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Assessment of expression of oxytocin-related lncRNAs in schizophrenia

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ABSTRACT

Background: Schizophrenia is a neuropsychiatric disorder characterized by a variety of clinical manifestations. This disorder has a complex inheritance. Oxytocinegic system has been shown to be implicated in the pathophysiology of schizophrenia. This system can alter social cognition through direct interaction with dopaminergic signaling, facilitating brain-stimulation reward, reduction of defense mechanism and stress reactivity, and modulation of social information processing through enhancing the greatness of social incentives. Long non-coding RNAs (lncRNAs) can affect activity of oxytocinegic system, thus contributing in the etiology of this disorder.

Methods: We designed the current study to appraise dysregulation of nine oxytocin-associated mRNAs and lncRNAs in the venous blood of patients with schizophrenia.

Results: Expression of *FOS* was up-regulated in total patients compared with total control group (Expression ratio (95% CI) = 13.64 (5.46–34.05), adjusted P value < 0.0001) and in female patients compared with female control group (Expression ratio (95% CI) = 32.13 (5.81–176), adjusted P value < 0.0001). Such pattern was also seen for *Lnc-FOXF1* (Expression ratio (95% CI) = 6.41 (2.84–14.3), adjusted P value < 0.0001 and Expression ratio (95% CI) = 14.41 (3.2–64.44), adjusted P value < 0.0001, respectively). *ITPR1* was down-regulated in total patients compared with total controls (Expression ratio (95% CI) = 0.22 (0.076–0.67), adjusted P value = 0.0079). ROC curve analyses demonstrated that *FOS* had the best AUC value among other genes in differentiation between patients and controls (AUC = 0.78).

Conclusion: The above-mentioned results imply dysregulation of oxytocin-related genes in the circulatory blood of patients with schizophrenia.

1. Introduction

Schizophrenia is a neuropsychiatric disorders pigeonholed by a variety of signs and symptoms, mainly positive symptoms including hallucinations and paranoid delusions (Hany et al., 2021). Affected individuals also have a variety of negative symptoms along with social dysfunction (Hany et al., 2021). Several hypotheses have been suggested to explain the pathoetiology of schizophrenia. While dopamine hypothesis is the most acknowledged one (Brisch et al., 2014), a number of other neurotransmitters and neuropeptides, namely glutamate, serotonin

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Table 1
Characteristic the studied genes.

Name/Gene symbol	Accession number	Location	Description	Function
ITPR1	NM_001099952.4	3p26.1	inositol 1,4,5-trisphosphate receptor type 1	calcium channel activity
TNS-AS1 (Lnc-TNS1)	NR_135524.1	2q35	Tensin1 antisense RNA 1	regulating gene expression
FOS	NM_005252.4	14q24.3	Fos proto-oncogene, AP-1 transcription factor subunit	Transcription regulation
LINC01116 (Lnc-MTX2)	NR_040001.2	2q31.1	long intergenic non-protein coding RNA 1116	regulating gene expression
RCAN1	NM_001285389.2	21q22.12	regulator of calcineurin 1	calcineurin-dependent signaling pathways
ZBTB14 (ZFP161)	NM_001143823.3	18p11.31	zinc finger and BTB domain containing 14	Transcription regulation
OXTR	NM_000916.4	3p25.3	oxytocin receptor	G-protein coupled receptor family
CAMK2D	NM_001221.4	4q26	calcium/calmodulin dependent protein kinase II delta	serine/threonine protein kinase
FENDRR (Lnc-FOXF1)	NR_033925.1	16q24.1	FOXF1 adjacent non-coding developmental regulatory RNA	It might promote the methylation of the promoters of target genes.

(Stahl, 2018), GABA (Deidda et al., 2014), cannabinoid (Tan et al., 2014), and neuropeptide Y (L LaCrosse and Foster Olive, 2013) have been reported to participate in the pathophysiology of this disorder. It has been revealed that serum of patients with schizophrenia contain exosome whose transplantation to animal models leads to induction of schizophrenia-related behaviors (Du et al., 2021). These exosomes encompass a number of dysregulated transcripts including miRNAs (Du et al., 2019).

Notably, oxytocin, as a hormonal neuropeptide has been found to regulate a number of brain functions that are altered in the context of schizophrenia (Goh et al., 2021). Oxytocin can alter social cognition through direct interaction with dopaminergic signals, facilitating brain-stimulation reward, reduction of defense mechanism and stress reactivity, and modulation of social information processing through enhancing the greatness of social incentives (Ellenbogen, 2017). The impact of oxytocinergic system in the pathoetiology of schizophrenia has also been confirmed through studies in animal models where knock-out of oxytocin has resulted in defects in the alteration in the glutamatergic module of the prepulse inhibition (Caldwell et al., 2009). However, a recent systematic review and meta-analysis has shown no reliable beneficial effects of intranasal oxytocin for the amendment of negative and positive symptoms in schizophrenia. Moreover, the results of dose-response meta-analyses have not allowed reaching any strong conclusion yet suggesting more efficacy of high doses of this type of treatment (Sabe et al., 2021).

Meanwhile, non-coding region of transcriptome has been shown to affect pathogenesis of schizophrenia (Ghafouri-Fard et al.; Gibbons et al., 2018). These transcripts can modulate functionality of synapses, neuronal interactions as well as neurotransmission (Ghafouri-Fard et al.). Recent *in silico* studies have suggested interactions between oxytocin and a number of long non-coding RNAs (lncRNAs). This analysis was based on assessment of GEO datasets and KEGG pathway analyses and has selected lncRNAs with higher possibility of relation with this pathway, based on the considered scores (Behtaji et al., 2021). Based on the importance of oxytocinergic system in the pathogenesis of schizophrenia and possible regulatory effects of lncRNAs on this system, we designed the current study to appraise dysregulation of oxytocin related mRNAs and lncRNAs in the peripheral blood of patients with schizophrenia.

2. Materials and methods

2.1. Cases and controls

This project was conducted in whole blood samples attained from 60 patients with schizophrenia (30 male patients and 30 female patients, mean age ± standard deviation (SD): 49.58 ± 9.53) and 60 healthy controls (same male/female ratio, mean age ± SD: 49.63 ± 10.94). Patients with schizophrenia were enrolled from medical centers affiliated with Shahid Beheshti University of Medical Sciences. They were evaluated through using the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (2013). Patients were under treatment with Clozapine (301 mg/day to 600 mg/day). All patients were resistant to treatment with other antipsychotic drugs. Blood samples were taken at the same time in the morning from all patients. Exclusion criteria were current substance abuse or cigarette smoking. Control subjects had no systemic disorder or psychiatric conditions and were evaluated using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). The study protocol was permitted by Ethical Committee of Shahid Beheshti University of Medical Sciences (Ethi-

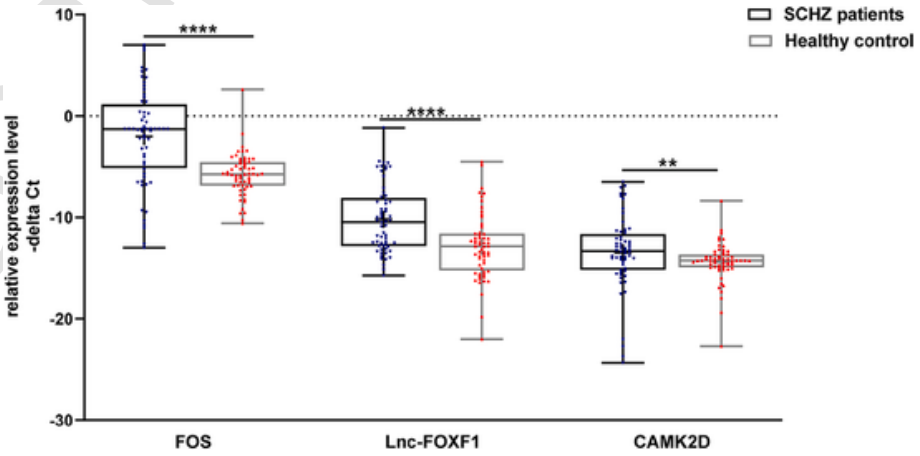

Fig. 1. Relative expression levels of differentially expressed genes in schizophrenia patients (total) and healthy controls (total) as described by –delta Ct values (Ct Housekeeping gene- Ct Target gene). – delta Ct Data were plotted as box and whisker plots. The median [line], mean [cross], interquartile range [box], and minimum and maximum values are shown. The non-parametric test (Mann-Whitney *U* test) was used to identify differentially expressed genes between two groups (**P value < 0.001 and ****P value < 0.0001).

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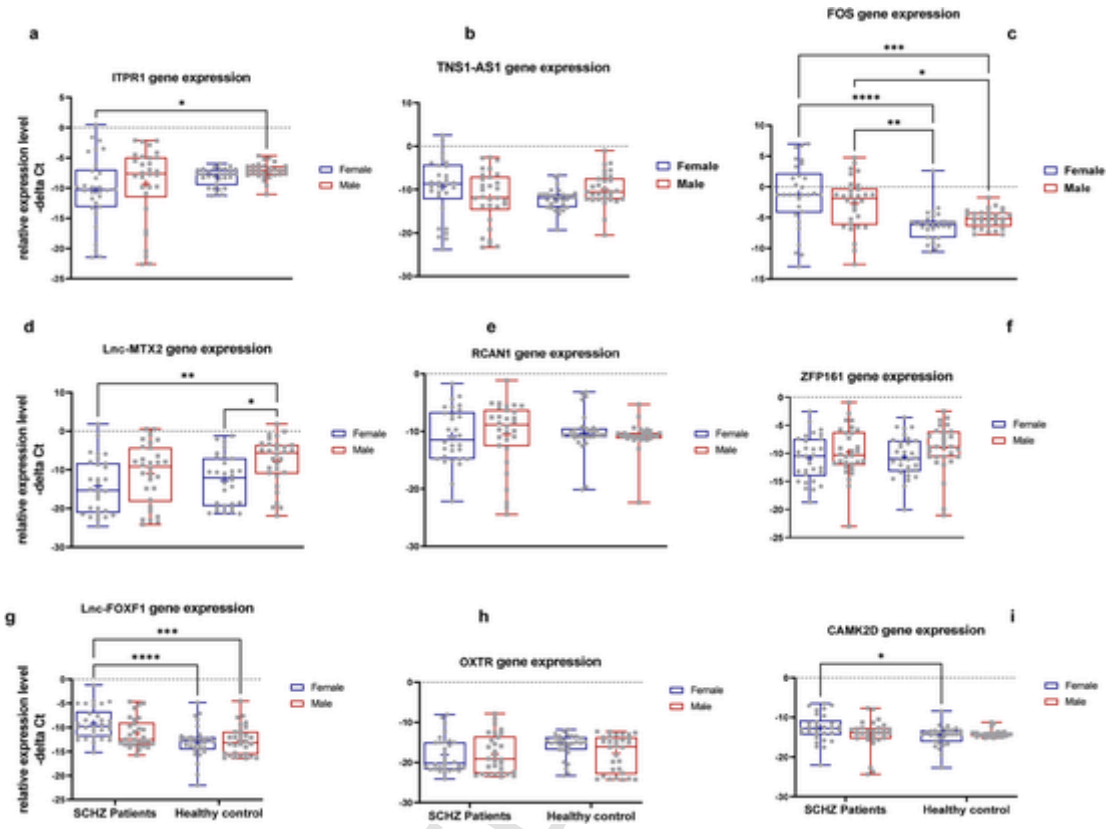

Fig. 2. Expressions of nine studied genes in schizophrenia patients' subgroups (male and female) versus control subgroups (male and female) as described by –delta Ct values (Ct Housekeeping gene- Ct Target gene). – delta Ct values were plotted as box and whisker plots showing the median [line], mean [cross], interquartile range [box], and minimum and maximum values. The two-way ANOVA was used to analyze the main effects (disease and gender) and the interactions between them in subgroups. (*P value < 0.05, **P value < 0.001 and ****P value < 0.0001).

Table 2
Graphpad prism output from analysis of effect of Group and Gender (Tests of Between-Subjects Effects) on expression of nine studied genes in cases compared to healthy controls.

Source of Variation	Group effect			Gender effect			interactions		
	SS[a]	F[b]	P value	SS	F	P value	SS	F	P value
ITPR1	137.2	7.29	**0.0079***	31.67	1.68	0.19	0.0008	0.000049	0.99
TNS1-AS	5.46	0.2	0.65	0.33	0.01	0.91	167.1	6.18	**0.014***
FOS	426.4	31.98	<**0.0001***	0.64	0.048	0.82	45.79	3.43	0.06
Lnc-MTX2	154.4	3.18	0.077	506.9	10.44	**0.001***	20.73	0.43	0.51
RCAN1	0.86	0.044	0.83	0.56	0.03	0.86	7.65	0.4	0.52
ZFP161	6.9	0.41	0.52	52.95	3.15	0.07	1.02	0.06	0.8
Lnc-FOXF1	215.8	20.79	<**0.0001***	23.66	2.27	0.13	40.86	3.93	**0.049***
OXTR	44.95	2.48	0.11	22.77	1.25	0.26	33.64	1.85	0.17
CAMK2D	25.64	3.02	0.08	9.25	1.09	0.29	34.46	4.06	**0.046***

[a] Sum of Squares.
[b] F of Variance.

cal code: IR.SBMU.RETECH.REC.1400.720) and all methods were performed in accordance with the relevant guidelines and regulations. Informed written consent forms were signed by all individuals.

2.2. Expression assays

All blood samples were stored at −70 ∘C until RNA extraction. Then they were subjected to RNA extraction using the RiboEx kit (GeneAll, South Korea). Then, approximately 75 ng of RNA was used for cDNA synthesis using the ExcelRT Reverse Transcription Kit II (SMOBIO, Taiwan). Expressions of oxytocin-related mRNAs and lncRNAs were measured in the ABI step one plus PCR system. Expressions of these transcripts were normalized to *B2M* expression level. RealQ Plus 2 × PCR Master Mix (Ampliqon, Denmark) was used for preparation the PCR reactions. Primers were similar to our recent study (Behtaji et al., 2021).

2.3. Statistical analysis

Statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA, USA). Expressions of nine studied genes in each sample were calculated using the Efficiency adjusted Ct of the normalizer gene- Efficiency adjusted Ct of the target gene. The normal/gaussian distribution of the values was accessed using the Kolmogorov–Smirnov test. Mann-Whitney *U* test was used to identify differentially expressed genes between patients and healthy controls. The two-way ANOVA test was used to analyze the effects of main factors

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Table 3
The results of expression ratio (fold change) of all nine studied genes in cases compared to healthy controls. The expression ratio of each gene (mean and 95% Confidence interval of mean) is shown as the ratio of expression of the first group compared to the second group in each column. P values were corrected for the number of genes.

		Total patients vs. Controls (60 vs. 60)	Male patients vs. Male Controls (30 vs. 30)	Female patients vs. Female Controls (30 vs. 30)	Female patients vs. Male patients (30 vs. 30)
ITPR1	Expression ratio (95% CI)	0.22 (0.076–0.67)	0.22 (0.03–1.71)	0.22 (0.03–1.7)	0.48 (0.06–3.68)
	Adjusted P Value	**0.0079***	0.23	0.22	0.79
TNS1-AS	Expression ratio (95% CI)	1.33 (0.36–4.9)	0.26 (0.02–3.31)	6.86 (0.61–77.7)	5.52 (0.48–62.24)
	Adjusted P Value	0.65	0.51	0.16	0.26
FOS	Expression ratio (95% CI)	13.64 (5.46–34.05)	5.79 (1.04–31.77)	32.13 (5.81–176)	2.6 (0.47–14.22)
	Adjusted P Value	**<0.0001***	0.04	**<0.0001***	0.46
Lnc-MTX2	Expression ratio (95% CI)	0.2 (0.03–1.18)	0.11 (0.004–2.98)	0.36 (0.01–9.51)	0.1 (0.004–2.65)
	Adjusted P Value	0.07	0.31	0.85	0.26
RCAN1	Expression ratio (95% CI)	1.18 (0.37–4.35)	1.26 (0.16–9.71)	0.62 (0.08–4.82)	0.77 (0.1–5.97)
	Adjusted P Value	0.75	0.99	0.93	0.98
ZFP161	Expression ratio (95% CI)	0.62 (0.22–1.78)	0.63 (0.09–4.25)	0.81 (0.12–5.5)	0.45 (0.06–3.05)
	Adjusted P Value	0.36	0.92	0.99	0.7
Lnc-FOXF1	Expression ratio (95% CI)	6.41 (2.84–14.3)	2.85 (0.63–12.8)	14.41 (3.2–64.44)	4.15 (0.92–18.6)
	Adjusted P Value	**<0.0001***	0.26	**<0.0001***	0.07
OXTR	Expression ratio (95% CI)	0.42 (0.14–1.24)	0.89 (0.12–6.45)	0.2 (0.02–1.48)	0.87 (0.12–6.34)
	Adjusted P Value	0.11	0.99	0.16	0.99
CAMK2D	Expression ratio (95% CI)	1.89 (0.92–3.91)	0.9 (0.23–3.5)	3.98 (1.02–15.45)	3.08 (0.79–11.95)
	Adjusted P Value	0.08	0.99	0.04	0.14

(disease and gender) on gene expression levels in subgroups of patients and controls. Correlations between gene expression levels in both patients and control samples were measured using Spearman's rank correlation coefficient since they were not normally distributed. The receiver operating characteristic (ROC) curves were depicted to appraise the diagnostic power of expression levels of differentially expressed genes. Youden's J parameter was measured to find the optimum threshold. P value < 0.05 was considered as significant.

3. Results

This study assessed expressions of nine oxytocin-related genes, namely *ITPR1*, *TNS-AS1* (*Lnc-TNS1*), *FOS*, *LINC01116* (*Lnc-MTX2*), *RCAN1*, *ZBTB14* (*ZFP161*), *OXTR*, *CAMK2D* and *FENDRR* (*Lnc-FOXF1*) in blood samples of patients with schizophrenia and controls. Table 1 shows the characteristics of studied genes.

After application of the non-parametric test (Mann-Whitney *U* test), we found that expression levels of *FOS*, *CAMK2D* and *FENDRR* (*Lnc-FOXF1*) were significantly different between cases and controls (Fig. 1).

Disease factor had significant effect on expressions of *ITPR1*, *FOS* and *Lnc-FOXF1* (P values = 0.0079, < 0.0001 and < 0.0001). Gender has significant effect on expression of *Lnc-MTX2* (P value = 0.001). The interaction between sex and disease was significant for *TNS1-AS*, *lnc-FOXF1* and *KAMK2D* genes (Fig. 2a, g and 2i). For other genes, there were no significant interactions between these two parameters (Fig. 2). Table 2 shows the effects of group and gender for all genes.

Expression of *FOS* was up-regulated in total patients compared with total control group (Expression ratio (95% CI) = 13.64 (5.46–34.05), adjusted P value < 0.0001) and in female patients compared with female control group (Expression ratio (95% CI) = 32.13 (5.81–176), adjusted P value < 0.0001). Such pattern was also seen for *Lnc-FOXF1* (Expression ratio (95% CI) = 6.41 (2.84–14.3), adjusted P value < 0.0001 and Expression ratio (95% CI) = 14.41 (3.2–64.44), adjusted P value < 0.0001, respectively). *ITPR1* was down-regulated in total patients compared with total controls (Expression ratio (95% CI) = 0.22 (0.076–0.67), adjusted P value = 0.0079) (Table 3).

ROC curve analysis revealed that *FOS* had the best AUC value among other genes in differentiation between patients and controls (AUC = 0.78). Table 4 and Fig. 3 show the detailed parameters of ROC curve analyses.

4. Discussion

Oxytocin is a nonapeptide made in the hypothalamus. This peptide has neurotransmitter activities in the brain and can affect social cognition, learning and memory, and stress (Shilling and Feifel, 2016). Most notably, several lines of evidence have shown therapeutic effects of oxytocin in schizophrenia (Shilling and Feifel, 2016). Thus, identification of expression pattern of oxytocin-related genes in these patients has practical significance in design of new therapeutic options. In the present project, we evaluated expression of nine oxytocin-related genes in the peripheral blood of these patients compared controls. Expressions of *FOS* and *Lnc-FOXF1* were higher in total patients compared with total control group and in female patients compared with female control subgroup. *CAMK2D* was also up-regulated in total patients compared with total control group.

FOS is a transcription factor participating in the regulation of neuronal plasticity and immune responses in humans (Zakharyan, 2016). This transcription factor is also implicated in the learning and memory processes, since its deficiency impairs long-term memory and synaptic transmission in mice (Fleischmann et al., 2003). Moreover, it is involved in the modulation of response of cells to mitogenic signals contributing in growth and differentiation of neurons (Vanhoutte et al., 1999). A recent bioinformatics analysis has shown that *FOS* is among the main differentially expressed mRNAs participating in the competing endogenous RNA network in schizophrenia (Sabaie et al., 2021). Moreover, a previous study has suggested participation of *FOS* gene in the

Table 4
The results of ROC curve analysis for 3 differentially expressed genes in patients with schizophrenia versus controls.

FOS				Lnc-FOXF1				KAMK2D			
AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value
0.78 ± 0.04	0.68	0.95	<0.0001	0.71 ± 0.04	0.55	0.8	<0.0001	0.64 ± 0.05	0.55	0.78	0.007

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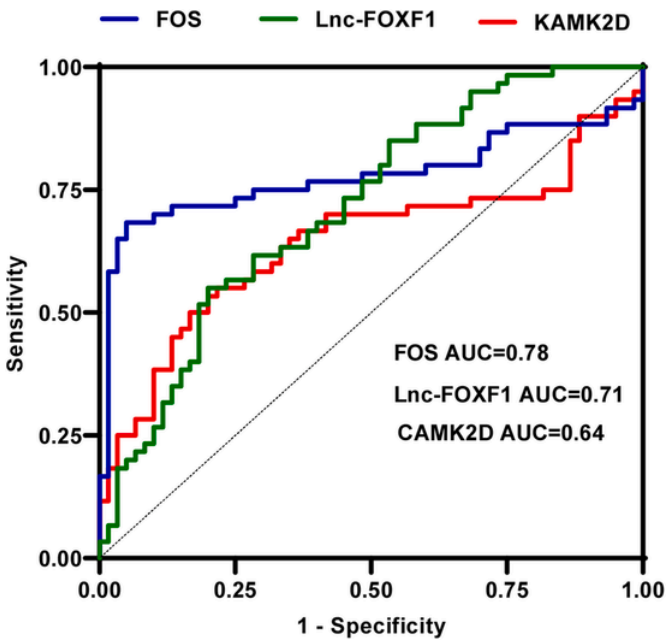

Fig. 3. ROC curves of *FOS*, *Lnc-FOXF1* and *KAMK2D* transcript levels for separation of patients with schizophrenia from healthy controls.

pathoetiology of schizophrenia (Boyajyan et al., 2015). This study has also revealed down-regulation of c-Fos proteins in the plasma samples of these patients compared with healthy subjects (Boyajyan et al., 2015). Although our preliminary results indicate participation of FOS in the pathoetiology of schizophrenia, the observed expression pattern in these patients is not in accordance with what has been observed in the latter study. This inconsistency might be explained by the differences in the expression assay techniques or ethnic-related factors.

Lnc-FOXF1 has been shown to affect immune response. It can act as a miR-423–5p sponge to inhibit the regulatory T cells-mediated immune escape (Yu et al., 2019). Future studies are needed to find whether it can affect pathogenesis of schizophrenia through alterations in immune responses. Moreover, this lncRNA can affect pyroptosis of microglia through protection against the ubiquitination-mediated degradation of NLRC4 (Wang et al., 2021).

The observed sex-specific up-regulation of *FOS* and *lnc-FOXF1* might indicate a specific role for these genes in the pathoetiology of schizophrenia in female subjects. The previously reported differential induction of Fos expression in the female rat brain has raised the possibility of modulation of expression of Fos by steroid hormones (Pfaus et al., 1996). The interactions between steroid hormones and lncRNAs have also been reported (Zhang et al., 2020).

ROC curve analysis revealed that *FOS* had the best AUC value among other genes in differentiation between patients and controls. However, our study has a limitation regarding lack of validation of ROC curve analyses results in an independent cohort of patients. In addition, lack of detailed characteristics of the sample, potential effects of medication on gene expression and lack of functional studies to confirm the impact of lncRNAs on oxytocin system are other limitations of our study. Cumulatively, the above-mentioned results imply dysregulation of oxytocin-related genes in the blood of patients with schizophrenia.

Ethics approval and consent to participate

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 Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.720). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Funding

Not applicable.

Uncited references

American Psychiatric Association, 2013.

CRediT authorship contribution statement

Mohammad Taheri : Supervision.

Declaration of competing interest

The authors declare they have no conflict of interest.

Data availability

Data will be made available on request.

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Not applicable.

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