to mention environmental factors.

DNA methylation is one of the epigenetic mechanisms may emerge as either an etiologic factor or results of schizophrenia medication therapy [7-8], as it is shown in gene-candidates and genome-wide studies [9-11]. Although genetic factors of this disease are widely investigated, the results of this studies allow only approximately suppose what etiologic factors may underlie schizophrenia and particularly hallucinatory-paranoid syndrome [12]. Together with other factors non-Mendelian character of inheritance, phenotype heterogeneity, and absence of specific biomarkers also become obstacles for genetic studies.

Analysis of Schizophrenia Gene database of Schizophrenia Research Forum by January 2017 has shown that during 1300 genetic studies significant integral indices of genetic mechanisms impairment have been obtained for some locuses, including methylene-tetra-hydro-folate reductase (MTHFR), D2 and D4 dopamine receptors, different NMDA receptor subunits (NR2A, GRIN2A) and serotonin transporter A4(SLC6A4). Some studies have also found dysbindin and neuregulin neuropeptides malfunction in schizophrenia [13]. However, in spite of the informative value of linked inheritance and schizophrenia-associated genes, interpretation of these data is complicated. According to current hypotheses, an important role in schizophrenia-associated abnormalities belongs to NMDA receptors hypofunction connected with dopamine system hyperactivity. Glutamate neurons are regulating other neurons functions, playing important role in schizophrenia pathogenesis. Deviations in GABA-ergic interneuron morphology [14] are also of great significance for schizophrenia mechanisms. Glutamatergic and GABA-ergic aberrations may be interconnected and induce invalid control of the signals to subcortical striatal dopamine system, this system being the

aim of antipsychotics. For example, discharging of dopamine neurons, considered to be a part of their normal response to environmental stimuli depend on NMDA receptors activation [15]. Results of these investigations indicate, that NMDA receptor may lead to schizophrenia-like dopamine system alterations, such as subcortical DA abundance and cortical D1 receptor multiplication[16]. The studies by Berretta et.al.reveal that NMDA antagonists induce some GABA-neurons variations taking place in schizophrenia [17].

Current epigenetic hypothesis assumes the role of aberrant gene expression in schizophrenia, for example, GAD-1 or GAD-67 of vesicle GABA transporter (VGAT), GABA transporter GAT-1, NR2 subunit that encodes an NMDA receptor [15-16], and affects GABA-ergic neurons. These processes are supposed to be determined by promoter hypermethylation-mediated by over-expression of DNA-methyltransferase-1 (and, presumably, other DNA-methyltransferases) [17]. There also exist supplementary epigenetic regulation mechanisms of cue promoters, expressing in GABA-ergic and NMDA-ergic neurons. Each of these mechanisms may decrease mRNA expression inhibiting the promotors [18].

Violation of reelin mRNA expression (RELN gene) leads to the imbalance of interaction between GABA-ergic and NMDA-ergic neurons, and this process can affect the violation of the inhibition neural networks of the cerebral cortex[19], [20].

Glycoprotein reelin takes part in the migration and positioning of neural pathways and neural stem cells in the early neuritogenesis, thus playing a significant role in the elimination of synapses (pruning processes) in neurodevelopment. It also modulates the synaptic plasticity, amplifies and supports the long-term potentiation, stimulates the development of dendrites and dendritic spines [21]. In the mature brain, reelin is secreted by GABA-ergic interneurons of temporolymbic system and neocortex.

To date, the results of the study of the relationship between RELN gene methylation and schizophrenia give rather controversial results. One of the early studies conducted on postmortem schizophrenic and control brain samples revealed that RELN gene hypermethylation is frequently found in schizophrenia [22]. These results, however, were not confirmed in the study by the pyrosequencing method [23] and another recent study, utilizing MSP and bisulfite sequencing with 9 patients and 4 healthy postmortem brain tissue samples [24]. The results of all these studies are statistically not significant probably because of a small number of postmortem brain samples.

Some studies point to reverse relationship between blood and brain in RELN expression level in schizophrenia [Tab. 1].

Tab.1 Reelin protein expression in different psychic diseases.

Name of disease	CSF	Blood	Brain	Reference
Autism spectrum disorder		Reelin expression decrease.	Reelin expression decrease. Prefrontal cortex, Cerebellum.	Keller et al. 2000; Fatemi et al. 2002
Schizophrenia	The absence of evident correlation between REELIN expression in CSF and schizophrenia			Ignatova et al. 2004
		The increase of Reelin expression		Fatemi et al. 2001b
			Reduction of mRNA expression in prefrontal cortex.	Eastwood and Harrison, 2006; Guidotti et al. 2000
			Reduction of mRNA and microRNA expression in hippocampus and cerebellum.	Eastwood and Harrison, 2006; Fatemi et al. 2005b
BAR		Reelin expression decrease.	Reduction of mRNA expression in prefrontal cortex.	Fatemi et al. 2001b Guidotti et al. 2000
			Reduction of Reelin expression in the hippocampus.	Fatemi et al. 2005b
			Reduction of Reelin expression in cerebellum.	Fatemi et al. 2000
Depression		Reelin expression decrease.		Fatemi et al. 2001

			The absence of REELIN microRNA expression changes in the hippocampus.	Fatemi et al. 2000
			The absence of mRNA changes in the prefrontal cortex.	Guidotti et al. 2000
			The absence of REELIN protein expression changes in the cerebellum.	Fatemi et al. 2005b

Literature data regarding increased RELN expression in the blood in schizophrenia compared to healthy controls is confirmed by postmortem studies, revealing the reduction of RELN mRNA in the brain of schizophrenics [25-26]. Reduction of RELN mRNA can contribute in dendrite length shortening and dendritic spines density lowering in prefrontal and other cortical areas, hippocampus, hypothalamus, amygdala, medulla oblongata and midbrain[27-28]. However, reelin expression studies in the peripheral blood were conducted in patients with negative symptoms predominance, and patients on antipsychotic therapy [29]. Thus, although these studies do not give confidence in reciprocal relations between RELN gene methylation in cerebral and peripheral blood flow, the notion that hypermethylation of gene RELN in cerebral blood flow in patients with schizophrenia takes place is generally accepted [30-31].

Our study was aimed at the differences in methylation between medication naive paranoid schizophrenia patients in acute psychosis and healthy controls using peripheral blood DNA analysis. These differences appear to be biological markers and could contribute to better understanding of biological and neurophysiological parameters malfunction.

MATERIALS AND METHODS

Subjects. The study was conducted on the clinical trial site of «Rosa» psychiatric hospital (department of acute psychosis) in collaboration with Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of Sciences (Laboratory of Psychophysiology). Group of patients 57 participants: (29 men, 28 women) in the acute psychotic period with predomination of the hallucinatory-paranoid syndrome at the age of 19 to 33 years. Paranoid

schizophrenia diagnosis (F 20.0) was confirmed by psychiatrists of acute psychosis department according to the criteria of the International Classification of Diseases X Edition (ICD-10). Total points of psychopathological symptoms severity assessed by PANSS scale in patients amounted 98.1 + 2.1. All patients were at the first psychotic episode and didn't receive antipsychotic treatment, before and during the experiment. Control group consisted of 53 healthy subjects (28 men, 25 women) at the age of 19 to 28 years. Participants of both patients and control group were without somatic and neurological disorders. Only statistically differences by sex, age and education level between groups ($p>0.05$) are discussed later.

Ethical agreement. Resolution of the ethics committee of the Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of Sciences was received before the start of the study.

Molecular-genetic methods. To assess the methylation level of RELN premotor screening of the DNA selected from peripheral blood leukocytes was performed. Blood samples were collected with specialized glass tubes containing K3EDTA solution (BD Vacutainer tm K3EDTA). DNA was extracted with gemolisys techniques and using magnetic nanoparticles in accordance with the manufacturer companies protocols («BiRet», «Sylex», Russian Federation). Employing the latter method allowed to acquire intact RNA together with DNA, valid for both methylation analysis, and for gene expression level analysis on cDNA after reverse transcription and RELN TaqMan RT-PCR.

PCR amplification of RELN promotor area fragments (near 550 b.p.), containing CpG dinucleotide sequence consisted 2 stages: initially first selected primer pairs were employed, amplification of large fragment (450 b.p.) was conducted, then more short fragment (320 b.p.) within it was amplificated. PCR conditions: 94°C /4 min× 1 cycle; 94°C /1 min, 61°C /2 min, 72°C /2 min × 5 cycles; 94°C /1 min, 61°C/1,5 min, 72°C/1,5-2 min × 25 cycles; 72°C/5 min × 1 cycle.

Methylation was investigated by DNA bisulfite transformation. Bisulfite transformation was performed with 1-2 mg of DNA, which was treated by bisulfite, with marginal changes. DNA was denaturated 0.3 N NaOH at 37°C within 15 minutes. 15 ml freshly (prepared) 10 mm hydroquinone were added in tubes with DNA samples, solutions were carefully mixed with minimum aeration inversion, 250 ml freshly prepared sodium bisulfite 3.6M, ph 5.0 was added into tubes, incubated at 37°C and solutions again were carefully mixed with minimum

aeration inversion. The reaction mixture was covered with mineral oil and incubated at 55°C within 16 hours in the dark. The water phase was transported into new tubes and deionized anion-exchange resin (bile-acid resin) columns. DNA was eluted by 120 ml of distilled water, centrifugation was used to remove traces of alcohol. 10 mkL 3N NaOH was added to 100 ml deionized DNA and incubated for 15 min at 37°C. DNA was precipitated/pelleted by 33 mm 10 M sodium acetate pH 7.8 and 300 ml chilled ethanol using glycogen as coprecipitation agent in ice water bath within 10 minutes, then centrifuged under 13000×g within 60 min. The precipitate was resuspended in 100 mkLTE pH 8,0.

Bisuphyte transformed DNA preparations were treated by nested PCR procedure, using specific primers to described above gene promoter areas, containing GC pairs. Acquired amplificates were rectified from primer excesses and nonspecific fragments by electrophoresis in 2% agarose and then bands cut from the gel were conveyed to the sequencing of the relevant RELN promoter areas («Stinol», Russian Federation).

Physiological study. Analysis of event-related potentials (ERPs) to the stimuli of different significance was done using standard protocols. The P100, N170, P200, P300, and N400 components latency and amplitude were analyzed. FMRI data to similar stimuli obtained from similar patients and control participants were studied and activation of different brain regions was analyzed [56-57].

RESULTS

Analysis of the results obtained showed the presence of RELN promoter zone demethylation -415 to -530 site -442 in schizophrenia patients compared to the control group which can indicate an increase of reelin protein expression.

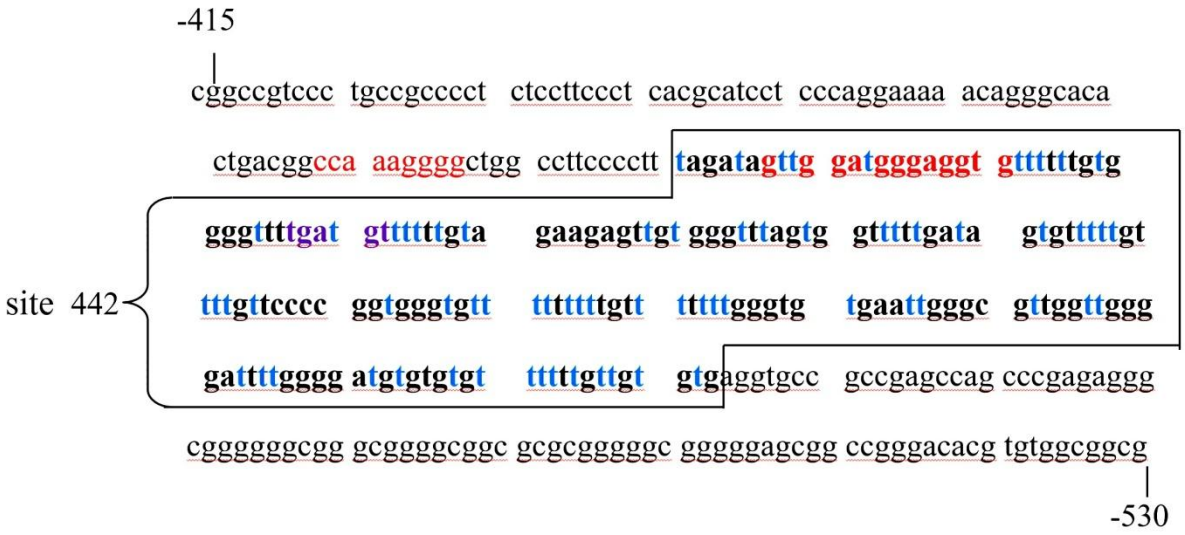

Fig.1. Methylation of the gene RELN obtained from peripheral blood (promoter region -415 to -530), site -442 in patients with schizophrenia is completely absent in 100% of cases, and in healthy controls, 100% is present in all CpG pairs.

DISCUSSION

In peripheral blood of in medication-naïve hallucinatory-paranoid schizophrenia patients opposite to norm RELN gene demethylation (promoter -415 to -530, site -442) is revealed. Literature data concerning relationships between RELN expression in cerebral and peripheral blood samples in schizophrenia are controversial [48] but majority points to RELN hypermethylation in schizophrenic patient's brain. This fact appears to be a key data relating RELN methylation status in peripheral tissues and its role in the development of schizophrenia.

Unmethylated CpG sites together form clusters, called CpG islands that can be found in many genes promoter areas. Thus, the fact that DNA methylation plays an important role in the regulation of protein expression is a predictable result [50]. However, not all DNAs are characterized by a unidirectional change of methylation and the expression level, particularly methylation level inversely correlates with reelin expression [51]. Thus RELN hypermethylation obtained in our study can point to the reduction of reelin expression in schizophrenia brain. In recent decades, the significant contribution of epigenetics to the etiology of schizophrenia has been found and experimentally confirmed [34]. Epigenetic studies, i.e., studies of non-affecting the gene structure changes, namely hypomethylation in

blood and hypermethylation in the brain of patients, leads to a violation of reelin protein expression in schizophrenia. The available number of studies of DNA methylation on postmortem brain samples in schizophrenia is limited, and most of them are obtained on small samples. Walton et .al. (2016), using peripheral blood samples of the epilepsy patients temporal lobe, showed that peripheral blood can be used as a surrogate substance of brain tissue. They conclude that some indicators obtained on peripheral methylation can serve as a brain methylation status marker [35]. Walton et.al. also assume that the disturbances of DNA methylation in schizophrenia affect neural connections through the metabolite precursors and signal peptides (reelin). Beside postmortem brain tissues and peripheral blood, urine and saliva can also be used to analyze epigenetic changes [36-37]. Available data about maternal feeding effects on DNA methylation in the brain and T-cells of the rhesus macaque, support the viewpoint that influence of the environmental is systematic and affects the whole genome, persisting until adulthood [38]. The approach estimating the overall methylation profile, (Davies et. al., 2012) confirms that DNA methylation patterns in the brain and peripheral blood are highly correlating [39]. In addition, a study by Klengel et.al., (2013) shows that demethylation has a global effect on immune cells and brain associated areas, particularly methylation is revealed through the correlations between genetic disorders and childhood trauma [40]. It should be noted that peripheral blood cannot completely substitute the complex structure of brain tissue and its components. The correlation level of DNA methylation between different brain structures and peripheral blood is highly variable [41]. According to the neuroinflammatory [42] and neuroontogenetic [43] hypotheses of schizophrenia, a closer connection with blood than with the brain tissue is found in microglia, being produced from blood monocytes, which are derived from hemopoietic precursor cells [44]. Thus, regardless of similarity between brain and blood changes, the difference in RELN methylation in patients and in control groups in our study may reflect a unique feature of schizophrenia and appear to be a peripheral marker of the disease. However, it should be mentioned that the difference in methylation may be a result of medication therapy.

The role of reelin protein in developmental processes was studied by Smallheiser et. al.; in adulthood, reelin is revealed in the blood and other peripheral organs [45]. The increase of extra-neural RELN expression has been found in liver and eye pathology [46-47], but the cause, leading to the increase of blood RELN expression, remains unknown.

Thus the fact that we have observed DNA demethylation in the CpG site of gene RELN promoter zone in patients with the hallucinatory-paranoid syndrome in schizophrenia indicates that a DNA RELN methylation variances can play an important role in the pathogenesis of schizophrenia.

The relationship between DNA methylation and neuroleptic therapy seems to be an important part of the problem, for Melas et.al., have described the interplay between DNA methylation in peripheral leukocytes and antipsychotic therapy [53]. Regarding this fact, it is important to note that in our study patients did not receive antipsychotic medication.

CONCLUSION

In this study, differences of RELN gene promoter zone methylation level in peripheral blood have been revealed in schizophrenia patients with a hallucinatory-paranoid syndrome. RELN demethylation- the loss of methyl groups affects mainly the region 5 'and the promoter zone of the gene, which leads to reelin expression increase in the peripheral blood of these patients. Data on reciprocal relationships between the methylation of RELN in the brain and in peripheral blood, being found only in schizophrenia, confirm the expression decrease of reelin protein in the brain. Since reelin is produced by GABA-ergic neurons and plays a role of a signal molecule in the process of forming connections between neurons; concentration of reelin being critical for the axon growth. Thus, a decrease of reelin expression distorts axon, dendrite guiding and aiming, disturbing of their function [55]. The decrease of reelin expression also leads to a disruption of neurotransmitter systems ratio: glutamate hyperfunctioning and abundance of dopamine, which can be connected this neuronal excitation/inhibition imbalance. This is also indicated by the incongruence of ERPs latency and amplitude and fMRI disturbances in patients with the hallucinatory-paranoid syndrome.

Reduction of reelin protein expression in the brain as a result of hypermethylation of RELN occurs both in ontogenesis and adult state when the methylation of RELN gene is "erased" during the lowering of the hydroxylation level of the methyl groups. This hypothesis requires further studying (including brain tissue samples).

Summarizing, in our studies, in patients with the hallucinatory-paranoid syndrome, at the molecular genetic and physiological levels, paradoxical correlations of blood/brain reelin expression and a combination of both ERP latency and amplitude increase as a manifestation of imbalance excitation and inhibition are found. This supports the suggestion about the

crucial role of RELN in the development of hallucinatory-paranoid syndrome in schizophrenia.

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