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LINC00632 relates to milder Th1/Th2 imbalance, attenuated nasal symptoms, and better response to therapy in allergic rhinitis patients

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Abstract
Objective: Long intergenic noncoding RNA 00632 (LINC00632) regulates nasal inflammation and $CD4^+$ T cell differentiation into T helper (Th) 2 cells in allergic rhinitis (AR). This study aimed to explore the relationship between LINC00632 and Th1/Th2 balance, and the clinical value of LINC00632 in AR patients.
Methods: In total, 120 AR patients, 20 non-atopic obstructive snoring patients as disease controls (DCs), and 20 healthy controls (HCs) were recruited. Their LINC00632 expressions in peripheral blood mononuclear cells were detected by RT-qPCR.
Results: LINC00632 expression was declined in AR patients compared with DCs and HCs (both $P < 0.001$). Moreover, LINC00632 could distinguish AR patients from DCs with an area under curve (AUC) of 0.795 (95% confidence interval [CI]: 0.701-0.889), and from HCs with an AUC of 0.895 (95%CI: 0.831-0.960). LINC00632 was positively related to Th1 cells ($P = 0.037$) and Th1/Th2 axis ($P < 0.001$) in AR patients. In addition, LINC00632 was inversely associated with Th2 cells ($P < 0.001$) and interleukin (IL)-4 ($P = 0.010$) in AR patients. Besides, LINC00632 was negatively related to rhinorrhea score ($P = 0.019$), itching score ($P = 0.008$), sneezing score ($P = 0.004$), and total nasal symptom score (TNSS) ($P < 0.001$), but no correlation between LINC00632 and congestion score was observed ($P = 0.093$). During treatment, LINC00632 was elevated, while TNSS score was reduced (both $P < 0.001$). Furthermore, LINC00632 increment was associated with the reduction of TNSS score during the therapy ($P = 0.005$).
Conclusion: LINC00632 relates to milder Th1/Th2 imbalance, attenuated nasal symptoms, and better response during 4-week therapy in AR patients.
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Introduction

Allergic rhinitis (AR) is a hypertensive immune reaction that occurs in the nasal epithelium when exposed to allergens.[1,2] The prevalence of AR ranges from 14.9% to 25.0% depending on the geographical location and age characteristics.[3-5] Although AR does not link to high mortality risk, a high incidence rate of commodities in AR patients has been reported.[6-8] Despite the application of symptom-modifying therapies, the lack of curative management options leads to frequent hospital visits and the absence of school or work in AR patients.[9-11] Hence, it is reasonable to identify the potential biomarkers to evaluate disease severity and monitor treatment response in AR patients, which might be helpful to improve overall AR management.

Long intergenic noncoding RNA 00632 (LINC00632) is a recently identified long noncoding RNA with close involvement in AR pathophysiology.[12,13] For instance, LINC00632 inhibits inflammatory cytokines and mucus production, which further prevents AR progression.[13] Moreover, LINC00632 suppresses the differentiation of $CD4^+$ T cells toward T helper (Th) 2 cells, which is a critical pathophysiological process for AR.[12,14] In the clinical field, only two studies report that LINC00632 is downregulated in AR patients compared to healthy controls (HCs).[12,13] However, the relationship between LINC00632 and Th1/Th2 balance as well as the clinical value of LINC00632 in AR patients was not addressed.

Therefore, this study aimed to explore the relationship between LINC00632 and Th1/Th2 dysregulation as well as its association with nasal symptoms and treatment responses during therapy in AR patients.

Materials and Methods

Participants

From April 2021 to October 2021, 120 AR patients were prospectively recruited. The inclusion criteria for AR patients were as follows: (1) diagnosed as AR according to Chinese Allergic Rhinitis Guidelines,[15] (2) age more than 18 years, and (3) willing to provide peripheral blood (PB) samples. Their exclusion criteria were as follows: (1) accompanied with other respiratory diseases besides allergic rhinitis, (2) complicated with diseases of cardiovascular, hepatic, and renal systems, (3) had an active infections, systemic inflammatory, or autoimmunity diseases, (4) had a solid tumor or hematological malignancies, and (5) pregnant or lactating women. Besides, 20 non-atopic obstructive snoring patients were included as disease controls (DCs) and 20 HCs were enrolled. The exclusion criteria for DCs and HCs were as follows: (1) had a history of AR, asthma, and chronic obstructive pulmonary disease (COPD), (2) had an allergic disease, systemic inflammatory, or autoimmunity diseases, (3) had a solid tumor or hematological malignancies, and (4) pregnant or lactating women. Every subject signed the written informed consent.

Clinical data and sample collection

After enrollment (W0), AR patients' demographics and disease features were collected in a case report form. The demographics included age and gender (male or female). The study features included individual nasal symptom score (INSS) and serum immunoglobulin E (IgE). Then, four symptom (rhinorrhea, sneezing, itching, and congestion) scales of INSS were summed to calculate the total nasal symptom score (TNSS). The TNSS score of AR patients was assessed again 4 weeks after enrollment (W4). The PB samples of AR patients were collected at W0 for LINC00632, Th (T helper) cell, inflammatory cytokines detection, and at W4 for LINC00632 detection. Besides, the PB samples of DCs and HCs were collected at W0 for LINC00632 detection. All AR patients were treated with inhaled glucocorticoids with or without oral anti-histamine agents and/or oral leukotriene receptor antagonists for 4 weeks after enrollment according to the Chinese Allergic Rhinitis Guidelines.[15]

Th cell determination

Within 24 hours after blood sample collection, peripheral blood mononuclear cells (PBMCs) were extracted by density gradient centrifugation (20°C, 1500 rpm, 25 min, without brake). The Th1 cells (%) and Th2 cells (%) in PBMCs were detected using flow cytometry with the employment of CellXVivo Human Th1/Th2 Cell Differentiation Kit (R&D System, United States). Later, the Th1/Th2 axis was calculated as Th1 cells (%) divided by Th2 cells (%).

Enzyme-linked immunosorbent assay (ELISA)

After PB samples kept intact at 37°C for half an hour, serum was isolated by centrifugation (4°C, 3000 rpm, 15 min). Then the concentrations of serum interferon-gamma (IFN-γ) and interleukin-4 (IL-4) were detected using Human IFN-γ or IL-4 ELISA Kit (R&D System, United States). The detection steps were carried out according to the manufacturer's protocols.

RT-qPCR assay

After extracting total RNA using PureZOL RNA isolation reagent (Bio-Rad, United States), reserve transcription was performed by iScript™ Reverse Transcription Supermix (Bio-Rad, United States). Later, the PCR reaction was performed using PCR (SYBR® Green Realtime PCR Master Mix (Toyobo, Japan). The primers were designed as per a previous study.[12] The quantification of LINC00632 expression was conducted based on a previous study.[16]

Statistical analysis

Differences in LINC00632 expression among the groups were compared using the Kruskal–Wallis test. Then, multiple comparisons were performed by Dunn post hoc test with Bonferroni correction. The diagnostic ability of LINC00632 was contrasted by the receiver operating characteristic (ROC) curve. The correlation of LINC00632 expression with Th 1 cells, Th2 cells, Th1/Th2 ratio, IFN-γ, IL-4, INSS score, and TNSS score as well as the correlation of LINC00632 change with TNSS change during treatment

was detected by Spearman's correlation test. Moreover, the Wilcoxon signed-rank test was applied for comparison of LINC00632 expression at W0 and W4. Besides, the paired t-test was applied for the comparison of TNSS scores at W0 and W4. The statistical analyses were performed by SPSS V 24.0 (IBM Corp., USA) and the figures were drawn by GraphPad Prism V 7.00 (GraphPad Software Inc., USA). A *P* value <0.05 indicated statistical significance.

Results

AR patients' features

The mean age of AR patients was 29.6±7.2 years (Table 1). There were 56 (46.7%) females and 64 (53.3%) males in AR patients. The mean rhinorrhea, itching, sneezing, congestion, and TNSS scores were 1.7 ± 0.8, 1.9 ± 0.7, 1.8 ± 0.8, 1.7 ± 0.8, and 7.1 ± 1.8, respectively. Furthermore, AR patients possessed a median serum IgE value of 303.0 IU/mL with an interquartile range (IQR) from 190.8 to 447.3 IU/mL. The median value of the Th1 cell ratio was 9.2% with an IQR of 7.7-11.2%. In addition, the median value of the Th2 cell ratio was 12.4% with an IQR of 10.3-15.4%. The detailed clinical features of AR patients were shown in Table 1.

Table 1 Clinical characteristics.

Items	AR patients (N = 120)
Age (years), mean±SD	29.6 ± 7.2
Gender, n (%)	
Female	56 (46.7)
Male	64 (53.3)
INSS, mean±SD	
Rhinorrhea score	1.7 ± 0.8
Itching score	1.9 ± 0.7
Sneezing score	1.8 ± 0.8
Congestion score	1.7 ± 0.8
TNSS score, mean±SD	7.1 ± 1.8
Serum IgE (IU/mL), median (IQR)	303.0 (190.8-447.3)
Th1 cells (%), median (IQR)	9.2 (7.7-11.2)
IFN-γ (pg/mL), median (IQR)	5.06 (3.58-6.41)
Th2 cells (%), median (IQR)	12.4 (10.3-15.4)
IL-4 (pg/mL), median (IQR)	28.6 (21.6-39.5)
Th1/Th2 axis, median (IQR)	0.743 (0.560-0.973)

Abbreviations: AR, allergic rhinitis; SD, standard deviation; INSS, individual nasal symptom score; TNSS, total nasal symptom score; IgE, immunoglobulin E; IQR, interquartile range; Th1, T helper 1; IFN-γ, interferon-gamma; Th2, T helper 2; IL-4, interleukin-4.

LINC00632 expression among AR patients, DCs, and HCs

LINC00632 expression varied among AR patients, DCs, and HCs ($P < 0.001$, Figure 1A). Further, post-hoc comparison displayed that LINC00632 expression declined in AR patients compared to DCs and HCs (both adjusted $P < 0.001$), while it did not differ between DCs and HCs (adjusted $P = 0.548$). Moreover, ROC curve analyses exhibited that LINC00632 could distinguish AR patients from DCs with an area under curve (AUC) of 0.795 (95% confidence interval [CI]: 0.701-0.889) (Figure 1B) as well as differentiate AR patients from HCs with an AUC of 0.895 (95%CI: 0.831-0.960) (Figure 1C).

Correlation of LINC00632 with Th1/Th2 dysregulation in AR patients

LINC00632 was positively related to Th1 cells ($r_s = 0.191$, $P = 0.037$) (Figure 2A), while it was inversely associated with Th2 cells ($r_s = -0.334$, $P < 0.001$) (Figure 2B). Moreover, LINC00632 was positively correlated with Th1/Th2 axis ($r_s = 0.353$, $P < 0.001$) (Figure 2C). Although no correlation of LINC00632 with IFN-γ (Th1 secreted cytokines) was observed ($r_s = 0.151$, $P = 0.099$) (Figure 2D), a negative correlation of LINC00632 with IL-4 (Th2 secreted cytokines) was discovered ($r_s = -0.234$, $P = 0.010$) (Figure 2E).

LINC00632, long intergenic noncoding RNA 00632; Th, T helper; IFN, interferon; IL, interleukin; AR, allergic rhinitis.

Association of LINC00632 with INSS and TNSS scores in AR patients

LINC00632 was negatively related to rhinorrhea score ($r_s = -0.215$, $P = 0.019$), itching score ($r_s = -0.241$, $P = 0.008$),

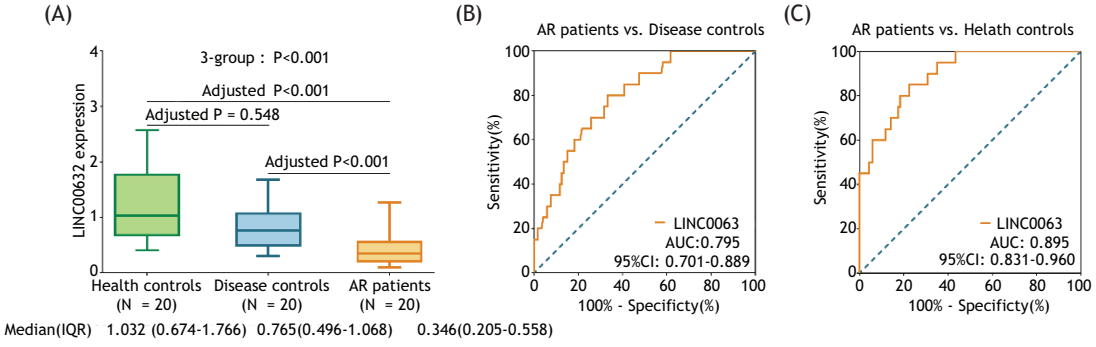

Figure 1 LINC00632 was downregulated in AR patients compared to DCs and HCs. Comparison of LINC00632 expression among AR patients, DCs, and HCs (A). ROC curves in distinguishing the AR patients from DCs (B) as well as from HCs (C). LINC00632, long intergenic noncoding RNA 00632; DCs, disease controls; HCs, healthy controls; AR, allergic rhinitis.

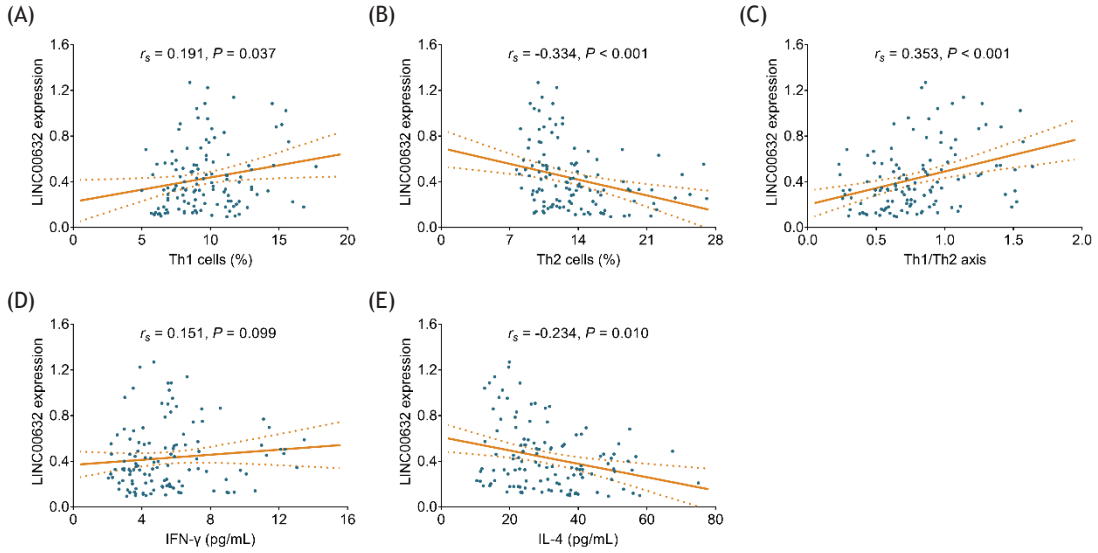

Figure 2 LINC00632 was related to Th1 and Th2 cells in AR patients. Correlation of LINC00632 with Th1 cells (A), Th2 cells (B), Th1/Th2 axis (C), IFN-γ (D), and IL-4 (E) in AR patients.

Table 2 Correlation of LINC00632 expression with INSS and TNSS scores in AR patients.

	LINC00632 expression	
Items	r_s	*P* value
INSS		
Rhinorrhea score	−0.215	0.019
Itching score	−0.241	0.008
Sneezing score	−0.262	0.004
Congestion score	−0.154	0.093
TNSS score	−0.384	<0.001

Abbreviations: LINC00632, long intergenic noncoding RNA 00632; INSS, individual nasal symptom score; TNSS, total nasal symptom score; AR, allergic rhinitis.

and sneezing score (r_s = −0.262, P = 0.004); but no correlation of LINC00632 with congestion score was observed (r_s = −0.154, P = 0.093). Moreover, LINC00632 was also negatively linked with TNSS score (r_s = −0.384, P < 0.001) (Table 2).

Longitudinal change of LINC00632 and its relationship with treatment efficacy in AR patients

LINC00632 was elevated at W4 compared to W0 (P < 0.001) (Figure 3A) while the TNSS score was reduced at W4 compared to W0 (P < 0.001) (Figure 3B). Moreover, the increment of LINC00632 during the 4-week therapy was related to the reduction of the TNSS score (r_s = −0.283, P = 0.005) (Figure 3C).

LINC00632, long intergenic noncoding RNA 00632; TNSS, total nasal symptom score; AR, allergic rhinitis; W, week.

Discussion

LINC00632 is initially reported as one of the deleted genes in hemophilia B patients with intellectual disability.[17,18] A recent bioinformatics study discovers that LINC00632 may be involved in acquiring resistance to immunomodulatory drugs in multiple myeloma, implying its potential connection to immune and/or immunity.[19] However, as a newly identified long noncoding RNA, LINC00632 is rarely

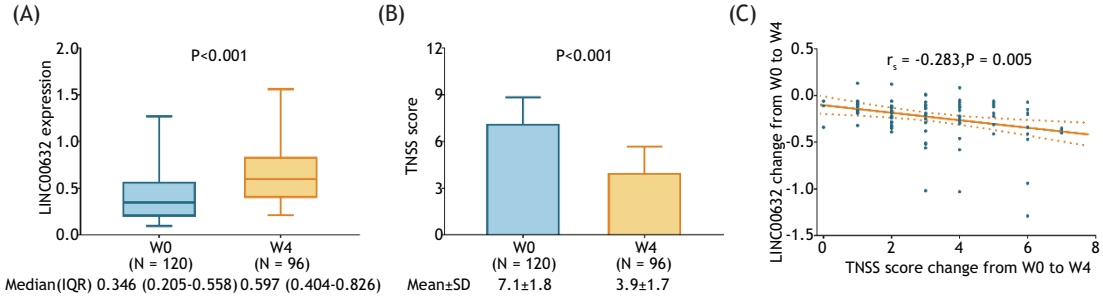

Figure 3 The change of LINC00632 was linked with the change in TNSS score in AR patients. Comparison of LINC00632 expression at W0 and at W4 (A). Comparison of TNSS score at W0 and W4 (B). Association between LINC00632 alteration and the change of TNSS score from W0 to W4 (C).

reported in the clinical field in patients with allergic diseases. Only two clinical studies explore the expression of LINC00632 in AR patients and HCs but their sample sizes are relatively small.[12,13] In addition, the clinical value of LINC00632 as a potential biomarker in AR patients requires further exploration. In line with these previous studies, it was observed that LINC00632 was downregulated in AR patients compared to HCs and DCs, also it could discriminate AR patients from HCs as well as from HCs. The possible reason to explain this finding was that the LINC00632-inhibited nasal inflammation and Th2 differentiation, thus leading to reduced AR risk.[12-14]

Moreover, in this study, it was also observed that LINC00632 was related to Th1/Th2 imbalance in AR patients, which could be explained as follows: LINC00632 inhibited the $CD4^+$ T cell differentiation toward Th2 cells through the mediation of the NF-κB pathway, thus an inverse relationship between LINC00632 and Th2 cell in AR patients was identified.[12,20,21] It was also noticed that a weak relationship of LINC00632 with IFN-γ and IL-4 in AR patients despite not reaching statistical significance, which could be explained as that: IFN-γ was partially secreted from Th1 cells, also IL-4 was partially secreted by Th2 cells, therefore the relationship between LINC00632 and these two cytokines might be weak and displayed no statistical significance. Furthermore, LINC00632 was inversely related to rhinorrhea, itching, sneezing, and TNSS scores, which could be explained as follows: LINC00632 was inversely related to Th2 cells as mentioned earlier, which further led to enhanced mucosal permeability and a reduced mucociliary clearance by Th2-mediated cytokines, thus resulting in impaired nasal epithelium integrity and an inverse relationship between LINC00632 and most parts of INSS score as well as TNSS score in AR patients.[22-24] Another interesting finding in the current study was that LINC00632 did not relate to the congestion score in AR patients.

Unfortunately, some studies report a low response in AR patients after the application of pharmacological therapies (including inhaled glucocorticoids, anti-histamine therapy, non-steroid anti-inflammatory drugs [NSAIDs], etc.).[25,26] Currently, some prognostic biomarkers have already been identified in response to AR treatment[27] while the correlation of LINC00632 with AR treatment has not been explored. In the present study, it was observed that LINC00632 was increased during treatment, and further its increment was linked with better treatment efficacy in AR patients. The possible reason to explain this finding was that upregulated LINC00632 during therapy was related to a reduction of nasal inflammatory response in AR patients as discussed earlier, which further indicated a lower TNSS score, thus the increment of LINC00632 during therapy was associated with a reduction of TNSS score in AR patients.[12,14,22]

The current study recruited 20 non-atopic obstructive snoring patients as DCs to eliminate the effect of obstructive nasal lesions on AR and to explore the LINC00632 expression in AR patients. However, several limitations occurred in the current study. For instance, the present study enrolled adult AR patients, while AR was more prevalent in children, therefore, further studies could investigate the correlation of LINC00632 with AR risk and severity in pediatric patients. Moreover, we only detected the LINC00632 expression from PBMCs, while its expression from other biological samples (i.e., nasal samples) could be determined in the future. Furthermore, the clinical application of LINC00632 in other allergic diseases (such as conjunctivitis and asthma) could be explored in future studies.

Conclusion

In conclusion, LINC00632 relates to milder Th1/Th2 imbalance and attenuated nasal symptoms, also its elevation during 4-week therapy may reflect treatment response in AR patients.

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