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Expression Analysis of Ermin and Listerin E3 Ubiquitin Protein Ligase 1 Genes in the Periphery of Patients with Schizophrenia

Sara Farhang[1,2] · Hani Sabaie[3] · Jalal Gharesouran[3] · Mohammad Reza Asadi[3] · Shahram Arsang-Jang[4] · Soudeh Ghafouri-Fard[5] · Mohammad Taheri[6] · Maryam Rezazadeh[3]

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Abstract

Schizophrenia (SCZ) is a severe mental disorder with an unknown etiology. Recent researches indicate that correct myelination and translational regulation play a role in the pathogeny of SCZ. This study evaluated the expression pattern of Ermin (*ERMN*) and Listerin E3 ubiquitin protein ligase 1 (*LTN1*) genes, which play a role in myelination and ribosome quality control, respectively. The expression of the *ERMN* and *LTN1* genes in the peripheral blood (PB) of 50 SCZ patients (male/female: 22/28, age (mean ± standard deviation (SD)): 35.9 ± 5.6) and 50 matched healthy controls (male/female: 23/27, age (mean ± SD): 34.7 ± 5.4) were assessed using quantitative polymerase chain reaction. Additionally, we used a bioinformatics approach based on microarray dataset analysis to examine the expression of these two genes in olfactory epithelium (OE) specimens. The expression of *ERMN* demonstrated no significant differences in PB samples among SCZ patients and healthy controls (adjusted *P*-value = 0.101). The expression of *LTN1* was significantly higher in PB samples obtained from female patients compared with sex-matched controls (posterior beta = 1.734, adjusted *P*-value < 0.0001). Significant correlations were found between expression of the mentioned genes in PB samples both among SCZ patients and among healthy controls ($r = 0.485$, $P < 0.001$ and $r = 0.516$, $P < 0.001$, respectively). According to our in silico findings, the *ERMN* expression levels in OE samples of SCZ were statistically higher than those in controls (log2FC = 1.93, adj.P.Val = 9.66E-15). On the contrary, *LTN1* expression levels in OE samples were statistically lower in SCZ cases versus controls (log2FC = − 0.77, adj.P.Val = 2.14E-06). Besides, a significant correlation was found between the expression of the mentioned genes in OE samples ($r = -0.60$, $P < 0.001$). In conclusion, the present study is the first evidence to highlight the expression of the *ERMN* and *LTN1* genes in the periphery of SCZ patients. Our findings may provide light on the SCZ's pathogeny.

Keywords *ERMN* · Expression · *LTN1* · Periphery · Schizophrenia

Introduction

Schizophrenia (SCZ) is a heterogeneous syndrome with a lifetime prevalence of close to 1% caused by complicated relationships between genetic and environmental factors. SCZ is among the top ten disorders responsible for disability-adjusted life years. SCZ is presented with but is not limited to a wide range of symptoms and signs like hallucinations, delusions (positive symptoms), decreased motivation, diminished emotions (negative symptoms), and attention and memory

✉ Mohammad Taheri
Mohammad_823@yahoo.com

Maryam Rezazadeh
Rezazadehm@tbzmed.ac.ir

1 Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

2 Rob Giel Research Center, University Medical Center Groningen, University Center for Psychiatry, University of Groningen, Groningen, Netherlands

3 Department of Medical Genetics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

4 Cancer Gene Therapy Research Center, Zanjan University of Medical Science, Zanjan, Iran

5 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6 Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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problems (cognitive symptoms). SCZ is a complex polygenic disorder, with over 100 responsible loci that each has a small effect (Marder and Cannon 2019; Keshavan et al. 2020). The majority of the genes identified in genome-wide association (GWAS) and gene expression analysis take part in various pathways connected to the immune system, the function of synapses, and the development of cytoskeleton (Marder and Cannon 2019). Oligodendrocyte-associated disruptions that directly impact myelination are suggested to be a crucial feature of SCZ pathogenesis because of the essential role of oligodendrocytes in brain connectivity (Cassoli et al. 2016; Kolomeets and Uranova 2019). Moreover, the disruption of brain translational regulation in SCZ progression is increasingly being taken into consideration. Translational control is closely linked to new processes like ribosome stalling and controlling ribosome quality. As a result, all of these factors may influence the pathogeny of this illness (Hui et al. 2019).

Comparing expression profiles from biospecimens between patients and controls is currently one of the major strategies to elucidate disease mechanisms and identify biomarkers (Iwamoto and Kato 2006). The complexity in reaching cells and tissues related to the disorder pathophysiology is a key obstacle to using this strategy for brain diseases. Reliable and relevant biological samples that can be collected longitudinally are urgently required (Horiuchi et al. 2013). In this study, we selected Ermin (*ERMN*) and Listerin E3 ubiquitin protein ligase 1 (*LTN1*) genes, which play a role in myelination and ribosome quality control, respectively, for further investigation because of their possible role in the pathogenesis of SCZ. It is noteworthy that altered expression of these two genes and the correlation between them were shown in our two recent studies on the peripheral blood (PB) of patients with multiple sclerosis (Salek Esfahani et al. 2019) and autism spectrum disorder (Shiva et al. 2021) as two brain diseases, suggesting that these two genes have the potential to reflect the link between the brain and the periphery. *ERMN*, also known as juxtanodin, encodes a myelinating oligodendrocyte-specific protein. This protein presents itself in a later phase during myelination. The outer cytoplasmic lip of the myelin sheath and the paranodal loops of mature neurons is where it is located (Brockschnieder et al. 2006). In SCZ, poor myelination may result in aberrant brain connections and persistent functional impairment (Flynn et al. 2003; Schmitt et al. 2019). *LTN1* encoded protein is a component of the ribosome quality control complex (RQC). This complex is involved in polybasic-mediated stalled protein degradation (Bengtson and Joazeiro 2010; Brandman et al. 2012; Defenouillère et al. 2013; Verma et al. 2013).

This study aims to evaluate the expression of *ERMN* and *LTN1* genes in the periphery of SCZ patients due to their involvement in oligodendrocyte-associated disturbances and RQC pathway disruption, as well as their possible uses in diagnosis, prognosis, and earlier treatment.

Materials and Methods

Participants and Samples

This study is performed within the framework of the Azeri recent-onset acute phase psychosis survey (ARAS) (Farhang et al. 2021). The study protocol was approved by the ethical committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1399.462). Fifty first-episode antipsychotic-naïve adult SCZ patients and 50 age and gender-matched healthy controls were enrolled. An experienced psychiatrist diagnosed first-episode SCZ patients based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for schizophrenia (Association 2013) by a Structured Clinical Interview for DSM-5 (SCID) (Shooshtari et al. 2007). Exclusion criteria were 22q11.2 deletion syndrome, intellectual disability, and substance use (except cigarette). The Mini-International Neuropsychiatric Interview (Sheehan et al. 1998) was used for the assessment of healthy controls. The existence of systemic disorders, psychiatric conditions, or pregnancy was regarded as exclusion criteria for the control group. Moreover, those who reported a major psychiatric condition in their first-degree relatives were excluded. After acquiring written informed consent from all participants and/or their caregivers, 10 ml of PB was collected.

Quantitative Polymerase Chain Reaction (qPCR)

Total RNA extraction was achieved from whole blood using a Hybrid-R™ Blood RNA purification kit (GeneALL, Seoul, South Korea) according to the manufacturer's protocol. The extracted RNA's concentration and quality were assessed with Nanodrop (Thermo Scientific, Wilmington, DE). cDNA was synthesized using the HyperScript™ kit (GeneAll) according to the manufacturer's instructions. Prepared cDNA was stored at − 20 °C for further use. The primers were designed by Oligo7 software. The used primers for *ERMN*, *LTN1*, and ubiquitin C (*UBC*) as the housekeeping gene are shown in Table 1. *UBC* was chosen because it has been introduced as one of the most stable housekeeping genes in schizophrenia studies (Weickert et al. 2010; Silberberg et al. 2009). The qPCR was carried out by the Step OnePlus™ Real-Time PCR and the RealQ Plus2x Master Mix (Ampliqon, Odense, Denmark).

Statistical Analysis for qPCR

Data were analyzed by the R v.4 software packages brms and stan. A comparison was made between the relative expression levels of *ERMN* and *LTN1* genes in the patients with SCZ and the healthy participants by the use of the

Bayesian quantile regression model. The impacts of sex and age were adjusted. The Bonferroni correction was used to adjust *P*-values for multiple comparisons. The adjusted *P*-values < 0.01 were taken as significant. A comparison was also made in the expressed levels of the tested genes between different age groups and between men and women.

Correlation Analysis

The correlation of the studied variables was assessed by Spearman correlation coefficients using the GGally package.

Bioinformatics Analysis Based on Microarray Dataset

In the present study, we utilized a bioinformatics strategy for mining data of the microarray dataset of the biopsied olfactory epithelium (OE) (GSE73129). We intended to identify expression changes of *ERMN* and *LTN1* in OE samples.

Gene Expression Profile Data Collection

The gene expression profile mentioned above was obtained from the NCBI Gene Expression Omnibus database (GEO, https://www.ncbi.nlm.nih.gov/geo/). A chip-based platform GPL570 (HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array was applied for the dataset. The GSE73129 contained 38 OE samples, of which 19 were from SCZ patients, and 19 were from healthy individuals (Horiuchi et al. 2016).

Data Preprocessing and Differentially Expressed Genes (DEGs) Identification

For background correction and quantile normalization of all primary data records, Robust Multichip Average (RMA) was employed (Irizarry et al. 2003). To lower the number of analyzed genes, an interquartile range filter (IQR across the samples on the log base two scale greater than median IQR) was employed, which was accompanied by an intensity filter a minimum of > 100 expression signals in a minimum of 25% of the arrays) intended to eliminate insignificant probe sets that are not expressed or altered (von Heydebreck et al. 2005). For quality control, the AgiMicroRna Bioconductor package was employed. We employed principal component analysis (PCA) to conduct a dimensional reduction analysis (Yeung and Ruzzo 2001), aiming to find similarities between each sample group using R software's ggplot2 package. Differential expression gene analysis (DEGA) was done between SCZ and normal samples using the linear models for microarray data (limma) R package (Ritchie et al. 2015) in Bioconductor (https://www.bioconductor.org/) (Huber et al. 2015). The Student *t*-test was utilized to detect statistically significant genes and the aberrantly expressed genes cutoff was set as (1) adjusted *P*-value < 0.001 and (2) |log2 fold-change (log2FC)| ≥ 0.585. The *P*-values were adjusted using the Benjamini–Hochberg method. The Pheatmap and Enhanced Volcano R packages were employed for drawing the DEGs' heat map and volcano plot.

Correlation Analysis

We also performed Pearson correlation analysis to investigate the correlation between *ERMN* and *LTN1* expression. We used Hmisc and psych packages for the calculation of the correlation and visualization.

Results

General Demographic Data

We examined 50 SCZ patients (male/female: 22/28) with age (mean ± standard deviation (SD)) of 35.9 ± 5.6 and 50 healthy controls (male/female: 23/27) with age (mean ± SD) of 34.7 ± 5.4, all with Turkish Azeri ethnic backgrounds.

Table 1 List of primers used in this study

Gene name	Gene reference ID	Primer sequences (5′-3′)
ERMN	NM_001304344.2 NM_001304345.2 NM_001009959.3 NM_001304346.2 NM_020711.3	Forward primerGACATTCAGAGAAGGGCATCAG Reverse primerAGGCTGCTCAGTAATCCTCTC
LTN1	NM_001320766.2 NM_015565.3 XM_017028316.2 XM_017028317.1	Forward primerAGATGAAGAAGAAGAGCCAGCCT Reverse primerAAAGCCCGAAGCTGTGATGATGC
UBC	NM_021009.7	Forward primerCAGCCGGGATTTGGGTCG Reverse primerCACGAAGATCTGCATTGTCAAGT

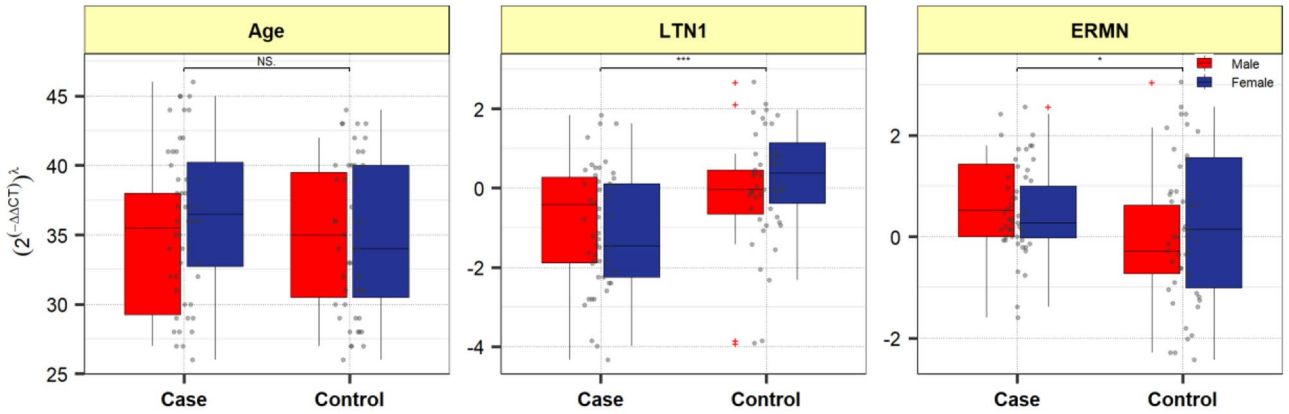

Fig. 1 Expression of *ERMN* and *LTN1* in cases and controls' blood samples. Values are depicted as gray dots. Means of expression levels and interquartile range are displayed

qPCR Data Analysis

Figure 1 shows *ERMN* and *LTN1* genes' relative expression levels in patients with SCZ and controls. The *ERMN* expression levels demonstrated no significant differences in PB samples among SCZ patients and healthy controls (adjusted *P*-value = 0.101). Considering the gender of study participants, the analysis showed that the *LTN1* expression levels were significantly higher only in female subjects (posterior beta = 1.734, adjusted *P*-value < 0.0001). Table 2 and Table 3 show the detailed data about the relative expression of *ERMN* and *LTN1*, respectively.

Correlation Analysis

No correlations were observed between *ERMN* and *LTN1* expressions and the ages of subjects. The expressed levels of the examined genes were correlated significantly both among SCZ patients and among healthy controls ($r = 0.485$, $P < 0.001$ and $r = 0.516$, $P < 0.001$, respectively) (Fig. 2).

Microarray Data Reanalysis

DEGs Identification

Before DEGA, background adjustment, normalization, gene filtering, and batch adjustment were done. To control the quality, the AgiMicroRna Bioconductor package was used. To analyze data distribution after normalizing, the gene expression dataset's box plots were illustrated (Supplementary File S1). Separate arrays in the box plots showed identical medians of expression level, indicating that the adjustment was done correctly. Furthermore, to show the spatial distribution of samples, a PCA plot was employed (Supplementary File S1). The details of the examined data's structure are displayed in PCA, and it helps discover similarities between samples. Two control samples were removed due to being spatially far from other control samples.

Based on the criteria of adjusted *P*-value < 0.001, and (2) |log2 fold-change (log2FC)| ≥ 0.585, a total of 2231 DEGs were identified in OE samples from GSE73129. Hierarchical

Table 2 Relative levels of *ERMN* in schizophrenia cases and controls according to the Bayesian quantile regression model

	ERMN	Posterior beta of $(2^{(-ddct)})^{\lambda}$	SE	Adjusted *P*-value*	95% CrI for beta
Total	Group, case vs. control	−0.778	0.31	0.101	[−1.41, −0.19]
	Sex, female vs. male	−0.118	0.28	0.480	[−0.73, 0.39]
	Age (years)	0.004	0.02	0.585	[−0.04, 0.04]
	Group * sex	0.451	0.45	0.324	[−0.43, 1.36]
Male	Case vs. control	−0.776	0.31	0.048	[−1.42, −0.15]
	Age	−0.014	0.03	0.473	[−0.08, 0.04]
Female	Case vs. control	−0.317	0.37	0.675	[−1.1, 0.42]
	Age	0.01	0.03	0.746	[−0.05, 0.07]

*Estimated from frequentist methods; *CrI*, credible interval, λ: power transformation value estimated from the Box-cox or Yeo-Johnson method

Table 3 Relative levels of *LTN1* in schizophrenia cases and controls according to the Bayesian quantile regression model

	LTN1	Posterior beta of $(2^{(-ddct)})^{\lambda}$	SE	Adjusted *P*-value*	95% CrI for beta
Total	Group, case vs. control	0.321	0.35	0.068	[−0.33, 1.04]
	Sex, female vs. male	−0.875	0.39	0.492	[−1.62, −0.04]
	Age (years)	−0.037	0.02	0.611	[−0.08, 0.01]
	Group * sex	1.352	0.5	< 0.0001	[0.32, 2.32]
Male	Case vs. control	0.276	0.35	0.532	[−0.38, 1]
	Age	−0.018	0.03	0.461	[−0.08, 0.04]
Female	Case vs. control	1.734	0.35	< 0.0001	[1.04, 2.43]
	Age	−0.053	0.03	0.08	[−0.12, 0.01]

*Estimated from frequentist methods; *CrI*, credible interval, λ: power transformation value estimated from the Box-cox or Yeo-Johnson method

clustering heatmap and volcano plot of DEGs are shown in Fig. 3.

The *ERMN* expression levels in OE samples of SCZ were statistically higher than those in controls (log2FC = 1.93, adj.P.Val = 9.66E-15). On the contrary, *LTN1* expression levels were statistically lower in SCZ cases versus controls (log2FC = −0.77, adj.P.Val = 2.14E-06) (Supplementary File S1).

Correlation Analysis

The Pearson correlation analysis between *ERMN* and *LTN1* was conducted to verify the relationship between these two genes in OE samples of SCZ patients. A significant correlation was detected between assessed genes' expression levels ($r = -0.60$, $P < 0.001$) (Fig. 4).

Discussion

SCZ is a public health problem with a typically multifactorial origin. Many scientists are interested in employing gene discoveries to achieve insights into SCZ's underlying biology (Foley et al. 2017). In the present study, we evaluated *ERMN* and *LTN1* expression in the PB and OE samples of SCZ patients and healthy individuals using qPCR and a bioinformatics approach based on microarray dataset analysis, respectively. The results are discussed below.

qPCR Data Analysis

Higher levels of *LTN1* were detected in PB samples obtained from female patients in comparison with the sex-matched controls. The reported observation could have resulted from sex-linked variations present in the phenotypes or fundamental mode of action of SCZ. The symptoms of SCZ are differences in terms of gender. This can be exemplified by males with SCZ who apparently show more negative symptoms and more severe manifestations clinically than women, in particular in social withdrawal and excessive use of drugs. Female patients with SCZ oftentimes demonstrate more disturbed moods and depressing symptoms as well as affective symptoms. It is interesting that these gender-related indications in male SCZ patients were also detected in individuals who are at elevated risk of the disorder (Rietschel et al. 2017). Such differences are attributable to sex-related factors, such as gonadal hormones and sex chromosomes (Li et al. 2016). Further investigations in the future can elaborate on the fundamental mode of action for the reported finding. The *LTN1* gene regulates protein quality by controlling the proteolytic targeting of unfinished polypeptides caused by ribosome stalling (Martin et al. 2020). The *LTN1* gene may play a role in the SCZ's pathogenesis by disturbing the RQC pathway, which has been demonstrated to impact translational regulation and brain activity (Hui et al. 2019). To the best of our knowledge, this is the first report on *LTN1* expression in SCZ cases. A previous GWAS in Africans recognized a variant in *LTN1* associated with initial pursuit acceleration in the SCZ spectrum and bipolar psychosis (Lencer et al. 2017).

We found that the *ERMN* expression levels demonstrated no significant differences in PB samples among patients with SCZ and controls. *ERMN* encoded protein is a member of the ezrin-radixin-moesin family, and in 2006, it was discovered to be a cytoskeletal protein. It has been revealed that this gene stimulates oligodendroglial cell differentiation and myelin sheath preservation via associating with the myosin phosphatase Rho-interacting protein (Mprip/p116RIP) and inactivates RhoA, which is a GTPase regulating the cytoskeleton rearrangement in differentiating cells (Wang et al. 2011). To the best of our knowledge, the present study is the first report on the expression of *ERMN* in SCZ patients' PB. According to previous researches, *ERMN* is downregulated in the anterior temporal lobe (Martins-de-Souza et al. 2009b) and elevated in the prefrontal cortex of SCZ patients (Martins-de-Souza et al. 2009a).

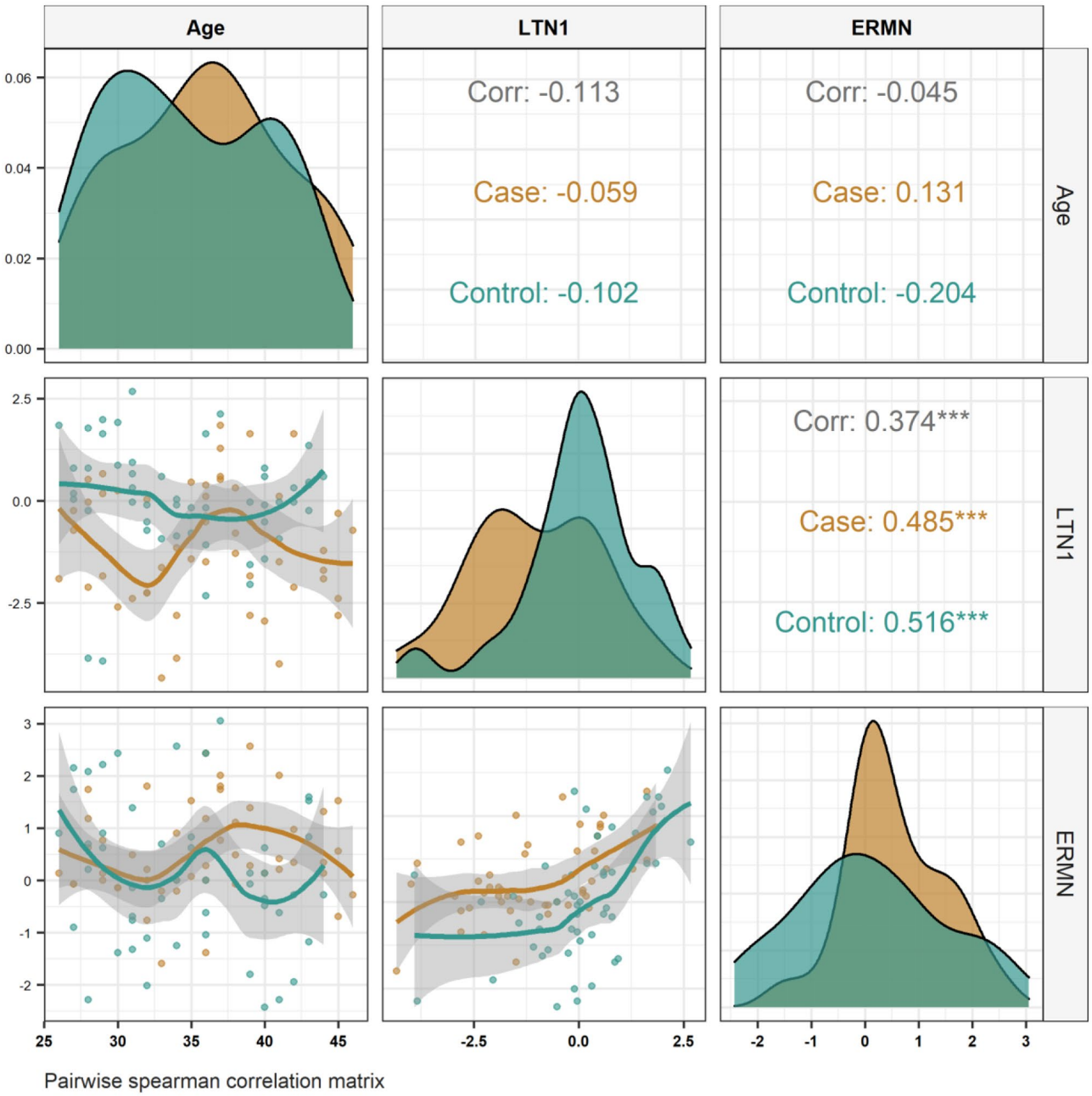

Fig. 2 The distribution of each variable is shown on the diagonal. The correlation coefficients plus the significance level as stars are displayed. *** is significant correlation at *P*-value < 0.001

Furthermore, a significant connection was discovered between *ERMN* and *LTN1* levels, indicating an interacting network, most likely due to translational regulation. According to the present findings, although *ERMN* and *LTN1* are significantly correlated directly, suggesting their interactional network, their functions in developing SCZ need to be reconsidered based on whole blood specimens since the changed expression patterns of *ERMN* were not sufficiently robust to be of significance. However, the observed results are introductory. One possible reason for this might be our limited sample size. Furthermore, although for gathering molecular data about the start or the path of mental disorder in living cases, the blood is often utilized due to its gathering simplicity, some groups have demonstrated that blood cells differ from brain cells in terms of expression patterns in SCZ studies. So, it is better to choose the OE that involves olfactory receptor neurons,

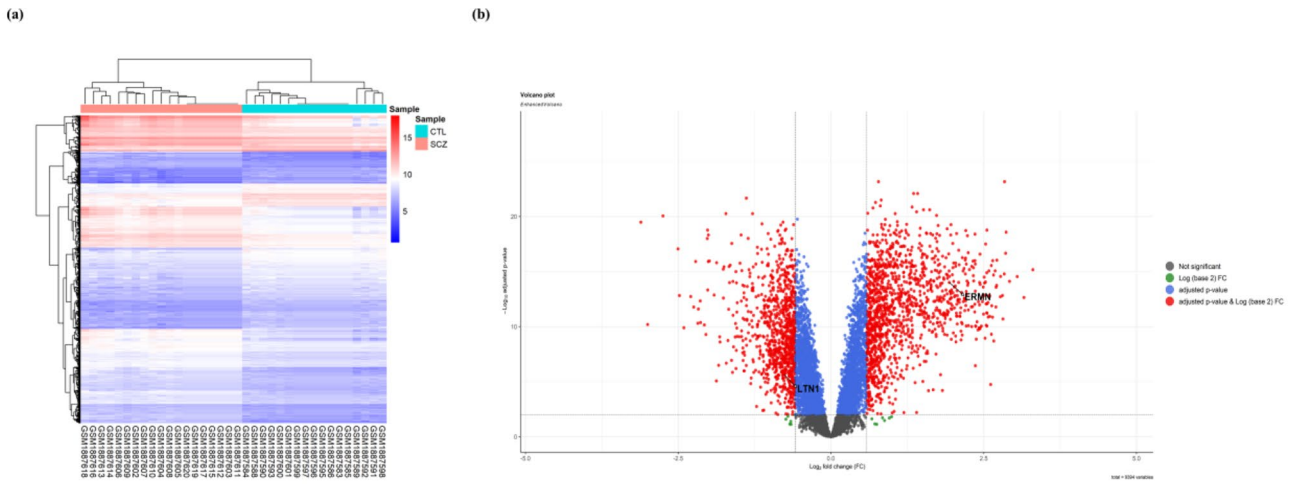

Fig. 3 Differentially expressed genes between schizophrenia (SCZ) samples and control (CTL) samples. (**a**) Heatmap of the differentially expressed genes (DEGs). High expressed genes are shown in red, while those expressed at low levels are blue. (**b**) Volcano plot for the DEGs. The DEGs were screened according to a |(log2FC) |≥0.585 and an adjusted *P*-value < 0.001

which the expression patterns of them are similar to developing brain cells (Horiuchi et al. 2016, 2013; Cascella et al. 2007; Borgmann-Winter et al. 2015).

Unfortunately, we did not have OE samples, so we decided to use a bioinformatics approach to assess the expression of these two genes in OE samples.

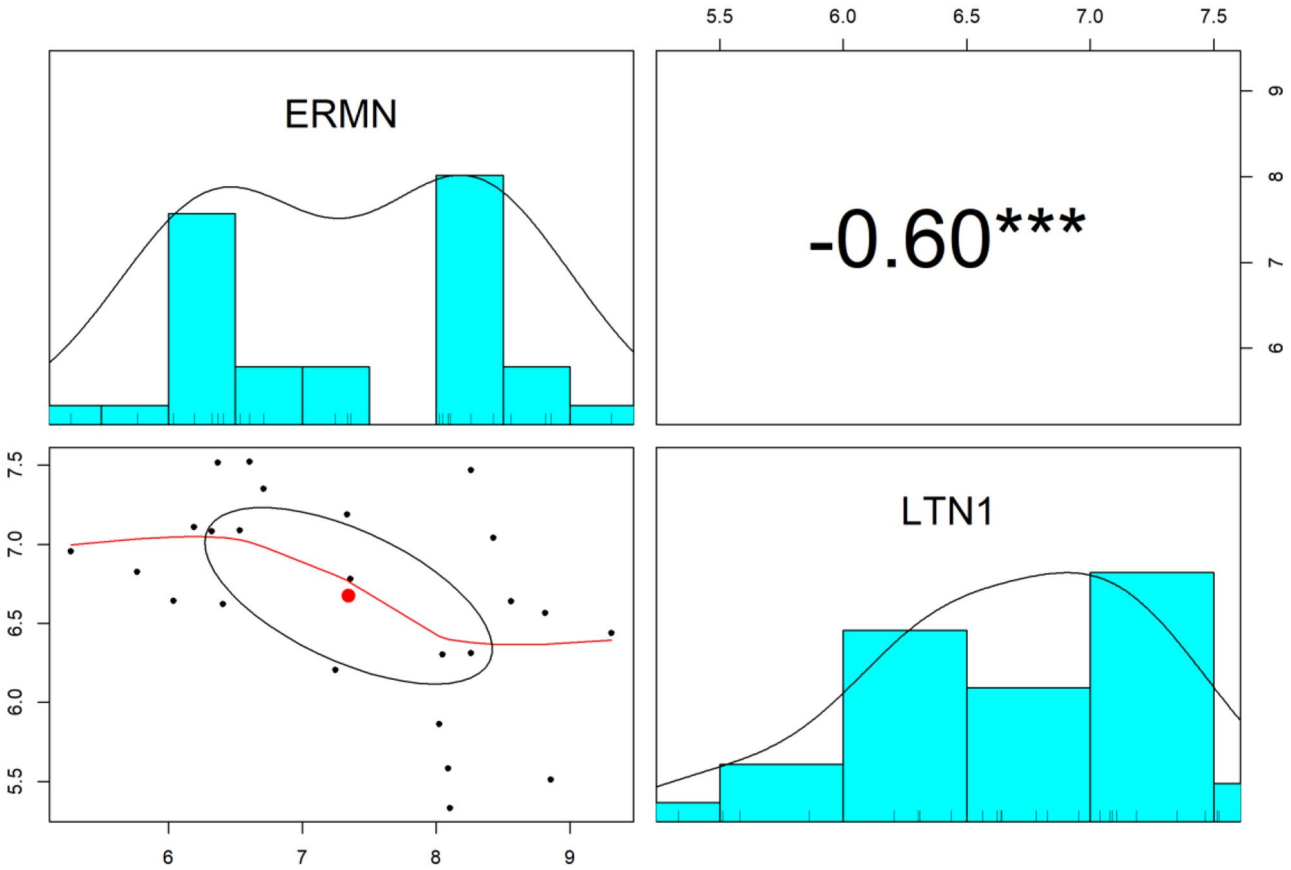

Fig. 4 The distribution of each variable is shown on the diagonal. The lower portion of the diagonal shows bivariate scatter plots with a fitted line. On the upper part of the diagonal, the correlation coefficients plus the significance level as stars are displayed. *** is significant correlation at *P*-value < 0.001

Microarray Data Reanalysis

We used a public database to download the expression profiles of OE tissue of SCZ to evaluate the DEGs in SCZ and normal tissues. Interestingly, our in silico analysis showed that the *ERMN* and *LTN1* expression levels significantly changed in OE samples among patients with SCZ and controls. Contrary to the results of assessing the expressions level of these two genes in the PB, higher levels of *ERMN* and lower levels of *LTN1* were detected in patients with SCZ in comparison with the controls. Furthermore, a significant negative connection was discovered between *ERMN* and *LTN1* levels. These results may suggest that the biological function of these two genes in OE was not similar to those in PB. These findings could also confirm that OE reflects brain changes in SCZ better than the blood.

Limitations

Our study has faced with some limitations. Firstly, a small sample size can cause the low statistical power of our study. Furthermore, we have not evaluated the expression of *ERMN* and *LTN1* in the sub-population of PB cells. Our results suggest a complicated interactive network between *ERMN* and *LTN1* which simple correlation analysis cannot detect that. Hence, future in vitro studies are desirable to evaluate the consequences of *ERMN* and *LTN1* genes dysregulation at the cellular level. Besides, functional studies would help to explore the role of the abovementioned genes in SCZ. Our study also has another limitation regarding the lack of validation experiments to prove the results of bioinformatics analysis.

Conclusion

In conclusion, the present study is the first evidence to highlight the expression of the *ERMN* and *LTN1* genes in the periphery of SCZ patients. Our results may offer new insights into the pathogenesis of SCZ. Further investigations using larger sample sizes and paired PB and OE samples from drug naïve cases can profoundly strengthen these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12031-021-01928-1.

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Author Contribution H.S., M.R., and M.T. wrote the manuscript and revised it. M.R.A., H.S., and J.G. supervised the study and performed the experiment. S.A.J. analyzed the data. S.F. was the clinical consultant and assessed patients for inclusion in the study. All authors read and approved the final version of the manuscript.

Availability of Data and Materials The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participant All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Tabriz University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of Publication Not applicable.

Competing Interest The authors declare no competing interests.

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