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Association of NrCAM Protein in an Iranian Sample of Patients with Schizophrenia

S.S. Karimian[a], M.T. Akbari[b,*], G. Javadi[a] and S.S. Sadr[c]

[a]*Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[b]*Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran*
[c]*Department of Psychiatry, Imam Hussein Hospital, Shahid Beheshti University, Tehran, Iran*

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ABSTRACT

Schizophrenia (SZ) is a chronic multi genetic and multifactorial neurodevelopment disorder. Neural cell adhesion molecule (NrCAM) gene, which was assessed in this investigation, has significant functions in the generation of neural cells. NrCAM interferes in synapse generation, axon guidance, proliferation, myelination and differentiation [1]. NrCAM mRNA differentially expresses while cortical neuron growth (GEO accession number GSE102350). Also, it has been proven that, malfunctions in the structure of neocortical cells associated with schizophrenia [2]. NrCAM involves in many signaling pathways and has been identified as an SZ biomarker in many studies [3]. This investigation intended to find significant changes in NrCAM protein expression in blood serum of SZ patients. Another purpose of this investigation is to evaluate the association of variant rs10235968 with NrCAM protein expression in patients' serum. In this study, 52 paranoid patients, and 33 healthy persons were selected. To evaluate protein expression, ELIZA method was used. Variant data of our previous study were used in this study (5). All data were interpreted using the unpaired t-test, ANOVA, and Chi-Square test using GraphPad Prism8.4.3. NrCAM protein expression in blood serum has shown a significant difference between patients and healthy group ($P = 0.0509$). The association of variant rs10235968 and NrCAM protein expression has not detected ($P = 0.9468$). In our research, for the first time, NrCAM expression was assessed as an SZ candidate biomarker in blood serum of Iranian patients.

Keywords: NrCAM protein, Schizophrenia, Biomarker, Blood serum

INTRODUCTION

Schizophrenia is a chronic and heterogeneous psychiatric disorder with a 1% prevalence, identified by hallucinations, delusions, disturbing emotions, and social withdrawal [4]. Several studies for pathogenesis of schizophrenia yet did not wholly explain exact etiology of the disorder. Given its high heritability of above 80%, research of genetic mechanisms implicated in schizophrenia has attracted more attention [5]. Recent investigations have significantly developed our knowledge to recognize mechanisms by which genetic risk is presented [6]. Heterogenic and multifactorial schizophrenia characters have perpetually limited biochemical characterization investigations and little proof of preclinical disorder models [7].

Many research types include; postmortem, imaging, pharmacological, and genetic analysis listed typical disease tracks, such as synaptic deficiencies, irregular neural network, and neurotransmission alterations [8]. Other malformations, such as abnormal inflammatory answers, oligodendrocyte changes, epigenetic alterations, mitochondrial dysfunction, and reactive oxygen species (ROS) irregularity, are often reported in schizophrenia [8b]. Network cross-talk within genetic and environmental factors through neurogenesis is responsible for increasing diversity of gene and protein expression in schizophrenia, creating irregular processes throughout neurodevelopment [8a]. The complexity of schizophrenia strengthens the necessity to determine molecular mechanisms, as that knowledge is crucial in distinguishing and approving drug targets and biomarkers [9]. Hence, explaining models related to the cause and onset of schizophrenia is necessary for developing medicines.

One strategy in generating a schizophrenia test is discovering a biomarker signature that distinguishes

*Corresponding author. E-mail: mtakbari@modares.ac.ir

schizophrenia patients from healthy people. Many types of research recognized several molecules associated with schizophrenia. Due to the absence of specificity, they are not likely to help as a disease test when used as a single biomarker. Although, recent investigations on other medical situations using gene expression methods have explained that biomarkers can give reproducible outcomes, which have confirmed valuable clinical applications of biomarkers [10].

In this study, NrCAM protein was chosen as a candidate biomarker to be evaluated in blood serum to find an association between NrCAM protein expression with schizophrenia in the Iranian patients with schizophrenia. We examined paranoid type patients with a long time of treatment and disease. Several investigations have examined NrCAM protein expression in SZ patients' blood [11] [3a]. There is a lack of study in the Iranian population to evaluate NrCAM protein levels among SZ patients. Furthermore, association analysis of NrCAM protein with rs10235968 genotypes was evaluated in this study. Variant rs10235968 which located in NrCAM promoter had genotyped in our former study and reported to be associated with schizophrenia [12].

Neural cell adhesion molecule (NrCAM) (OMIM #601581) is a subgroup of the immunoglobin (Ig) superfamily observed in the nervous system. NrCAM is usually surface membrane protein with multiple Ig domains and is located in 7q31.1, including 34 exons spanning over 316 kb (by OMIM) [13]. NrCAM involves in super pathways includes; L1CAM interactions, developmental biology (Axon guidance), cell adhesion molecules (CAMs), WNT signaling and interactions between L1 and Ankyrins (by GeneCard). Northern Blotting method has revealed a 2 kb transcript of NrCAM in the all-brain tissues. The 7.0 kb transcript of NrCAM expresses pretty much in the brain medulla, adrenal, and adrenal cortex. This ankyrin-binding protein is implicated in neuron-neuron adhesion and improves directional signaling when axonal cone extension. NrCAM is additionally expresses in non-neural tissues and may have a widespread function in cell-cell interaction through signaling from, and its intracellular domain to the actin cytoskeleton through directional cell movement [3b]. Abnormality of NRCAM may change various developmental processes, including the synapse role, and development of Ranvier node linked to myelin cover [14,15]. Besides, NRCAM role's disturbance correlates with psychiatry disorders, including schizophrenia, autism, Alzheimer's disease, mathematics disability, and drug addiction [1].

Here, we have used the ELISA method to evaluate the NrCAM protein level in blood serum of 52 patients with schizophrenia paranoid type, and 32 healthy subjects. This study's principal goal was to discover whether NrCAM protein expression alteration can be identified as a biomarker in SZ blood serum vs. healthy control. Moreover, genotype association of rs10235968 with NrCAM expression in the serum of patients was assessed. rs10235968 located in NrCAM promoter. In our previous study, allele T in rs10235968 had reported being associated with schizophrenia [16]. Also, association of other variables (Table 1) with NrCAM protein expression were evaluated.

MATERIALS AND METHODS

Clinical Samples

All participants include patients and healthy people were not relative. Patients were clinically diagnosed with SZ by an expert psychiatrist, using *the Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) symbolism. Positive and Negative Syndrome Scale (PANSS) interview was taken from all patients to determine the severity of positive and negative syndromes. All patients received high average scores (70 ≥) on PANSS interview (Table 1). All patients were diagnosed as paranoid subtype, and they were under antipsychotic medicines at the time of sample acquisition. Science and Research university's ethical committees approved protocols of this study. Consent letter was taken from patients and those who took care of them. This study was conducted according to the Declaration of Helsinki.

A whole 85 participants (case = 52, control = 32) with an average age of 35 ± 15 in patients and 32 ± 10 in controls were recruited. Patients were selected from Emam Hossein Psychiatry Hospital and AHEBA Institute. Healthy subjects collected from Tehran Medical Genetics Laboratory staff, and a group of students from Islamic Azad University of Science and Research in Tehran. In this study, all participants were demographically matched (Table 1). Pedigree of both patient and healthy groups was recorded to

Table 1. Demographics Table of Subjects

Subjects	SZ	Control
n	52	33
(M/F)%	70.1/29.9	69.8/30.2
Age	35 ± 15	32 ± 10
SCZ family history%	40.3	N
Age at onset%	21.43 ± 7.32	na
Addiction%	7	N
Season of birth%		
Spring	21.6	na
Summer	27.9	na
Fall	11.3	na
Winter	39.1	na
Under medication	All	N
PANSS score	70 ≥	na

M/F: male/female, na: not available, PANSS: positive and negative syndrome scale, SCZ: schizophrenia; Y/N: yes/no.

determine any family history of psychiatric disorders and physical diseases. Control group with a family history of mental disorders, and medical conditions such as type II diabetes, hypertension, cardiovascular or autoimmune diseases were eliminated. None of the healthy subjects had particular physical and mental sickness. It is worth noting that, patient and healthy groups participated in this study had participated in our previous study, as well, and all of them had genotyped at variant rs10235968.

Serum Samples

Blood samples (5 ml) were taken from both groups and transferred into serum tubes and were kept in room temperature for two hours to blood coagulation. Then, samples were centrifuged at 4000 × g for 5 min. After centrifuge, serum part of the blood sample was isolated and was stored at -80 °C before ELISA assay.

ELISA Assay

Immunoassay was conducted utilizing RayBiotech Human NrCAM ELISA kit (ELH-NrCAM-5) the USA, an *in vitro* enzyme-linked immunosorbent assay for this quantitative study of human NrCAM serum. GenCard website recommended RayBiotech Human ELISA assay kit. A particular human NrCAM antibody covered bottom of 96-wells. Assay was calibrated applying standards. Standards and specimens were pipetted into wells, and NrCAM in the serum samples were joined to the wells. Wells were rinsed, and biotinylated anti-Human NrCAM antibody was added, and following rinsing unchained biotinylated antibody, HRP-conjugated streptavidin was added in the wells. The wells were rinsed again, and a TMB substrate liquid was subjoined to the wells, and color emerged the amount of NrCAM bound. Stop solution turn blue color into yellow, and strength of color was discovered at 450 nm with ELISA

reader immediately. Test was validated by employing standards.

Data Analysis

Data analysis were conducted utilizing GraphPad Prism 8.4.3. t-test was conducted to identify significant changes in NrCAM Protein expression between patient and control groups. PANSS questionary's efficacy was determined by Cronbach's Alpha, based on standardized items (0.726). In this study, all participants had been genotyped at rs10235968 locus in our previous study, and the results had been recorded. In this study, Genotype frequency data of rs10235968 from our former study were assessed to find any association with NrCAM protein expression in blood serum of the patients. Association between rs10235968 genotypes and NrCAM protein expression was evaluated by ANOVA test. Besides, association analysis between NrCAM protein among patients with SZ family history, the season of birth, age, gender, addiction, and age at onset data was determined using the Chi-Square test. All these analysis were carried out to estimate these variables' influence on distinguished marker candidates' significance. *P*-values of less than 0.05 were calculated to determine statistical significance.

Bioinformatics Research on NrCAM Gene

Bioinformatics research on NrCAM in the NCBI-GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?) was conducted to find NrCAM expression data which have been recorded yet, to interpret the results we have achieved in this study.

RESULTS

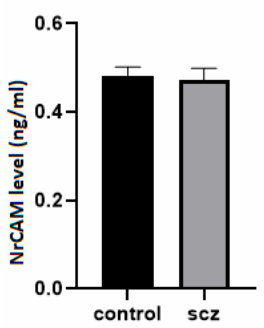
SZ patients and Control Subjects

Case and control groups demographically matched (P = 0.09). Demographic pieces of information of all subjects were shown in Table 1.

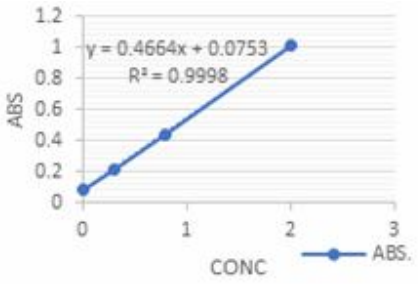
NrCAM Protein Association

In this study, ELISA test indicated changes in NrCAM protein expression in blood serum among cases and controls. Kolmogorov-Smirnov analysis determined that NrCAM protein expression was normally distributed. A significant difference in NrCAM protein expression among case and control groups was detected.

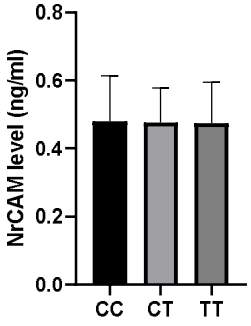
NrCAM protein was altered significantly among schizophrenia patients compared to healthy subjects applying unpaired t-test (P = 0.0509). Graph 1 shows the bar chart of NrCAM protein level among patients and healthy subjects. Graph 2 shows the standard graph in ELISA analysis.



(Graph 1)



(Graph 2)



(Graph 3)

Genotypic Association

All patients and healthy subjects had genotyped at variant rs10235968 in our former study. Considering rs10235968 genotype frequency data in our previous study, the association analysis of rs10235968 genotypes with NrCAM protein expression was performed among the patients using ANOVA test. According to the obtained results, no genotypic association of the rs10235968 genotypes and NrCAM protein expression was observed among the patients (P = 0.9468). Graph 3 shows the bar chart of NrCAM protein expression frequency in the different genotypes.

Other Variables Association

There is no association between NrCAM protein expression in the patients with SZ family history, addiction, the season of birth, age, gender, and age at onset (Table 2).

Bioinformatic Research

According to bioinformatic researches on NrCAM expression, in NCBI-GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE26535, expression profiling of the brain by array analysis have reported importance of NrCAM. A microarray study with the GEO accession number GSE102350 on rat embryo source has reported, NrCAM mRNA transcripts differentially expressed in cortical cells growth. This data has been verified by QGP and smRNA FISH.

Another investigation by array found in NCBI-GEO database with the GEO accession number GSE26535 has determined signaling pathways controlling white matter's self-renewal glial progenitor cells and has designated critical functions of NrCAM in brain maturation.

DISCUSSION

In our previous study, association of schizophrenia with NrCAM's variants were evaluated, and the results were shown, allele T of rs10235968 significantly associated with schizophrenia in the Iranian population. rs10235968 located in the CpG island of NrCAM promoter and probability can affect gene expression [17]. In this study, we have evaluated the alteration of NrCAM protein expression in blood serum of the patients. Also, association of genotype frequency of rs10235968 with NrCAM protein expression have evaluated in the Iranian patients with schizophrenia.

Cell-cell adhesion molecule encoded by NrCAM is crucial for forming neurons and axons, synaptic flexibility, myelination, and highly coordinated brain functions such as memory and learning [18]. According to bioinformatics research on NrCAM with GSE26535 ID in NCBI-GEO database, NrCAM mRNA transcripts differentially expressed in cortical neuron growth which indicates role of NrCAM in cortical developments. On the other hand, schizophrenia is associated with malfunction and abnormal density of neural cells in cortical layers [2,19]. Research, on prefrontal cortical network, proposed cortical growth, maybe changed throughout gestation in schizophrenia [20]. Besides, due to bioinformatics research on NrCAM with GSE26535 ID, NrCAM is a modulator of the RTPZ signaling pathway that differentially overexpressed in glial progenitor cells in white matter which implicates importance of NrCAM responsibility in development of white matter. Reduction in white matter volume has been reported in schizophrenia, and a map of magnetization transfer ratio has shown abnormality in myelination in white matter in both first episode and chronic samples of schizophrenia [21]. Glial progenitor cells are plentiful in adult human white matter. The RTPZ pathway, coupled with another signaling pathway, controls the self-maintenance of adult human white matter progenitor cells (WMPCs) and can be regulated to produce oligodendrocytic or astrocytic differentiation. Verifications of a glial network describes a fundamental level for good brain development [22]. Glial-derived growth factors control generation and maturation of glial cells, powerfully affect maturation and evolution of oligodendrocytes as well as myelination [23,24]. Furthermore, glial cells can maintain brain function by protecting neurons and supporting different brain sections to communicate with each other. They produce a protecting layer of fat around neurons, called myelin. Nevertheless, sometimes cells do not provide sufficient myelin due to genetic deficits, which is one of the most critical factors in the progress of schizophrenia. If myelin is not produced enough, a neural network capable of communication between neurons does not develop, imply that it takes longer for the glial cells to grow [25].

A form of proof likewise involves dysregulation of glial

Table 2. Association of NrCAM Protein in the Patients with other Variables

	SZ family history Vs NrCAM Protein expression	Season of birth Vs NrCAM Protein expression	Gender Vs NrCAM Protein expression	Age at onset Vs NrCAM Protein expression	Addiction Vs NrCAM Protein expression	Age Vs NrCAM Protein expression
P-Value	0.9999	0.6178	0.7734	0.4216	0.4256	0.9999

processes in schizophrenia. A potential road heading to cognitive malfunction in schizophrenia is unusual myelination, which can modify synaptic structure and role [25-26]. Hence, NrCAM can affect to neurodevelopment process through myelination, and cause disorders like schizophrenia.

Association between NrCAM and schizophrenia has been published frequently [1,3b,27]. NrCAM is also active in CAM's signaling pathways, and CAM's signaling pathways has an essential responsibility in brain's cognitive functions. In schizophrenia, cognitive functions of the brain are damaged. It has previously reported that CAM's signaling pathways have been associated with schizophrenia disorder in Chinese and European populations [28].

Therfore, NrCAM has a critical role in SZ development through many signaling pathways mentions above. Variants located in the promoter of NrCAM probably impact on protein expression.

Furthermore, NrCAM is amongst top applicant genes in a convergent functional genomic study [3b]. These data confirm that NrCAM has a fundamental role in cell connectivity and cell adhesion in schizophrenia.

Moreover, in research utilizing microarray-based genome-wide DNA methylation, concentrating on 8.5-kb regions within transcription start sites (TSSs), DNA methylation profiles of mouse neurospheres from telencephalons at embryonic days, and an adult brain was examined. They understood tissue-dependent and differentially methylated zones (T-DMRs) with altered DNA methylation statuses at genes associated with neural development and linked to neurodevelopmental disorders in humans, such as NrCAM [29]. In confirmation of the above study, a lot of evidence has been obtained, which includes: reduced NrCAM expression in the post-mortem brain [30] and human blood serum [3a] of schizophrenia patients and, altered NrCAM expression in the brain of a mouse model of schizophrenia [31].

In our study, it was hypothesized that NrACM protein would decrease in blood serum of schizophrenia patients. Our study using ELISA kit showed the amount of NrACM protein in case and control groups has differentially expressed. But there is no association between genotype frequency of rs10235968 and NrCAM protein expression in serum among the patients. In other study, Schwarz and his colleagues utilizing HumanMAP multiplexed antigen immunoassay platform comprising 181 analytes has reported a protein biomarker signature in blood serum for schizophrenia that NrCAM protein was included within biomarker signature [3a]. After all, in this study, we evaluated the validity of ELISA approach to measurement of the NrCAM protein level in blood serum. The results we have achieved were proven, that this approach can distinguish differences of the NrCAM protein level among the patients and healthy subjects. Also, we were looking for association between variables including age at onset, SCZ family history, gender, age, the season of birth, addiction, and NrCAM expression in the patients but, we were not found any association. Decreased NrCAM protein in serum of the patients, which was seen in this study, was in line with the results in other studies.

Classifying biomarkers that can be used as diagnostic or predictor of therapy response in the patients with schizophrenia will be an essential step towards providing personalized treatment [32].

To confirm the results of this study using large sample size is recommended. Studies have shown that using medicines change protein levels in serum [3a]. Therefore, using naïve patients for recognizing a biomarker signature is recommended.

CONCLUSIONS

There is an association between NrCAM protein expression and schizophrenia. The NrCAM protein level in blood serum of the patients intended to decrease. Genotype association between rs10235968 and NrCAM protein expression was not found, even though rs10235968 has reported being associated with schizophrenia in our previous study. Furthermore, there is no association between NrCAM expression and other variables like; age at onset, SCZ family history, gender, age, the season of birth, and addiction.

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REFERENCES

[1] T. Sakurai, Mcb. Neurosci. 49 (2012) 351.
[2] C. Beasley, D. Cotter, I. Everall, Scz Rsrch 58 (2002) 63.
[3] N. Andreasen, The Lancet 346 (1995) 477.
[4] P.F. Sullivan, K.S. Kendler, M.C. Neale, Arch. of Gen. Psych. 60 (2003) 1187.
[5] A. Kumar, S. Agarwal, S.R. Phadke, Y. Jaiswal, Gene 535 (2014) 97.
[6] P. Giusti-Rodríguez, P.F. Sullivan, J. Clin. Investig 123 (2013) 4557.
[7] B.J. Mowry, J. Gratten, Mol. Psychiatry 18 (2013) 38.
[8] P.C. Guest, D. Martins-de-Souza, E. Schwarz, H. Rahmoune, M. Alsaif, J. Tomasik, C.W. Turck, S. Bahn, Genome Med. 5 (2013) 25.
[9] L.A. Sass, J. Parnas, Schizophr. Bull. 29 (2003) 427.
[10] J.M. Nascimento, D. Martins-de-Souza, npj Scz. 1 (2015) 1.
[11] S.E. Hyman, Nature 508 (2014) S20.
[12] C. Sotiriou, L. Pusztai, NEJM. 360 (2009) 790.
[13] E. Schwarz, R. Izmailov, M. Spain, A. Barnes, J.P. Mapes, P.C. Guest, H. Rahmoune, S. Pietsch, F.M. Leweke, M. Rothermundt, Biomark. Insights 5 (2010) BMI. S4877.
[14] H. Le-Niculescu, M. McFarland, C. Ogden, Y. Balaraman, S. Patel, J. Tan, Z. Rodd, M. Paulus, M. Geyer, H. Edenberg, Am. J. Med. Genet. Part B: Np. Genet 147 (2008) 134.
[15] E. Schwarz, P.C. Guest, H. Rahmoune, L.W. Harris, L. Wang, F. Leweke, M. Rothermundt, B. Bogerts, D. Koethe, L. Kranaster, Mol. Psychiatry 17 (2012) 494.
[16] S.S. Karimian, M.T. Akbari, S.S. Sadr, G. Javadi, Basic and Clin. Neurosci. 11 (2020) 595.
[17] K. Dry, S. Kenwrick, A. Rosenthal, M. Platzer, Gene 273 (2001) 115.
[18] M. Ayalew, H. Le-Niculescu, D. Levey, N. Jain, B. Changala, S. Patel, E. Winiger, A. Breier, A. Shekhar, R. Amdur, Mol. Psychiatry 17 (2012) 887.
[19] H. Yu, W. Bi, C. Liu, Y. Zhao, D. Zhang, W. Yue, Prog. NeuroPsychopharmacol. Biol. Psychiatry 51 (2014) 140.
[20] J.R. Sanes, M. Yamagata, Annu. Rev. Cell Dev. 25 (2009) 161.
[21] K. Feinberg, Y. Eshed-Eisenbach, S. Frechter, V. Amor, D. Salomon, H. Sabanay, J.L. Dupree, M. Grumet, P.J. Brophy, P. Shrager, Neuron 65 (2010) 490.
[22] G. Javadi, S.S. Sadr, BCN 0-0.
[23] D.L. Benson, L.M. Schnapp, L. Shapiro, G.W. Huntley, Trends Cell Biol. 10 (2000) 473.
[24] A.J. Price, A.E. Jaffe, D.R. Weinberger, Mol. Psychiatry (2020) 1.
[25] L. Garey, J. Anat. 217 (2010) 324.
[26] P. Kalus, D. Senitz, H. Beckmann, J. Neural Trasm. 104 (1997) 549.

[27] S. Gulsuner, T. Walsh, A.C. Watts, M.K. Lee, A.M. Thornton, S. Casadei, C. Rippey, H. Shahin, D. Braff, K.S. Cadenhead, Cell 154 (2013) 518.
[28] S. Flynn, D. Lang, A. Mackay, V. Goghari, I. Vavasour, K. Whittall, G. Smith, V. Arango, J. Mann, A. Dwork, Mol. Psychiatry 8 (2003) 811.
[29] J. Stiles, T.L. Jernigan, Neuropsychol. Rev. 20 (2010) 327.
[30] S.A. Back, P.A. Rosenberg, Glia 62 (2014) 1790.
[31] T. Benn, C. Halfpenny, N. Scolding, Glia 36 (2001) 200.
[32] H.C. Wilson, C. Onischke, C.S. Raine, Glia 44 (2003) 153.
[33] N. Takahashi, T. Sakurai, Neurobiol. Dis. 53 (2013) 49.
[34] N. Takahashi, T. Sakurai, K.L. Davis, J.D. Buxbaum, Prog. Neurobiol. 93 (2011) 13.
[35] M. Kubicki, R.W. McCarley, M.E. Shenton, Curr. Opin. Psychiatry. 18 (2005) 121.
[36] M.E. Atz, B. Rollins, M.P. Vawter, Psychiatr. Genet. 17 (2007) 55.
[37] L. Matzel, J. Babiarz, D. Townsend, H. Grossman, M. Grumet, Genes, Brain Behav. 7 (2008) 470.
[38] Z. Zhang, H. Yu, S. Jiang, J. Liao, T. Lu, L. Wang, D. Zhang, W. Yue, PloS one 10 (2015) e0144719.
[39] K. Hirabayashi, K. Shiota, S. Yagi, BMC Genet. 14 (2013) 82.
[40] P. Roussos, P. Katsel, K.L. Davis, P. Bitsios, S.G. Giakoumaki, J. Jogia, K. Rozsnyai, D. Collier, S. Frangou, L.J. Siever, Arch. Gen. Psychiatry 69 (2012) 7.
[41] H. Le-Niculescu, Y. Balaraman, S. Patel, J. Tan, K. Sidhu, R. Jerome, H.J. Edenberg, R. Kuczenski, M.A. Geyer, J.I. Nurnberger Jr, Am. J. Med. Genet. P. B: Npc. Genet. 144 (2007) 129.
[42] F. Eskandari, J.I. Webster, E.M. Sternberg, Arthritis Res. Ther 5 (2003) 1.
[43] L.W. Harris, M. Wayland, M. Lan, M. Ryan, T. Giger, H. Lockstone, I. Wuethrich, M. Mimmack, L. Wang, M. Kotter, PLoS One 3 (2008) e3964.
[44] N. Müller, M.J. Schwarz, Expert Rev. Neurother. 6 (2006) 1017.