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ORIGINAL ARTICLE

Deregulation of NF-κB associated long non-coding RNAs in bipolar disorder

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Abstract
Long non-coding RNAs (lncRNAs) are major genetic factors whose disruption lead to many diseases, including nervous system diseases. Bipolar disorder (BD) is a neuro-psychiatric disease with no definitive diagnosis and incomplete treatment. Regarding the role of NF-κB-associated lncRNAs in the neuro-psychiatric disorders, we examined the expression of three lncRNAs, DICER1-AS1, DILC, and CHAST, in BD patients. To assess lncRNA expression in peripheral blood mononuclear cells (PBMCs) of 50 BD patients and 50 healthy individuals, Real-time PCR was used. Additionally, some clinical characteristics of BD patients were investigated via an analysis of ROC curves and correlations. Based on our results, the expression level of CHAST increased significantly in BD patients in comparison with healthy people, in BD men compared with healthy men, as well as in BD women in comparison with control females ($p < 0.05$). A similar increase in expression was observed for DILC and DICER1-AS1 lncRNAs in female patients compared with healthy women. Whereas compared to healthy men, DILC was decreased in diseased men. Based on the results of the ROC curve, the area under the curve (AUC) for CHAST lncRNA was 0.83 with a P value of 0.0001. So, the expression level of CHAST lncRNA could play a role in the pathobiology of the BD and be considered a good putative biomarker for individuals with bipolar disorder.

Keywords Long non-coding RNAs · Biomarker · Bipolar disorder · DICER1-AS1 · DILC · CHAST

Introduction

Non-coding RNAs with more than 200 nucleotides are commonly determined as long Non-coding RNAs (lncRNAs) (Aliperti et al. 2021). Any aberrant lncRNA expression may lead to neurodevelopmental or neuropsychiatric disorders such as bipolar disorder (BD) (Yoshino and Dwivedi 2020; Ghafouri-Fard et al. 2021). For instance, downregulation of ANRIL (Antisense non-coding RNA in the INK4 locus) results in the NF-kB reduction and facilitates cognitive functions recovery in rat hippocampus (Bella and Campo 2021).

Additionally, lncRNAs contribute to a wide range of physiological and pathological processes and pathways (Loda and Heard 2019; Han and Chang 2015; Morlando et al. 2014). For example, the NF-κB signaling pathway plays important roles in the controlling growth and development of neurons as well as regulating the plasticity of neurons, inflammatory responses, and cell survival via lncRNAs (Fang et al. 2017; Ren et al. 2020; Gupta et al. 2020b).

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Moreover, crosstalk between NF-κB signaling and other signaling pathways including Wnt/β-catenin and Notch pathways regulates crucial functions in the neurodevelopmental processes and neurological inflammation (Shih et al. 2015). Furthermore, NF-κB plays crucial roles in sleep, depression, decreased activity, and anhedonia (Irwin et al. 2008; Fang et al. 2019). NF-κB has also been deregulated in schizophrenia, bipolar disorder, and Major Depression (Miklowitz et al. 2016; Safa et al. 2020c). Based on a recent study, the expression levels of several NF-κB family members enhanced in the prefrontal cortex of bipolar disorder (Roman et al. 2021; Elhaik and Zandi 2015). Three famous NF-κB-related lncRNAs are namely CHAST, DILC, and DICER1-AS1 in PBMC of patients with BD.

The cardiac hypertrophy–associated transcript (CHAST) which is found at the 17q21.3 locus involved in the NF-κB signaling pathway indirectly via Wnt signaling (Viereck et al. 2016). An analysis of 50 patients with schizophrenia as a mental disorder characterized by continuous or recurrent episodes of psychosis and 50 healthy participants using the Real-Time PCR revealed that CHAST expression was higher in the schizophrenia patients with the area under the Receiver Operating Characteristic (ROC) curve of 0.79 ($P < 0.0001$) (Safa et al. 2020b).

Another NF-κB-related lnc-RNA is lnc-DILC (lncRNA downregulated in liver cancer stem cells) which locates at the chromosomal locus 13p34 and suppresses interleukin (IL)-6/STAT3 signaling resulting from IL-6 transcriptional inactivation. Lnc-DILC controls the association between TNF-α/NF-κB signaling and IL-6/STAT3 (Zhang et al. 2019; Gu et al. 2018; Wang et al. 2016). Yujie Liu et al. reported that DILC downregulation increased the survival of primary microglia, suppressed apoptosis, and inhibited the (IL)-6 and IL-1β production in microglia. In contrast, DILC overexpression showed opposite functions. Furthermore, silencing DILC decreased neuropathic pain through SOCS3-induced JAK2/STAT3 pathway suppression (Liu et al. 2020).

Another lncRNA is DICER1-AS1 which is found at the 14q32.13 locus and is expressed in 25 tissues including the brain and regulates autophagy by adjusting the miR-30b/ATG5 axis (Gu et al. 2018). It is noteworthy that autophagy is a process involved in various cellular functions associated with the NF-κB signal transduction pathway (Trocoli and Djavaheri-Mergny 2011). Autophagy participates in the physiology of the central nervous system by controlling homeostasis. Disturbance in this process causes neurological dysfunction in schizophrenia (Schneider et al. 2016). DICER1-AS1 was overexpressed in schizophrenic patients compared with healthy people (Safa et al. 2020a).

Based on the regulatory functions of lncRNAs on the NF-κB signaling pathway (Gupta et al. 2020b) and the previous report of an association between the NF-κB signaling pathway and bipolar disorder (Miklowitz et al. 2016; Teshnizi et al. 2022; Jones et al. 2021), In the present study, we investigated expression of these 3 LncRNAs in the NF-κB signaling pathway, we aimed to evaluate these lncRNAs in the peripheral blood mononuclear cells (PBMCs) of the BD compared with matched healthy individuals and also assess their potential as BD biomarkers.

Materials and methods

Participants and ethical considerations

Our studied population involved 50 BD patients and 50 healthy controls. All BD patients diagnosed with bipolar type 1 disorder and in a depressive episode. Considering features such as people's age, race, and history of mental, and neurological diseases.

The necessity of confidentiality of people's information and the freedom to participate in the research has been explained to all of the participants. Subsequently, all participants and the parents of the participants under 18 years old filled out the consent forms.

Sample collection and RNA extraction

Five ml of peripheral blood was obtained from all individuals in EDTA tubes. The blood samples were centrifuged at 3000 rpm for 10 min to separate the Buffy coat. Total RNA was drawn out from the PBMCs using the RNX kit (EX6101, Cinnagen, Tehran, Iran) according to the manufacturer's guidelines. Qualitative and quantitative assessments of extracted RNA were done by both gel electrophoresis and the spectrophotometer. DNaseI (Fermentas, Lithuania) was applied for removing DNA contamination.

cDNA production and real-time PCR assay

cDNA was produced by 3 µg of purified total RNA and High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems, PN: 4,375,575), based on the manufacturer's rules. The lncRNA expression was measured in comparison with B_2M as an internal control using related primers (Table 1). Quantitative Real-time PCR was executed in the ABI 7500 sequence detection system (Applied Biosystem, Foster City, CA, USA) using 10 µl of BIOFACT™ 2X Real-Time PCR Master Mix, 10 ng cDNA, and 200 nM of each primer. All experiments were done at least twice. Means of ΔCT for cases and controls were calculated, and finally, the fold changes of gene expressions were measured by

Table 1 Primers used in RT-qPCR

Gene names	Primer	primer sequences	Product size (bp)
CHAST	F	GCAGAGGGTGCCAACTTGTA	109
	R	TCTCAGGGAAATCAGATTGCGG	
DILC	F	CTCTGGAGCCATACGTGACA	96
	R	TCAGGTCACTTGTGCCGTT	
DICER1-AS1	F	TGGGATTACGGGCGTGAG	102
	R	CCTGGGCACTCCTTCAGC	
B2M	F	AGATGAGTATGCCTGCCGTG	104
	R	CGGCATCTTCAAACCTCCA	

Table 2 Demographic and clinical features of BD patients and controls

	Cases	*Controls*
Number	*50*	*50*
Sex	*70*	*70*
Male (%)	*30*	*30*
Female (%)		
Mean age (range)	*36 (17–56) year*	*34 (14–52)*
Disease duration (range)	*4 (1–14) year*	-
Onset age (range)	*32 (15–48) year*	-

ratio $= 2^{-\Delta\Delta Ct}$ as explained by Livak (Livak and Schmittgen 2001).

Statistical analysis

All of the statistical analyses were performed in Graph Pad Prism 9 (Graph Pad Software, Inc., San Diego, CA, USA). Kolmogorov–Smirnov test was used for the normality assessments of the data distribution. Differences in the lncRNA expression between patients and controls were evaluated by t-test. The association between the expression of lncRNAs and the clinical characteristics of patients was measured by Pearson's correlation coefficient. P-value < 0.05 was considered statistically significant. The ROC curve was used to evaluate the specificity and sensitivity of genes as biomarkers.

Results

Cases and controls

Demographic and clinical information of 50 BD type I patients and 50 control individuals who participated in this study is shown in Table 2.

Gene expression levels in participants

Examining the expression of three lncRNAs showed that the expression level of *CHAST* has increased significantly (18.13 times) in BD patients compared to healthy people with a P-value < 0.0001 (Fig. 1A). *DILC* gene with a P-value of 0.93 and *DICER1-AS1* gene with a P-value of 0.23 also enhanced in BD patients, but they were not statistically significant (Fig. 1B and C).

Furthermore, expressions of lncRNAs *CHAST* (P < 0.0001) and *DILC* (P = 0.0468) were significantly different between male BD patients and male controls. But, there was no significant difference for the *DICER1-AS1* gene.

On the other hand, a significant overexpression between BD women and healthy women was seen for *CHAST*, *DICER1-AS1*, and *DILC* genes with P values of 0.0003, 0.0382, and 0.0032, respectively. Table 3 demonstrates the outline of the relative expression (fold change) analysis of lncRNAs in BD patients and healthy controls.

Correlation analysis

There was a significant positive correlation between expression levels of all pairs of lncRNAs genes (Fig. 1D-F; Table 4). Furthermore, there was no considerable correlation between the level of expressions of lncRNAs in BD patients with age, disease duration, and the onset age of the disease (Table 4).

ROC curve analysis

The ROC curve of *CHAST* for sensitivity and specificity showed that its expression could be considered a BD biomarker, our results showed that the difference in *CHAST* expression between BD and control groups with the area under the curve (AUC) equal to 0.83 with P < 0.0001 is statistically significant (Fig. 2). The sensitivity and specificity for *CHAST* gene are equal to 92% and 62%, respectively.

Discussion

NF-κB pathway plays important functions in the pathophysiology of neuropsychiatric disorders including bipolar disorder. For instance, Roman et al. (2021) showed that NF-κB1-related members such as NF-κB2, RelA, and cRel overexpressed in BD patients relative to healthy controls (Roman et al. 2021). Another study in Adolescents BD patients has reported up-regulation of the IL-1β and NF-κB2 (Miklowitz et al. 2016). On the other hand, the interaction between lncRNAs and NF-κB-related genes has been shown in the pathogenesis of human disorders (Gupta et al. 2020a). Various lncRNAs control the activity and expression of NF-κB family members and NF-κB signaling pathway genes (Ren et al. 2020; Feng et al. 2022). In the

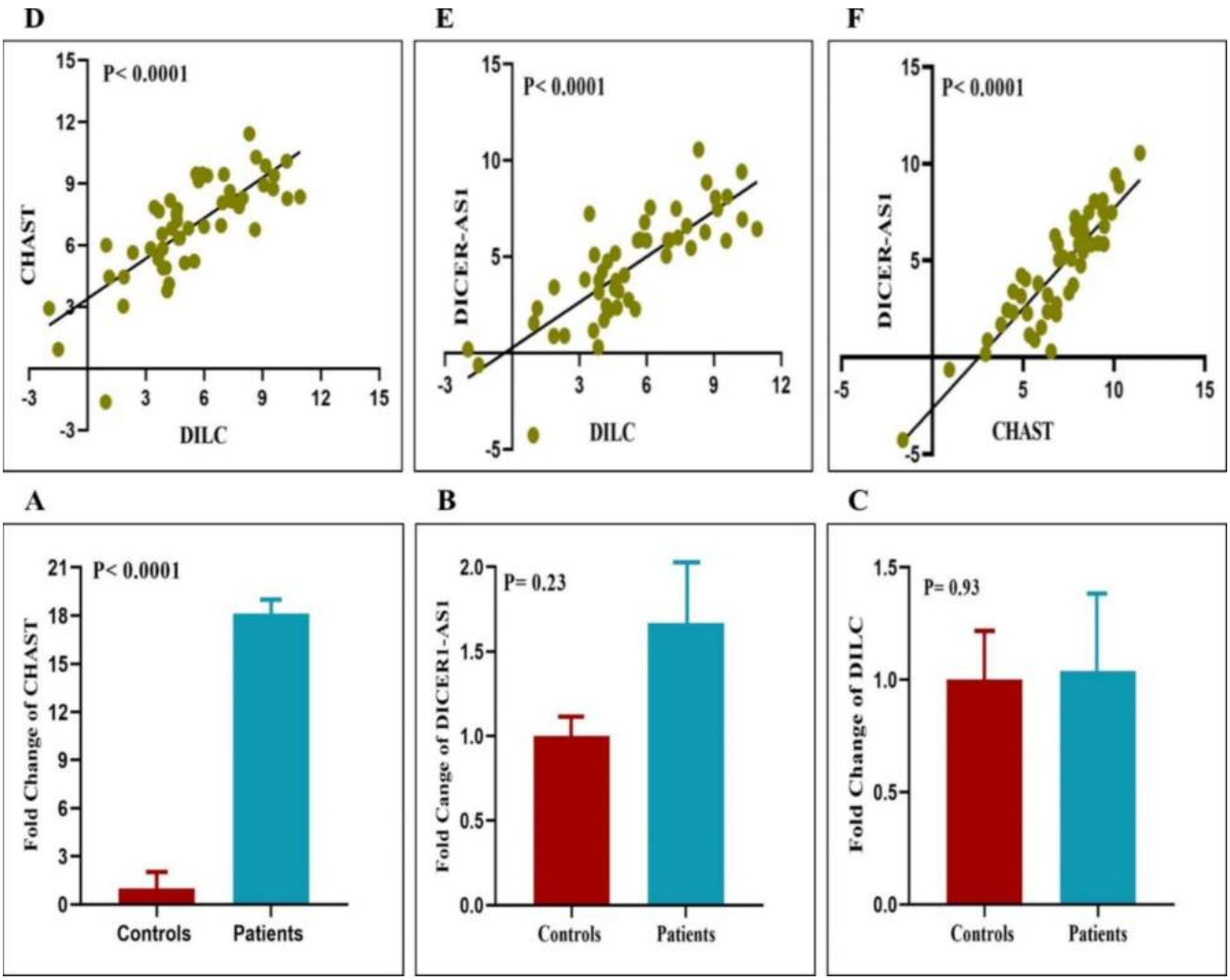

Fig. 1 Expression analysis (Fold Change) of lncRNAs in the PBMCs from BD and control people. (**A**) *CHAST*, (**B**) *DILC*, and (**C**) *DICER1-AS1* expression in BD patients compared to healthy individuals. Expression levels of lncRNA in each sample were normalized to B_2M expression. Pairwise correlation analysis between expression levels of (**D**) DILC and CHAST, (**E**) DILC and DICER-AS1, (**F**) CHAST and DICER-AS1 in the BD group

Table 3 Relative expression of lncRNAs in BD patients and healthy controls

lncRNAs	*Parameters*	*Total patients (n = 50)/ total controls (n = 50)*	*Male patients (n = 35)/ male controls (n = 35)*	*Female patients (n = 15)/ female controls (n = 15)*
CHAST	*Fold change*	*18.13*	*14.93*	*24.95*
	P-value	*< 0.0001*****	*< 0.0001*****	*0.0003****
DILC	*Fold change*	*1.04*	*0.32*	*15.24*
	P-value	*0.93*	*0.047**	*0.0032***
DICER1-AS1	*Fold change*	*1.66*	*1.07*	*4.63*
	P-value	*0.23*	*0.88*	***0.0382****

present study, we examined the expression of three NF-κB-related lncRNAs in the PBMC of patients with BD and healthy controls. Among the studied lncRNAs, *CHAST* was significantly up-regulated in cases, whereas *DICER1-AS1* and *DILC* did not exhibit significant differences between BD patients and controls. It was found that the expression of all three lncRNAs increases significantly in BD women compared to healthy ones, although the results were different in men. So in male patients, *CHAST* gene increases, *DILC* decreases, and *DICER1-AS1* presences no significant difference. Our *CHAST* ROC curve showed an AUC of 0.83 which means the correct positive rate is higher than the false

Table 4 Pairwise correlation between expression levels of lncRNAs in the BD group

Correlation	Patient Age	Age at onset	Disease duration	DICER1-AS1	DILC
CHAST	P = 0.69 r = 0.05	P = 0.68 r = 0.05	P = 0.90 r = 0.01	P < 0.0001**** r = 0.8938	P < 0.0001**** r = 0.7749
DILC	P = 0.97 r = 0.004	P = 0.84 r = 0.02	P = 0.62 r = -0.07	P < 0.0001**** r = 0.8065	
DICER1-AS1	P = 0.58 r = 0.07	P = 0.60 r = 0.07	P = 0.69 r = 0.05		

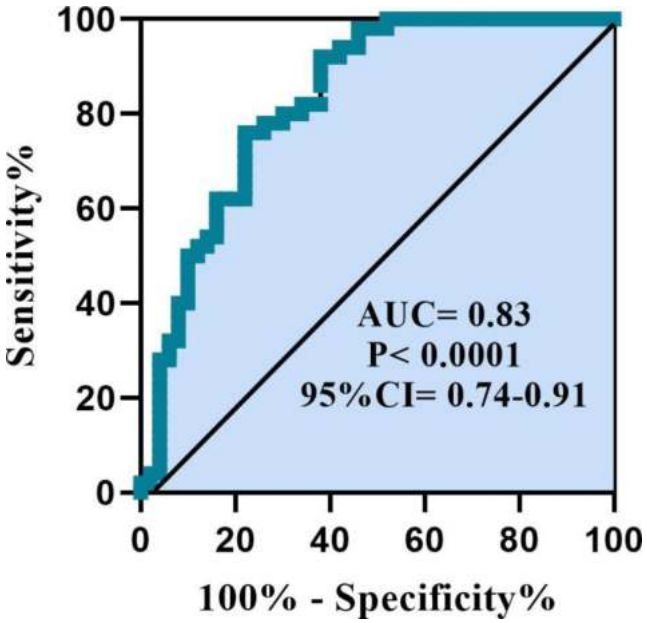

Fig. 2 ROC curve analysis of *CHAST*

positive one. Also, the sensitivity and specificity are equal to 92% and 62%, respectively. And the cut-off point of this gene is < 9.512. Therefore, this gene contains biomarker capability.

CHAST is a lncRNA with full-length transcription and the control ability at transcriptional as well as posttranscriptional levels. CHAST can be inhibited by prohypertrophic factors, such as phenylephrine (PE) and isoproterenol (ISO whereas the nuclear factor of the activated T cell (NFAT) can induce it (Viereck et al. 2016). Meanwhile, there is an interaction between NF-κB signaling and NFAT signaling for the regulation of the cytokines' expression in T cells (Khalaf et al. 2013).

The calcineurin-NFAT pathway also plays a key role in the normal function of the CNS and the pathobiology of neurological disorders (Kipanyula et al. 2016). For example, the Ca^{2+}-dependent calcineurin/NFAT signal transduction pathway is accompanied by neuronal growth and axonal guidance within vertebrate development. Each different NFAT class is involved in various stages of neurodevelopment. NFAT adjusts axonal growth via neurotrophic signaling in neuronal populations. Furthermore, NFAT transcription complexes lead to neuron growth via guides like netrin to accelerate the novel synapse development and help with building neural circuits in the brain. NFAT transcriptional complexes can induce various gene categories within the developing and adult nervous systems (Nguyen and Di Giovanni 2008). For example, as in schizophrenia patients, *CHAST* was overexpressed, it could be considered a schizophrenia biomarker (Safa et al. 2020a), which was in parallel with our findings.

Regarding the association of *CHAST* with the NFAT pathway, *CHAST* increase may be a result of the over-activation of this pathway in bipolar disorder. Hyperactive calcineurin/NFAT signal transduction may lead to synaptic plasticity under pathological conditions (Kipanyula et al. 2016). Figure 3 depicts a summary of potential interactions between CHAST lncRNA, NFAT signaling, and NF-κB signaling.

Based on the evidence, changes in the activity of the calcineurin/NFAT pathway and its endogenous regulators in the nervous system, microvascular endothelial cells, astrocytes, microglia, Schwann cells, oligodendrocytes, and neurons lead to the neurological pathogenesis (Kipanyula et al. 2016).

Calcineurin/NFAT is also involved in psychiatric disorders, epilepsy, as well as brain and spinal cord injuries (Kipanyula et al. 2016; Anderson et al. 2015). The activation of GABAA receptors (GABAA) with calcineurin/NFAT4 signaling decreased anxiety and improves hippocampal neurogenesis in mice, so treatments targeting this pathway might improve mood (Quadrato et al. 2014). According to similar evidence from pharmacology and postmortem investigation, antipsychotic drugs which recover some symptoms of CNS diseases change calcineurin expression patterns in the human brain. In the CNS, calcineurin signaling functions in GABAergic synaptic development (Kipanyula et al. 2016).

The endogenous peptide neurotensin, which acts on the dopamine D2 receptor via calcineurin also blocks long-term elevations in presynaptic dopamine release in schizophrenia and other severe mesencephalic disorders (Piccart et al. 2015). Dopamine as a neurotransmitter mediates the mood cycle and enhances transmission during the BD manic phase (Salvadore et al. 2010; Lahera et al. 2013). Based on the dopamine hypothesis, dopamine enhancement causes a second-order homeostatic decrease in the dopaminergic receptors' quantity and sensitivity which leads to the decline of dopamine transmission in the depression period (Salvadore et al. 2010).

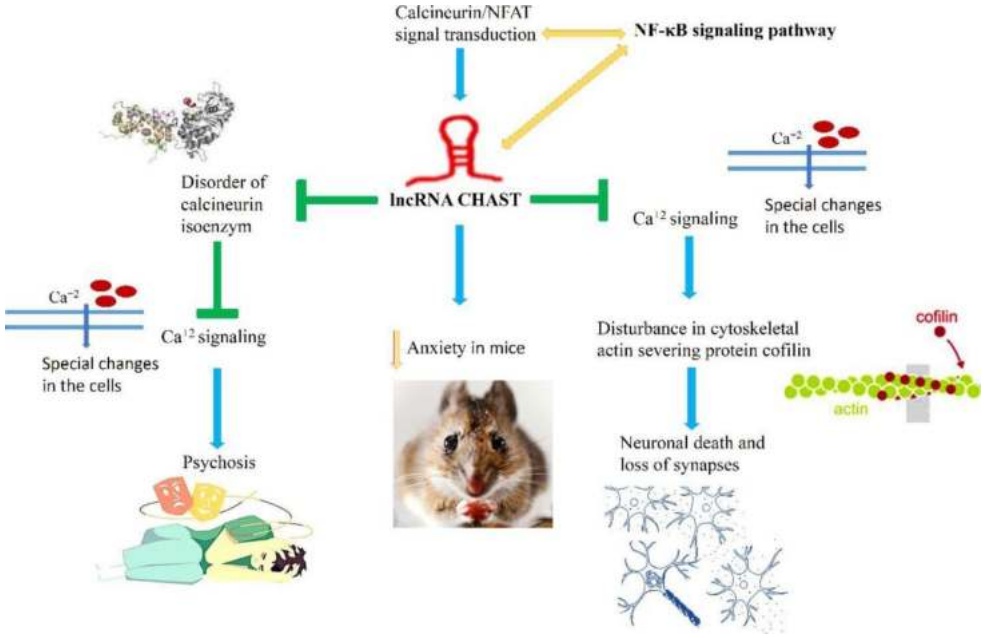

Fig. 3 The potential interactions between CHAST lncRNA, NFAT signaling, and NF-κB signaling that may result in Neuronal death, loss of synapses, and Psychosis in BD patients as well as Anxiety in BD mice

In a study on the DILC effect on neuropathic pain, quantitative PCR analysis in the spinal cord revealed that DILC overexpressed in rats suffering from bilateral chronic constriction injury (bCCI). Whereas DILC siRNA intrathecal administration significantly improved mechanical twitch thresholds (MWT) and paw withdrawal threshold delays (PWTL), decreased neural cold sensitivity, and blocked inflammatory protein synthesis in bCCI mice via underexpressed DILC (Liu et al. 2020). With regards to western blot results, DILC down-regulation by DILC siRNA transfection upregulated SOCS3 and downregulated p-Janus kinase 2 (p-JAK2) and p-STAT3 signaling and their downstream agents in primary microglia. Additionally, the DILC downregulation increased the primary microglia survival, blocked the apoptosis process, and prohibited the interleukin (IL)-6 and IL-1β expression in microglia through TNF-α/NF-κB signaling. Nerve injury induces microglia, which compromises 5 to 10% of glia production in the CNS and releases different chemical mediators like pro-inflammatory cytokines, leading to the alteration of the neurons' function and increase of immune responses (Tsuda et al. 2005; Huang et al. 2018). Microglia correct induction is beneficial to the body, and their apoptosis increased nerve damage (Rich et al. 1987; Groves et al. 2003). Therefore, DILC knockdown plays a protective role in the development of neuropathic pain. DILC knockdown decreases neuropathic pain by blocking the JAK2/STAT3 pathway(Liu et al. 2020).

The next evaluated lncRNA is DICER1-AS1 which was reported unregulated in osteosarcoma cells by microarray and RT-PCR analyses. Based on in vitro cell functional experiments, DICER1-AS1 knockdown prohibited osteosarcoma cells proliferation, migration, and invasion. Moreover, DICER1-AS1 knockdown ATG5, LC3-II, and Beclin 1 proteins, which suppressed osteosarcoma cell autophagy. DICER1-AS1 participates in neoplasm growth with various mechanisms, especially autophagy. In addition, DICER1-AS1 targets miR-30b via its 3'-UTR (Gu et al. 2018) and adjusts autophagy via the miR-30b/ATG5 axis. Autophagy involves the physiology of the nervous system by changing homeostasis which leads to neurological dysfunction and schizophrenia (Schneider et al. 2016). In Safa et al. study, DICER1-AS1 was overexpressed in schizophrenia patients (Safa et al. 2020a). On the other hand, antipsychotic drugs may reduce autophagy genes in some parts of the brain in schizophrenia individuals (Schneider et al. 2016; Zhang et al. 2007). Therefore, the increased DICER1-AS1 in schizophrenia patients may be a compensatory mechanism for increased autophagy (Safa et al. 2020a).

This research, however, is subject to some limitations. The small sample size is the first limitation of our study. Second, lack of evaluation of the effects of medications on the expression of lncRNAs. Finally, we investigated lncRNA expression in peripheral blood tissue and did not assess expression levels in the brain.

Conclusions

According to our results, lncRNA CHAST may play an important role in BD pathogenesis and could work as a diagnostic candidate, however, we suggest testing it again not only in a large clinical population but to apply the results to BD diagnosis and treatment.

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Authors' contributions R.GH. and M.M. wrote the manuscript and performed the experiment, M.T., S. M. N and Z.S.F. designed the study, analyzed the data, and revised the manuscript. All the authors read and approved the final manuscript.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant All procedures were in accordance with the ethical standards of national research committee and with the 1964 Helsinki declaration. 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.

Consent of publication Not applicable.

Competing interests None.

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