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Long noncoding nuclear enriched abundant transcript 1_2 is a promising biomarker for childhood-onset systemic lupus erythematosus

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ABSTRACT

Importance: Systemic lupus erythematosus (SLE) is a diffuse connective tissue disease with complex clinical manifestations and prolonged course. The early diagnosis and condition monitoring of SLE are crucial to disease prognosis.

Objective: To assess the diagnostic value of long noncoding RNA (lncRNA) nuclear enriched abundant transcript 1 (NEAT1) in childhood-onset SLE (cSLE).

Methods: Fifty-seven children diagnosed with SLE, 40 children diagnosed with juvenile idiopathic arthritis (JIA), and 40 healthy children were included. Peripheral blood samples from each patient were collected. A quantitative polymerase chain reaction was used to confirm the expression of lncNEAT1_1 and lncNEAT1_2 in peripheral blood. Associations among parameters were analyzed using the Mann-Whitney U test or independent sample t-test.

Results: The expression of both lncNEAT1_1 and lncNEAT1_2 in patients with cSLE were significantly higher than that of healthy control and patients with JIA. Receiver operating characteristic curves revealed an area under the curve (AUC) of 0.633 (95% confidence interval [CI], 0.524–0.742; $P = 0.024$) for lncNEAT1_1. The AUC of lncNEAT1_2 was 0.812 (95% CI, 0.727–0.897; $P < 0.0001$) to discriminate individuals with cSLE from health control and children with JIA with a sensitivity of 0.622 and a specificity of 0.925. Moreover, lncNEAT1_2 expression was higher in patients with cSLE presenting with fever, lupus nephritis, elevated erythrocyte sedimentation rate, active disease activity, and decreased C3 level, compared with those without these conditions. However, no similar correlation was observed for lncNEAT1_1.

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Interpretation: The expression of lncNEAT1_2 was significantly elevated in children with SLE, especially those with fever, renal involvement, and low C3 levels. These findings suggest that lncNEAT1_2 may represent a potential biomarker for cSLE.

KEYWORDS
Biomarker, Children, LncRNA, SLE, NEAT1

INTRODUCTION

Systemic lupus erythematosus (SLE) is a typical autoimmune disease, characterized by the interaction between innate and adaptive immune systems, the loss of immune tolerance to autoantigens, and the production of antibodies.[1] The production of double-stranded DNA and other nuclear autoantibodies are the main features of the disease. The etiology of SLE is still unclear. The combination of genetic and epigenetic tendencies with environmental factors plays an important role in the development of SLE. Childhood-onset SLE (cSLE) accounts for 20% of the total patients with SLE,[2] presenting different clinical manifestations from adults, characterized by a more acute onset and more organ involvement.[1,3]

Within the human genome, 98% of the products are noncoding RNAs. Those longer than 200 nucleotides are classified as long noncoding RNAs (lncRNAs).[4] The abundance of lncRNAs is substantial, as evidenced by data from the NONCODE database version 6.0, revealing 96 411 lncRNA genes and 173 112 lncRNA transcripts in the human genome. lncRNAs have been demonstrated to exert influence over genetic output at nearly every stage of the gene life cycle, including epigenetic regulation, chromatin remodeling, transcription, posttranscriptional control, and protein metabolism.[5] Consequently, lncRNAs are likely to play pivotal roles in disease progression. Aberrant expression of lncRNAs has been observed in various conditions, including cancer; neurodegenerative diseases; diabetes; and autoimmune diseases such as SLE, autoimmune thyroid diseases, systemic sclerosis, osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis.[4,5]

Nuclear enriched abundant transcript 1 (NEAT1), a lncRNA, is encoded on chromosome 11q13.1 and is widely and constitutively expressed in many tissues and cell types.[6,7] It plays an important role in tumor and immune diseases. Studies have shown that lncRNA NEAT1 (lncNEAT1) was highly expressed in patients with SLE,[8,9] and we found that lncNEAT1 showed an increasing trend in cSLE.[10] LncNEAT1 contains two transcripts: lncNEAT1_ 1 (3.7 kb) and lncNEAT1_ 2 (23 kb),[10–12] but the expression levels of lncNEAT1_ 1 and lncNEAT1_2 in cSLE are not clear, and there are no studies on the relationship between lncNEAT1 expression and clinical characteristics of cSLE.

Considering the uniqueness of cSLE and the importance of lncNEAT1, it is necessary to explore the lncNEAT1 expression in cSLE and its correlation with clinical phenotype.

METHODS

Ethical approval

The study was approved by the Research Ethics Committee of Beijing Children's Hospital (2019-k-98). Informed consent was obtained from all the guardians of the participants.

Patients and specimens

Patients with cSLE from January 2020 to December 2022 were obtained from the Department of Rheumatology of Beijing Children's Hospital (Beijing, China). All patients with SLE fulfilled at least four of the revised criteria for SLE by the American College of Rheumatology.[13] The age-matched control group included healthy volunteers (healthy control [HC]) and children diagnosed with juvenile idiopathic arthritis (JIA) (except systemic-onset JIA). The disease activity was assessed according to the SLE disease activity index (SLEDAI) at the time of blood collection.[14] Peripheral blood samples (2 mL) from each patient were collected in tubes containing ethylenediaminetetraacetic acid. After collection, samples were transferred immediately into liquid nitrogen and stored in a freezer at −80°C until RNA extraction. All participants were from the Han Chinese population.

RNA extraction

Total RNA was extracted from whole blood using the Trizol Reagent (Life Technologies) and then purified with a miRNeasy Serum/Plasma Kit (Qiagen), according to the manufacturer's instructions. RNA was detected using an ultraviolet-visible Spectrophotometer (NanoDrop 2000;

TABLE 1 Primers used for reverse transcription-quantitative polymerase chain reaction validation

Name	Sequence
lncNEAT1_1 _F	5'-GTGGCTGTTGGAGTCGGTAT-3'
lncNEAT1_1 _R	5'-AAACCACGGTCCATGAAGCA-3'
lncNEAT1_2 _F	5'-ACATTGTACACAGCGAGGCA-3'
lncNEAT1_2 _R	5'-CATTTGCCTTTGGGGTCAGC-3'
GAPDH_F	5'-TGAACGGGAAGCTCACTGG-3'
GAPDH_R	5'-TCCACCACCCTGTTGCTGTA-3'

Abbreviation: GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

Thermo Scientific) at 260-nm absorbance. Moreover, purity and integrity were assessed by agarose gel electrophoresis.

Quantitative polymerase chain reaction analysis

Moloney murine leukemia virus reverse transcription (Promega) was used to synthesize cDNA. Quantitative polymerase chain reaction (qPCR) analysis and data collection were performed on the ABI 7900HT qPCR system using the primer pairs listed in Table 1. Glyceraldehyde 3-phosphate dehydrogenase was used as an internal control of lncNEAT1.

Statistical analysis

All statistical analyses in this study were performed using the Statistical Product and Service Solutions 16.0 software package (IBM) and GraphPad Prism 6.0 (GraphPad Software). Data are presented as median (interquartile range). For qPCR analysis, fold changes are shown as mean ± standard deviation of three independent experiments for each triplicate. Associations between parameters were analyzed using the nonparametric Mann-Whitney *U* test or independent sample *t*-test. The clinical diagnostic value of a given lncNEAT1 was verified using receiver operating characteristic (ROC) curve analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients with cSLE

Fifty-seven children with cSLE were included in this study, and 40 healthy children and 40 children with JIA were selected as controls. The clinical and laboratory characteristics of the patients with cSLE or JIA and the HC are summarized in Table 2.

TABLE 2 Clinical characteristics of patients with cSLE and JIA, and HC

Clinical characteristics	cSLE ($n = 57$)	JIA ($n = 40$)	HC ($n = 40$)
Sex (male/female)	15/42	10/30	10/30
Age (years)	11.4 (8.5–13.2)	11.3 (9.1–13.0)	11.6 (9.0–13.5)
Fever	13 (22.8)	3 (7.5)	0
Rash	29 (50.9)	0	0
Arthritis	5 (8.8)	40 (100)	0
Leukopenia	5 (8.8)	0	0
Thrombocytopenia	7 (12.3)	0	0
Lupus nephritis	30 (52.6)	0	0
ANA (positive)	57 (100.0)	2 (5)	0
Anti-ds-DNA antibody	25 (43.8)	0	0
CRP (mg/L)	4.5 (1.4–8.0)	3.5 (1.3–9.6)	NA
ESR (mm/h)	16.5 (9.8–34.8)	13.3 (5.0–27.5)	NA
Low C3 level	47 (82.5)	NA	NA
Low C4 level	34 (59.6)	NA	NA
SLEDAI	6.0 (2.0–12.0)	NA	NA

Data presented as *n* (%) or median (interquartile range).
Abbreviations: ANA, antinuclear antibody; CRP, C-reactive protein; cSLE, childhood-onset systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; HC, healthy control; JIA, juvenile idiopathic arthritis; NA, not applicable; SLEDAI, systemic lupus erythematosus disease activity index.

Differences in the expression of lncNEAT1 in peripheral blood

LncNEAT1 contains two transcripts: lncNEAT1_1 and lncNEAT1_2, which were detected in the peripheral blood of patients with cSLE or JIA and the HC group by reverse transcription-qPCR analysis. The expression of lncNEAT1_1 in patients with cSLE was significantly higher than in HC (1.53 ± 1.09 *vs.* 1.00 ± 0.45; $P = 0.006$) or in children with JIA (1.53 ± 1.09 *vs.* 0.87 ± 0.40, $P = 0.011$). The expression of lncNEAT1_2 in patients with cSLE (1.80 ± 1.10) was also significantly higher than in HC (0.90 ± 0.35) or in children with JIA (0.76 ± 0.34) (all $P < 0.001$) (Figure 1). However, there was no significant difference in the expression of lncNEAT1_1 and lncNEAT1_2 between children with JIA and HC (all $P > 0.05$).

Potential diagnostic values of lncNEAT1 in peripheral blood of patients with cSLE

We performed a ROC curve analysis to validate the diagnostic potential of lncNEAT1 as a biomarker of cSLE. The analysis revealed an area under the curve (AUC) of 0.633 (95% confidence interval [CI], 0.524–0.742; $P = 0.024$) for lncNEAT1_1, exhibiting a sensitivity of 0.259 and a specificity of 1.000 with a cutoff of 1.92. For lncNEAT1_2, the analysis showed an AUC of 0.812 (95% CI, 0.727–0.897; $P < 0.0001$) in discriminating children with cSLE from JIA

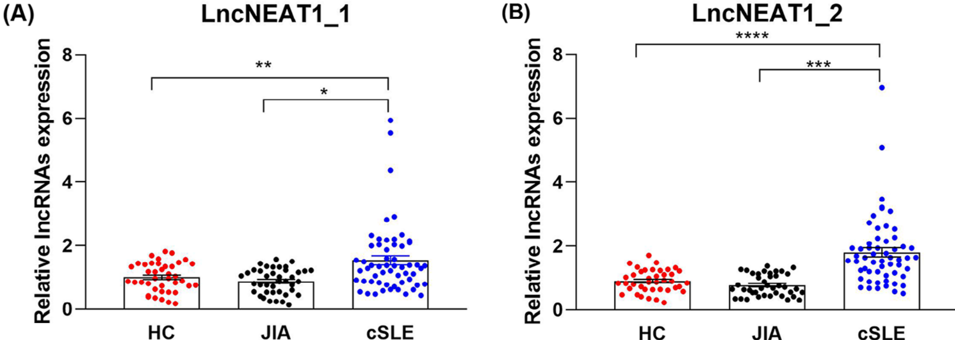

FIGURE 1 RT-qPCR quantified the relative levels of (A) long noncoding nuclear enriched abundant transcript 1 (lncNEAT1)_1 and (B) lncNEAT1_2 in peripheral blood from cSLE ($n = 57$), health control ($n = 40$), and JIA patients ($n = 40$). Glyceraldehyde 3-phosphate dehydrogenase was used as an internal control. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$. cSLE, childhood-onset systemic lupus erythematosus; HC, healthy control; JIA, juvenile idiopathic arthritis. RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

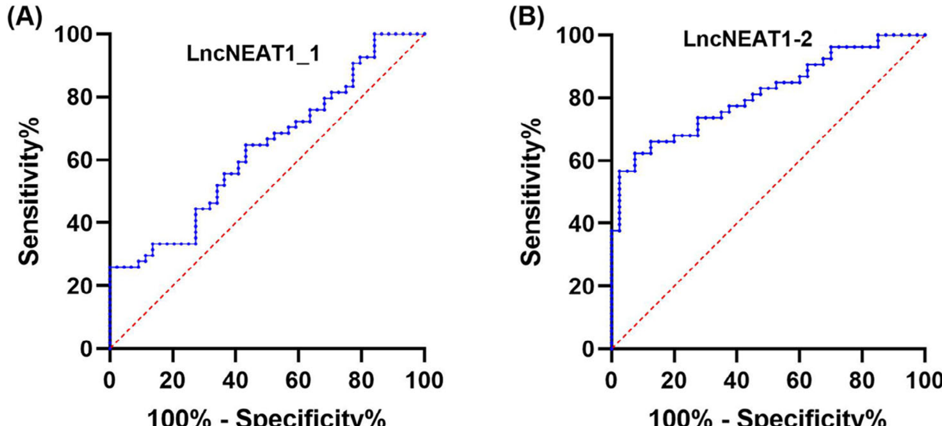

FIGURE 2 ROC curves for long noncoding nuclear enriched abundant transcript 1 (lncNEAT1) in peripheral blood in patients with cSLE and controls. (A) For lncNEAT1_1, the AUC was 0.633 (95% confidence interval [CI], 0.524–0.742; $P = 0.024$). The cutoff value was 1.92, yielding a sensitivity of 0.259 and a specificity of 1.000. (B) For lncNEAT1_2, the AUC was 0.812 (95% CI: 0.727–0.897, $P < 0.0001$). The cutoff value was 1.27, yielding a sensitivity of 0.622 and a specificity of 0.925. AUC, area under the curve; cSLE, childhood-onset systemic lupus erythematosus; ROC, receiver operating characteristic.

and HC, with a sensitivity of 0.622 and a specificity of 0.925 (Figure 2). The results indicated that lncNEAT1_2 had a better diagnostic value for cSLE compared with lncNEAT1_1.

Correlation between lncNEAT1 expression and cSLE clinical characteristics

To further clarify the clinical significance of lncNEAT1_1 and lncNEAT1_2, we analyzed their expression levels in relation to the clinical features of 57 patients with cSLE (Figure 3). The results revealed that lncNEAT1_2 expression showed a significant increase in children with fever compared with those without fever ($P < 0.001$); in children with lupus nephritis compared with those without ($P = 0.008$); in children with an elevated erythrocyte sedimentation rate (ESR $\geq$ 20 mm/h) compared with those with normal ESR ($P = 0.001$); in children with active disease (SLEDAI $\geq$5) compared with those with stable disease ($P < 0.001$); and in children with low C3 level ($P = 0.037$). However, no significant correlation was observed between lncNEAT1_2 expression and the presence of rash, arthritis, leukopenia, thrombocytopenia, C-reactive protein levels, and complement C4 levels. We also did not find a significant correlation between the expression of lncNEAT1_1 and any of these clinical manifestations.

DISCUSSION

SLE is a diffuse connective tissue disease with complex clinical manifestations and a prolonged course. cSLE is often associated with multiple system injuries such as kidney, lung, nervous, digestive, and blood systems.[15,16] The early diagnosis and condition monitoring of cSLE are crucial to disease prognosis. At present, there are few biomarkers to predict system damage, so early warning and diagnosis are difficult to achieve. Transcriptome sequencing showed that there were many new

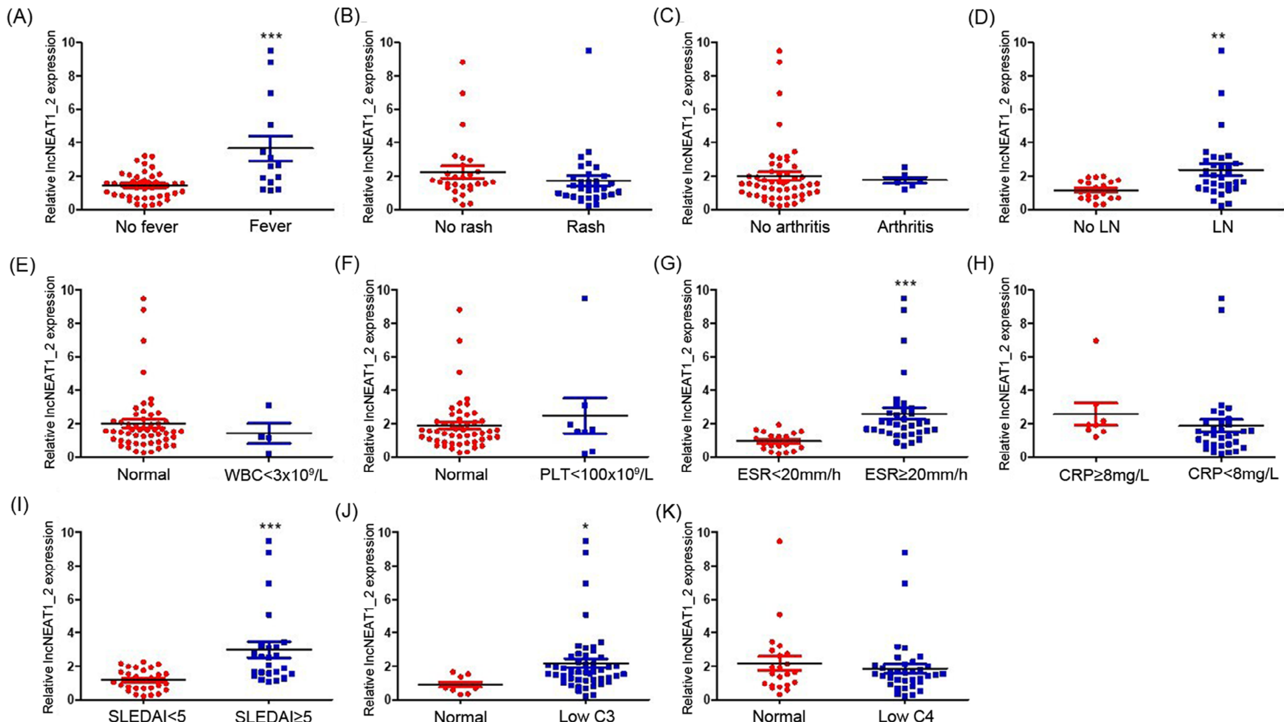

FIGURE 3 Relative expression of long noncoding nuclear enriched abundant transcript 1_2 (lncNEAT1_2) in cSLE patients with different clinical characteristics. (A) Fever; (B) rash; (C) arthritis; (D) LN; (E) leukopenia; (F) thrombocytopenia; (G) ESR; (H) CRP; (I) SLEDAI; (J) C3; (K) C4. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. CRP, C-reaction protein; cSLE, childhood-onset systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; LN, lupus nephritis; PLT, platelet; SLEDAI, systemic lupus erythematosus disease activity index; WBC, white blood cells.

lncRNAs in peripheral blood mononuclear cells, serum, and exosomes of patients with SLE or animal models.[8,10,17,18] Many lncRNAs are dysfunctional and may play a key role in the development of SLE.[19,20] In patients with SLE, an imbalance of lncRNAs such as GAS5, lncNEAT1, TUG1, linc0949, and linc0597 can be used as new biomarkers and therapeutic targets.[8] The expression of GAS5 is decreased in $CD4^{+}$ T cells and B cells in patients with SLE compared with normal controls. Furthermore, GAS5 expression is negatively correlated with ESR and SLEDAI-2K scores. Overexpression of GAS5 can suppress miR-92a-3p, resulting in upregulation of the transcription factor E4BP4 and inhibition of normal $CD4^{+}$ T cell activation. The GAS5/miR-92a-3p/E4BP4 pathway may play a role in suppressing $CD4^{+}$ T cell activation in SLE.[21,22] Additionally, the expression of lncRNA TSIX is elevated in monocyte-derived dendritic cells of patients with SLE, and the level of TSIX expression is positively correlated with the SLEDAI score.[23]

LncNEAT1, a lncRNA with a length of about 4 kb, has an obvious correlation with tumors. Its expression was significantly increased in lung cancer, esophageal cancer, colon cancers, and other tumor diseases. It can participate in disease pathogenesis through diverse mechanisms.[24–26] lncNEAT1 is not only involved in the occurrence and development of tumors but also in immune regulation, which plays a crucial role in regulating immune response.[27,28] It has been reported that lncNEAT1 is associated with disease activity in adult patients with SLE.[29] In this study, the expression of lncNEAT1 was significantly increased in cSLE and has a clear correlation with fever, renal involvement, SLEDAI, ESR, and low C3 level. These results indicate that lncNEAT1 is a potential biomarker for the diagnosis of cSLE.

LncNEAT1 contains two transcripts, which are tissue specific and play different roles. During the progression of MRL/*lpr* lupus in mice, the total lncNEAT1 expression level in granulocytic myeloid-derived suppressor cells (G-MDSCs) was significantly increased, while the expression of lncNEAT1_2 was not. In G-MDSCs isolated from 6-week-old wild-type mice, the expression of lncNEAT1_1 was much higher than that of lncNEAT1_2, indicating lncNEAT1_1 is the main transcript in G-MDSCs of lupus in mice.[30] Although numerous studies have examined the clinical relevance of lncNEAT1 in patients with SLE,[18,29] there has been no separate detection of lncNEAT1_1 and lncNEAT1_2 expression in these patients. In this study, we observed significantly elevated expression levels of both lncNEAT1_1 and lncNEAT1_2 in cSLE compared with HC and patients with JIA. The increase in lncNEAT1_2

was more pronounced compared to lncNEAT1_1. Importantly, lncNEAT1_2 presents an obvious correlation with clinical features such as fever, renal involvement, and disease activity, while such correlation was not evident for lncNEAT1_1. This indicates that lncNEAT1_2 may be a potential biomarker for cSLE disease diagnosis and activity monitoring. Further research is needed to explore the mechanism of lncNEAT1_2 in lupus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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