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Upregulation of VDR-associated lncRNAs in Schizophrenia

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Abstract

Vitamin D receptor (VDR) signaling has been found to contribute to the pathology of numerous neuropsychiatric diseases including schizophrenia. Notably, VDR signaling has a functional relationship with many long non-coding RNAs (lncRNAs) such as *SNHG6*, *LINC00346* and *LINC00511*. We calculated expression of these lncRNAs in the venous blood of patients with schizophrenia versus healthy individuals. Expression of *SNHG6* was significantly higher in cases versus controls (posterior beta = 0.552, adjusted *P* value < 0.0001). This pattern of expression was detected in both men (posterior beta = 0.556, adjusted *P* value < 0.0001) and women (posterior beta = 0.31, adjusted *P* value = 0.005). Expression of *LINC00346* was also higher in cases versus controls (posterior beta = 0.497, adjusted *P* value < 0.0001) and in distinct sex-based comparisons (posterior beta = 0.451, adjusted *P* value = 0.009 among men and posterior beta = 0.214, *P* value = 0.004 among women). Expression of *LINC00511* was higher in cases versus controls (posterior beta = 0.318, adjusted *P* value = 0.01). While sex-based comparisons revealed significant difference in expression of *LINC00511* among female subgroups (posterior beta = 0.424, adjusted *P* value = 0.016), such comparison showed no difference among male cases and male controls (adjusted *P* value = 0.295). The expression levels of *SNHG6* distinguished patients with schizophrenia from controls, with AUC = 0.932. *LINC00346* and *LINC00511* distinguished between the two groups with AUC values of 0.795 and 0.706, respectively. Therefore, these lncRNAs might be used as markers for schizophrenia.

Keywords Schizophrenia · lncRNA · SNHG6 · LINC00346 · LINC00511

Introduction

As a psychiatric disorder with a lifetime prevalence of 4/1000 (Bhugra 2005), schizophrenia affects three major aspects of mental health, leading to positive, negative, and cognitive symptoms (American Psychiatric Association 2013). Although the main cause of schizophrenia is not clear, several lines of evidence point to an association between vitamin D receptor (VDR) signaling and the pathology of this condition. First, previous studies have reported the presence of VDR protein and vitamin-D-metabolizing enzymes in brain tissues (Eyles et al. 2005; Cui et al. 2013). Moreover, vitamin D deficiency has been suggested to increase the risk of schizophrenia (McGrath 1999). Vitamin D deficiency has also been reported to interact with eminent epidemiologically authenticated risk factors for this disorder (Cui et al. 2021). It can also affect brain function during postnatal and adulthood periods (Cui et al. 2021). Experiments in animals have demonstrated that developmental vitamin D deficiency can lead to enlargement of

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lateral ventricles in adult animals (Eyles et al. 2003; Feron et al. 2005). Moreover, developmental vitamin D deficiency has affected signaling cascades associated with calcium-binding proteins and mitochondrial function (McGrath et al. 2008). We recently described upregulation of *VDR*, *CYP27B1*, and *CYP24A1* levels in venous blood samples of patients with schizophrenia versus healthy participants (Asadzadeh Manjili et al. 2018; Ghafouri-Fard et al. 2021a). In addition, we identified long non-coding RNAs (lncRNAs) including *SNHG6*, *LINC00346* and *LINC00511* that functionally interact with VDR (Kholghi Oskooei et al. 2018; Ghafouri-Fard et al. 2021b). Subsequently, we measured the expression of these lncRNAs in patients with epilepsy and reported elevated expression of *LINC00511* in these patients. Moreover, we demonstrated an inverse correlation between expression of *LINC00346* and vitamin D levels in male patients (Mazdeh et al. 2019). In the present investigation, we aimed to assess the association between expression levels of *SNHG6*, *LINC00346* and *LINC00511* and schizophrenia in a cohort of Iranian subjects. As recent studies have indicated the contribution of a vast number of lncRNAs in the pathology of schizophrenia (Gibbons et al. 2018), we hypothesized that these VDR-associated lncRNAs might influence the pathogenesis of schizophrenia via modulation of VDR signaling.

Materials and Methods

Enrollment of Cases and Controls

A total of 50 patients with schizophrenia (33 male and 17 female, mean age ± standard deviation [SD]: 49.59 ± 9.59) and 50 healthy controls (33 male and 17 female, mean age ± SD: 49.78 ± 11.89) were enrolled in this study. Patients with schizophrenia were enrolled from those referred to Shahid Beheshti University of Medical Sciences-affiliated hospitals. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM–5) was used for diagnosis of schizophrenia (American Psychiatric Association 2013). All patients were under treatment with the standard dose of clozapine (300 mg/day to 600 mg/day). Exclusion criteria were substance abuse or cigarette smoking. Control subjects were assessed using the Mini-International Neuropsychiatric Interview (Sheehan et al. 1998). Those with systemic diseases, psychiatric disorders or pregnancy were excluded from the control group. The study protocol was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.290). Informed written consent forms were obtained from all cases and controls.

Experiments

Three milliliters of venous blood was obtained in EDTA-containing Falcon tubes. Blood samples were subjected to RNA extraction using a commercial kit (GeneAll Biotechnology Co., Seoul, Korea). After extraction, total RNA was converted to complementary DNA using the High-Capacity cDNA synthesis kit (Thermo Fisher Scientific, Gent, Belgium). The expression of *SNHG6*, *LINC00346* and *LINC00511* was quantified in all specimens using Ampliqon Master Mix (Ampliqon A/S, Odense, Denmark). Cycling reactions were performed in a StepOnePlus Real-Time polymerase chain reaction (PCR) system (Applied Biosystems, Foster City, CA, USA). *B2M* was chosen as normalizer. Table 1 shows the primer sequences.

Statistical Methods

Relative levels of *SNHG6*, *LINC00346* and *LINC00511* transcripts were quantified in all specimens using the Ln [Efficiency$^{\Delta CT}$] method. Comparisons were performed using the Bayesian regression model. *P* values were calculated from frequentist methods. Correlations between the expression of *SNHG6*, *LINC00346* and *LINC00511* were estimated using Spearman correlation coefficients. Statistical methods were performed in R version 4 software using the pROC,

Table 1 Primers used for amplification of *SNHG6*, *LINC00346* and *LINC00511* lncRNAs

Gene name	Sequence 5′→3′	Primer length	Product size (bp)
B2M	F: AGATGAGTATGCCTGCCGTG R: GCGGCATCTTCAAACCTCCA	20 20	105
SNHG6	F: AGGGAGGAAGAAGCGCGAA R: TCGCAGAGCCCAGCTACG	19 18	85
LINC00346	F: TGCCCTGGACATTCATGGAC R: CTGGACAAGCCCACTCTAGC	20 20	150
LINC00511	F: TCCCACCAGGAAGTTTAGCAG R: GCCTCTCAAGAGGTGGTCC	21 19	87

qreg, Stan and loo packages. The power of the transcription levels of *SNHG6*, *LINC00346* and *LINC00511* in distinguishing between cases and controls was measured by constructing receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC).

Results

The relative expression levels of *SNHG6*, *LINC00346* and *LINC00511* in the peripheral blood samples of cases and controls are displayed in Fig. 1.

Expression of *SNHG6* was significantly higher in cases versus controls (posterior beta = 0.552, adjusted *P* value < 0.0001). This pattern of expression also detected in both men (posterior beta = 0.556, adjusted *P* value < 0.0001) and women (posterior beta = 0.31, adjusted *P* value = 0.005).

LINC00346 was also overexpressed in cases versus controls (posterior beta = 0.497, adjusted *P* value < 0.0001) and in distinct sex-based comparisons (posterior beta = 0.451, adjusted *P* value = 0.009 among men and posterior beta = 0.214, *P* value = 0.004 among women).

Expression of *LINC00511* was higher in cases versus controls (posterior beta = 0.318, adjusted *P* value = 0.01). While sex-based comparisons revealed significant differences in expression of *LINC00511* among female subgroups (posterior beta = 0.424, adjusted *P* value = 0.016), such comparison showed no difference among male cases and controls (adjusted *P* value = 0.295). Table 2 shows the association between schizophrenia and expression levels of *SNHG6*, *LINC00346* and *LINC00511*, based on the results of a Bayesian quantile regression model.

Expression quantities of *SNHG6* and *LINC00346* were inversely correlated with age among total participants (correlation coefficients = −0.422 and 0.289, respectively). However, such correlation was not detected among cases or controls. Expression of *LINC00511* was not correlated with age in any comparison. Significant pairwise correlations were demonstrated between all pairs of lncRNAs in both cases and controls except for *SNHG6*/*LINC00346 SNHG6*/*LINC00511* pairs among controls (Fig. 2).

The expression levels of *SNHG6* distinguished patients with schizophrenia from controls, with AUC = 0.932. *LINC00346* and *LINC00511* distinguished the two groups with AUC values of 0.795 and 0.706, respectively (Fig. 3).

Discussion

VDR is a receptor that mediates the effects of vitamin D in target cells. VDR regulates the expression of several genes and induces various intracellular signaling cascades

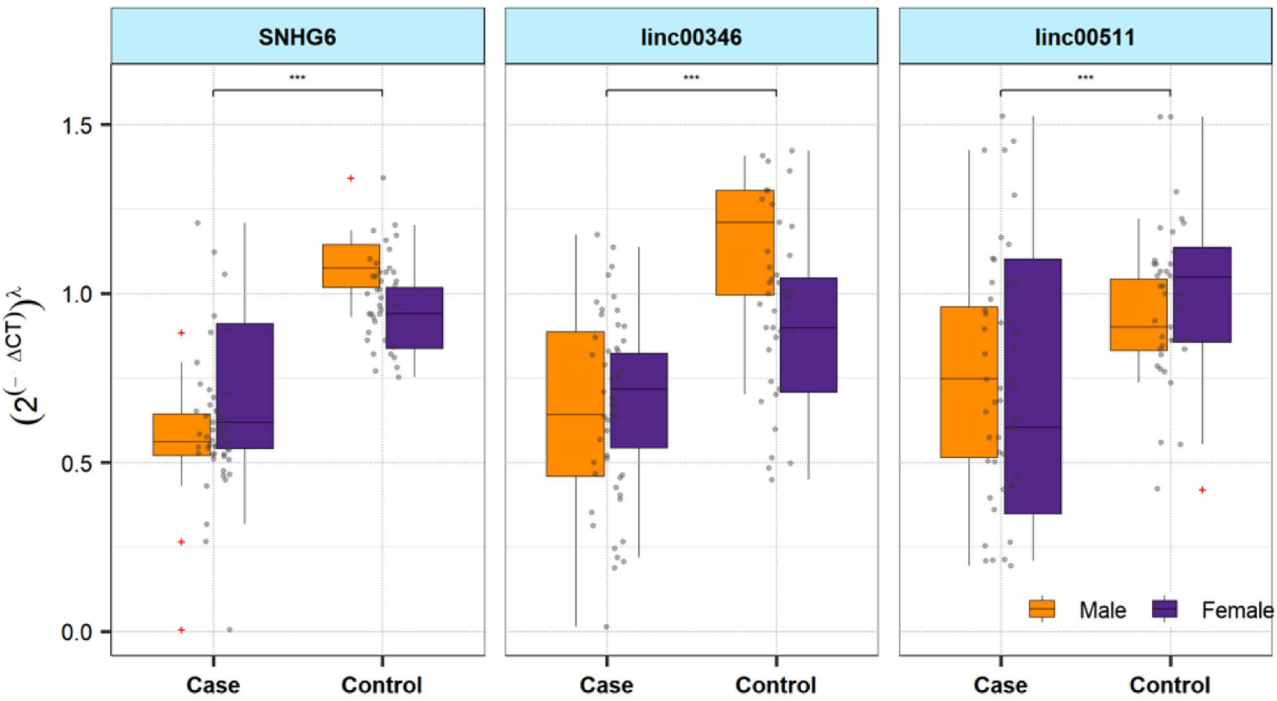


Fig. 1 Expression levels of *SNHG6*, *LINC00346* and *LINC00511* in patients with schizophrenia and controls based on their sex (Ct values of target genes and housekeeping genes were subtracted to find the relative expression value in each sample. These values were corrected by efficiency values. Each point shows the relative expression value of a certain gene in a sample)

Table 2 Association between schizophrenia and expression levels of *SNHG6*, *LINC00346* and *LINC00511*, based on the results of Bayesian quantile regression model

Groups	Comparisons	*SNHG6*				*LINC00346*				*LINC00511*			
		Posterior beta of $(2^{(-ddct)})^{\lambda}$	SE	Adjusted *P* value*	95% CrI for beta	Posterior beta of $(2^{(-ddct)})^{\lambda}$	SE	Adjusted *P* value*	95% CrI for Beta	Posterior beta of $(2^{(-ddct)})^{\lambda}$	SE	Adjusted *P* value*	95% CrI for beta
Total	Group, Control vs. case	0.552	0.05	< 0.0001	[0.45, 0.65]	0.497	0.1	< 0.0001	[0.31, 0.71]	0.318	0.13	0.01	[0.06, 0.55]
	Sex, Female vs. Male	0.077	0.05	0.073	[−0.02, 0.18]	0.004	0.09	0.57	[−0.17, 0.2]	−0.048	0.12	0.842	[−0.29, 0.18]
	Age (years)	0.002	0	0.215	[−0.001, 0.005]	0.001	0	0.598	[−0.004, 0.007]	0.005	0	0.179	[−0.001, 0.01]
	Group * Sex	−0.238	0.07	0.009	[−0.37, −0.11]	−0.282	0.12	0.014	[−0.54, −0.05]	0.116	0.15	0.18	[−0.17, 0.42]
Male	Control vs. case	0.556	0.06	< 0.0001	[0.45, 0.67]	0.451	0.13	0.009	[0.2, 0.72]	0.302	0.18	0.295	[−0.07, 0.57]
	Age	0.002	0	0.596	[−0.002, 0.01]	0	0	0.783	[−0.01, 0.01]	0.003	0	0.374	[−0.01, 0.01]
Female	Control vs. case	0.31	0.05	0.005	[0.22, 0.41]	0.214	0.07	0.004	[0.07, 0.35]	0.424	0.12	0.016	[0.18, 0.64]
	Age	0.002	0	0.435	[−0.003, 0.01]	0.003	0	0.677	[−0.004, 0.011]	0.006	0.01	0.444	[−0.005, 0.017]

*Estimated from frequentist methods; CrI: credible interval, λ: power transformation value estimated from optimal transformation method (λ = 0.177, 1/0.154 and λ = 1/0.151, for *SNHG6*, *LINC00346* and *LINC00511*, respectively). When the interaction effects were significant, we conducted subgroup analysis by sex to interpret the associations.

(Ryan et al. 2015). As a transcription factor, VDR has been shown both to be regulated by lncRNAs and to modulate the expression of lncRNAs. Several interactions have been demonstrated between lncRNAs and VDR in diverse biological processes (Bikle 2021). Genome-wide studies have identified thousands of vitamin D receptor elements throughout the genome (Carlberg 2014), indicating the diversity and pleiotropy of the molecular effects of vitamin D. Investigations in animal models have supported the impact of VDR signaling in the development of schizophrenia (Schoenrock and Tarantino 2016). VDR signaling has been shown to affect the expression of certain lncRNAs (Jiang and Bikle 2014). The lncRNAs *SNHG6*, *LINC00346* and *LINC00511* have been suggested to interact with this signaling pathway (Kholghi Oskooei et al. 2018). Although the impact of VDR-related cascades in the development of schizophrenia has been well recognized (Cui et al. 2021), the effects of these lncRNAs in this psychiatric condition have not previously been investigated. Therefore, we measured the expression of *SNHG6*, *LINC00346* and *LINC00511* lncRNAs in the circulation of patients with schizophrenia treated with clozapine and healthy subjects. Most notably, all three assessed lncRNAs were found to be overexpressed in patients. A previous study did not indicate that this antipsychotic drug had a medium to large distinctive gene expression signature in peripheral blood in comparison with other antipsychotic drugs (Harrison et al. 2016).

SNHG6 has been shown to act as competing endogenous RNA (ceRNA) for miR-101-3p to affect the expression of ZEB1 (Chang et al. 2016). Meanwhile, ZEB1 is widely expressed in the central nervous system and contributes to neurodevelopmental processes (Miyoshi et al. 2006) and differentiation of neurons (Ravanpay et al. 2010). *ZEB1* has also been identified as a genomic risk locus for schizophrenia (Børglum et al. 2014). Based on the reported role of *SNHG6* in sequestering miR-101 and decreasing its bioavailability (sponging) (Chang et al. 2016), the detected upregulation of this lncRNA in patients with schizophrenia is expected to result in downregulation of miR-101 levels. However, miR-101 has been among upregulated miRNAs in postmortem brain samples obtained from patients with schizophrenia (Beveridge et al. 2010). This discrepancy might be due to different levels of this miRNA in the brain and circulation. Future studies should assess the expression of this miRNA in the venous blood of patients with schizophrenia and unravel the association between its expression in the circulation and central nervous system.

Notably, *LINC00346* has been shown to affect the expression of MMP9 through sponging of miR-101-5p (Tong et al. 2020). This lncRNA also sponges miR-342-5p (Cui et al. 2020), miR-148b (Li et al. 2020) and miR-34a-5p (Xu et al. 2019). All of these miRNAs have been suggested as circulating markers for neurodegenerative or psychiatric

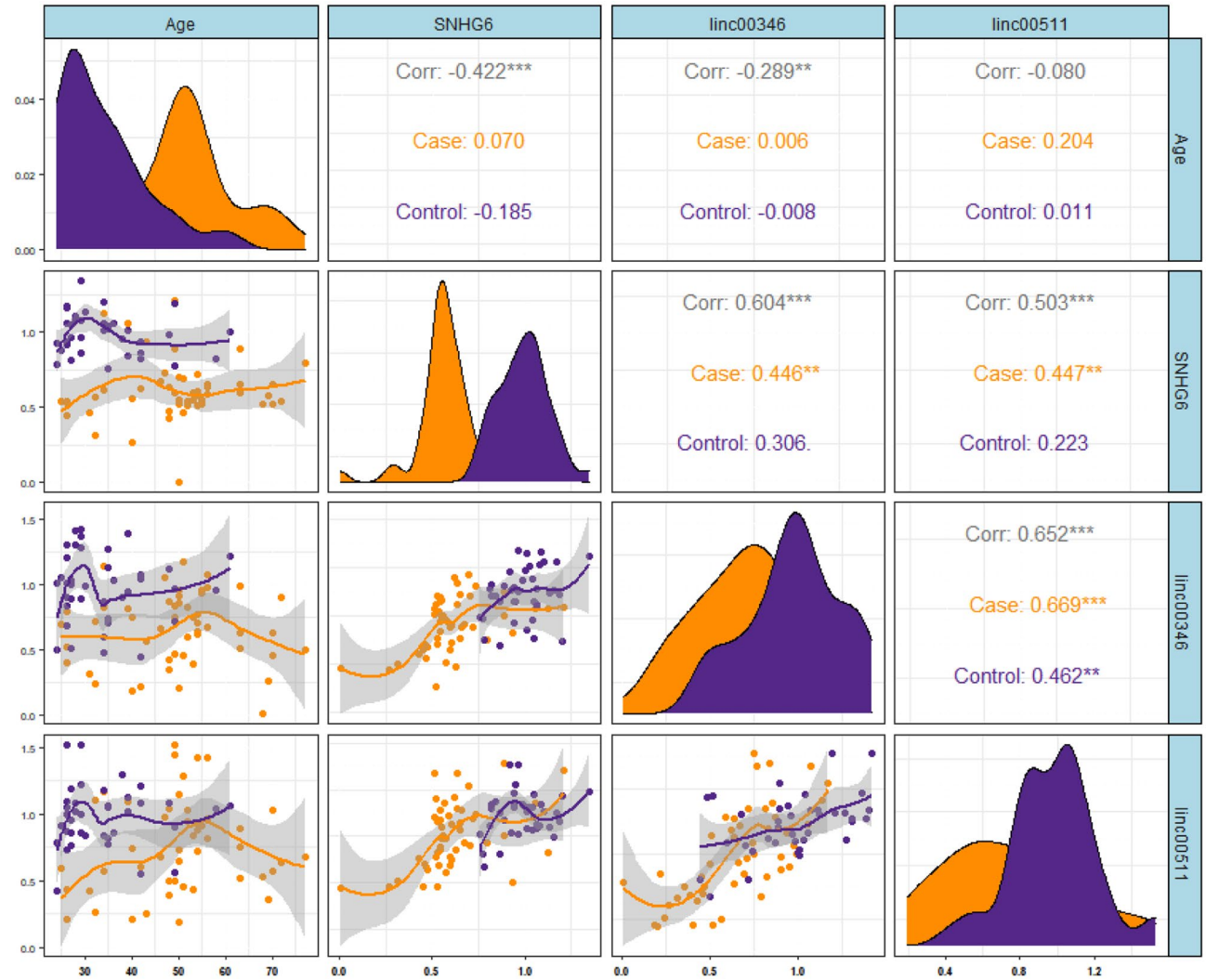


Fig. 2 Correlation coefficients between expression levels of *SNHG6*, *LINC00346* and *LINC00511* and age of study participants (first row), as well as pairwise correlations between expression levels of *SNHG6*, *LINC00346* and *LINC00511* in cases (orange), controls (dark blue) and total participants (gray). ***P* value < 0.005, ***P value < 0.001

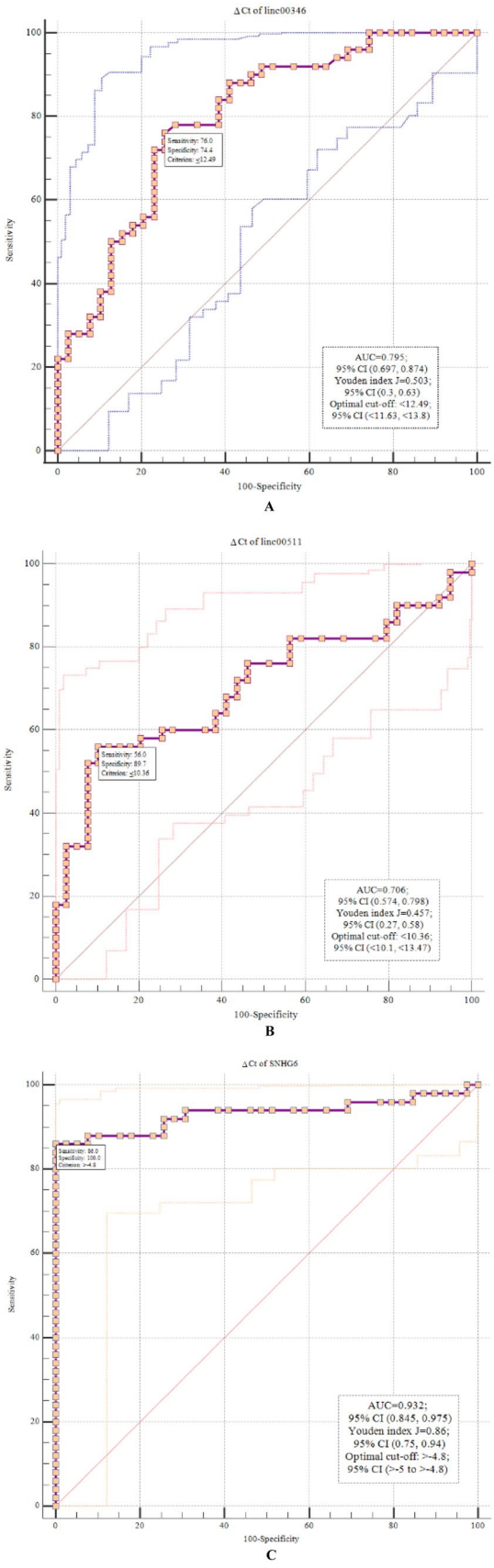
disorders (reviewed in Van den Berg et al. 2020). However, their role in the pathogenesis of schizophrenia has not been assessed. Therefore, we recommend a comprehensive evaluation of the expression of miRNAs and lncRNAs in schizophrenia to construct the lncRNA/miRNA interaction network in this disorder.

LINC00511 acts as a ceRNA for hsa-miR-29b-3p (Zhao et al. 2018). Notably, expression of miR-29b has been diminished in the prefrontal cortex of patients with schizophrenia (Perkins et al. 2007).

Expression amounts of *SNHG6* and *LINC00346* were inversely correlated with age among total participants. However, such correlation was not detected among cases or controls. Expression of *LINC00511* was not correlated with age in any comparison. Significant pairwise correlations were demonstrated between all pairs of lncRNAs in both cases and controls except for *SNHG6*/*LINC00346 SNHG6*/*LINC00511* pairs among controls. Therefore, we can suggest that correlation between some pairs of lncRNAs might be affected by the presence of schizophrenia.

The expression levels of *SNHG6* distinguished patients with schizophrenia from controls, with AUC = 0.932. *LINC00346* and *LINC00511* distinguished the two groups with AUC values of 0.795 and 0.706, respectively. Therefore, *SNHG6* can be suggested as an appropriate marker for detection of schizophrenia.

Taken together, the results of the current study show dysregulation of three VDR-associated lncRNAs in the circulation of patients with schizophrenia and suggest that these lncRNAs might be used as peripheral markers for schizophrenia. However, we note the small sample size, lack of functional experiments and lack of verification in



◂ **Fig. 3** ROC curves demonstrating the power of *LINC00346* (**A**), *LINC00511* (**B**) and *SNHG6* (**C**) distinguishing between patients with schizophrenia and healthy subjects

independent samples from other countries as limitations of our study. Thus, we propose to verify these results in larger patient samples, particularly drug-naïve individuals, to determine the effects of antipsychotic drugs on gene expression.

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Authors' Contributions MT and SGF wrote the manuscript and revised it. RE and FP supervised the study and performed the experiment. SAJ analyzed the data. MS was the clinical consultant and assessed patients for inclusion in the study. All authors approved 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 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. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for Publication Not applicable.

Competing Interests The authors declare they have no conflict of interest.

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