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RESEARCH ARTICLE

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Aberrant expression of long non-coding RNA PVT1 in allergic rhinitis children: Correlation with disease risk, symptoms, and Th1/Th2 imbalance

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Abstract

Background: Long non-coding RNA plasmacytoma variant translocation 1 (lnc-PVT1) exacerbates inflammation and induces T helper (Th) 1/Th2 imbalance in allergic diseases, but its clinical role in allergic rhinitis (AR) remains unclear. Hence, we conducted this study to compare lnc-PVT1 expression among AR children, disease controls (DCs), and health controls (HCs), aiming to investigate its clinical application in AR children.

Methods: Sixty AR children, 30 DCs, and 30 HCs were enrolled in the study, and then, their lnc-PVT1 expression in peripheral blood mononuclear cell was detected. Serum interferon-gamma (IFN-γ), interleukin 10 (IL-10), Th1, and Th2 cells in AR children were also analyzed. Besides, lnc-PVT1 was also detected at Week (W)4 after treatment in AR patients.

Results: Lnc-PVT1 was upregulated in AR children compared with DCs and HCs (both $p < 0.001$). Lnc-PVT1 was positively related to nasal rhinorrhea score, itching score, congestion score, and total nasal symptom score (TNSS) in AR children (all $p < 0.050$), instead of sneezing score ($p = 0.115$). Lnc-PVT1 negatively associated with Th1 cells in AR children ($p = 0.028$) also exhibited a negative correlation trend with IFN-γ (but without statistical significance) ($p = 0.065$). Differently, lnc-PVT1 was positively related to Th2 cells ($p = 0.012$) and IL-10 ($p = 0.021$) in AR children. Besides, lnc-PVT1 and TNSS were reduced at W4 after treatment in AR children (both $p < 0.001$); notably, lnc-PVT1 expression decline was correlated with TNSS decline during treatment ($p = 0.013$).

Conclusion: Lnc-PVT1 works as a biomarker, whose aberrant expression is related to disease severity, Th1/Th2 imbalance, and its decrement can reflect treatment outcome in AR children.

KEYWORDS
allergic rhinitis, disease severity, Long non-coding RNA plasmacytoma variant translocation 1, Th1/Th2 imbalance, treatment efficacy

Yujun Sun and Jingjing Han contributed equally to this work.

1 | INTRODUCTION

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated immune disease characterized by allergic symptoms in nasopharynx (including nasal rhinorrhea, itching, sneezing, and congestion), which is frequently occurred in children.[1–3] Currently, AR affects nearly 2%–25% of children worldwide with an increasing incidence ranging from 8.5% to 14.6%[4,5]; moreover, the incidence of AR is also elevated in children (4.9%-20.4%) over the last two decades in China.[6] Additionally, it is reported that approximately 75% of AR children develop complications, such as asthma, conjunctivitis, upper airway cough syndrome, and secretory otitis media.[7] Unfortunately, these uncomfortable symptoms and diverse complications bring sleep disruption to AR children and greatly impact their school performance as well as quality of life.[8,9] Aiming to attenuate these symptoms, according treatments (including antihistamines, intranasal corticosteroids (ICS), leukotriene receptor antagonists, and allergen immunotherapy) have been continually developed; however, AR is hard to be completely cured so far and its recurrence in children is still common, which represents challenges for clinicians.[10–13] Hence, exploring biomarkers can offer novel approaches to help identify children with high AR risk and further to individualize AR management.

Long non-coding RNA plasmacytoma variant translocation 1 (lnc-PVT1), located on chromosome 8q24, is originally known as an oncogene in human cancers.[14–16] In recent years, several evidence finds that lnc-PVT1 moderates inflammatory response, $CD4^+$ T-cell apoptosis, differentiation, and secretion of cytokines in autoimmune diseases (such as Sjögren's syndrome (SS) and rheumatoid arthritis (RA)) and also in allergic diseases (including asthma).[17–21] For instance, one study exhibits that lnc-PVT1 disturbs $CD4^+$ T-cell polarization and activates immune response in SS.[17] Notably, lnc-PVT1 is reported to motivate T helper type 1 (Th1)/T helper type 2 (Th2) imbalance in asthma, which is also relevant to the etiology of AR.[22–24] Consequently, we speculated that lnc-PVT1 might play essential role in regulating inflammatory and immune response in AR children. However, there is no relevant study focusing on the clinical role of lnc-PVT1 in AR children yet.

Therefore, we conducted this study to explore the correlation of lnc-PVT1 with disease severity, Th1 and Th2 cells, as well as its clinical value on revealing treatment efficacy in AR children.

2 | METHODS

2.1 | Subjects

A total of 60 AR children who were treated from March 2020 to February 2021 were consecutively enrolled in this study. The children were diagnosed as AR according to the guideline of pediatric allergic rhinitis[25] and aged from 2 to 14 years. The AR children with severe infections, autoimmune diseases, cancers, or hematological malignancies were excluded from the study. Besides, during the same period, 30 children with non-allergic nasal diseases were enrolled in the study as disease controls (DCs), and another 30 healthy children were enrolled as health controls (HCs). The study was approved by Institutional Research Ethics Committee.

2.2 | Data documents

For all eligible children, the demographics and serum IgE level were recorded. Besides, for AR children, individual nasal symptom score (INSS) and total nasal symptom score (TNSS) were scored before treatment (at Week 0 (W0)) to evaluate the disease severity, and then, TNSS was assessed again after treatment (at Week 4 (W4)).

2.3 | Treatment

AR children were mainly treated with medications in monotherapy or combination, such as intranasal corticosteroid, anti-leukotriene drugs, and long-acting beta2-agonists (LABA). The medication regimen was chosen for the corresponding AR children according to the actual disease conditions.

2.4 | Sample collection and assessment

For AR children, peripheral blood (PB) samples were collected at W0, and then, peripheral blood mononuclear cell (PBMC) and serum were separated. Sequentially, PB samples were also collected at W4, and PBMC was isolated. For disease controls and health controls, PB samples were collected for the separation of PBMC.

PBMC samples of all subjects were applied to detect lnc-PVT1 expression by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The specific experimentation was in the following section. PBMC samples of AR children were applied to examine the proportions of Th1 and Th2 cells in $CD4^+$ T lymphocytes by flow cytometric analysis using Human TH1/TH2 Cell Differentiation Kit (R&D System, Bio-Techne China Co. Ltd., Shanghai, China). Serum samples of AR children were applied to examine the levels of interferon-gamma (IFN-γ) (Th1 cell cytokine) and interleukin 10 (IL-10) (Th2 cell cytokine) by enzyme-linked immunosorbent assay (ELISA) using commercial Human IFN-γ/ IL-10 ELISA Kit (R&D System, Bio-Techne China Co. Ltd., Shanghai, China). The specific procedures of flow cytometric analysis and ELISA were performed according to the instructions provided by manufacturers.

2.5 | RT-qPCR assay

RT-qPCR assay was used to detect the expression of lnc-PVT1 in PBMCs of AR children at W0 and W4 as well as of DCs and HCs

at recruitment. Total RNA was extracted by RNeasy Protect Mini Kit (Qiagen, Duesseldorf, Nordrhein-Westfalen, Germany), and then, reserve transcription was completed using PrimeScript™ RT reagent Kit (Takara, Dalian, Liaoning, China). After that, qPCR was achieved by Terra™ qPCR Direct SYBR® Premix (Clontech, Mountain View, CA, USA). The relative expression of lnc-PVT1 was calculated by $2^{-\Delta\Delta Ct}$ method, using GAPDH as the internal reference. Besides, qPCR primers were designed referring to the previous study.[26]

2.6 | Statistics

Statistical analysis and graph construction were respectively completed using SPSS 24.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism 6.01 (GraphPad Software Inc., San Diego, California, USA). Differences in clinical characteristics among groups were compared using one-way analysis of variance (ANOVA) test, chi-squared test, or Kruskal–Wallis *H* rank-sum test. Comparison of lnc-PVT1 expression among groups was analyzed using Kruskal–Wallis H rank-sum test, followed by multiple comparisons with Bonferroni method. The performance of lnc-PVT1 expression in identifying different subjects was evaluated using receiver operating characteristic (ROC) curve. Correlations between variables were determined using Spearman's rank correlation test. Correlation of lnc-PVT1 with age, gender, medication and disease type was determined using Wilcoxon rank-sum test or Kruskal–Wallis H rank-sum test. Changes in lnc-PVT1 expression and TNSS over time were analyzed using Wilcoxon signed-rank test. Correlation between lnc-PVT1 expression decline from W0 to W4 and TNSS decline from W0 to W4 was analyzed using Spearman's rank correlation test. A *P* value less than 0.05 indicated a statistical significance.

3 | RESULTS

3.1 | Clinical characteristics

In the current study, the mean ages of AR children, DCs, and HCs were 6.4 ± 2.7 years, 7.3 ± 1.8 years, and 7.4 ± 2.1 years, respectively ($p = 0.074$), with 31 (51.7%) males and 29 (48.3%) females in AR children group, 12 (40.0%) males and 18 (60.0%) females in DC group, and 13 (43.3%) males and 17 (56.7%) females in HC group ($p = 0.529$) (Table 1). Furthermore, there was no difference in height or weight among these three groups (both $p>0.050$), except that IgE level was varied among all subjects ($p < 0.001$). Besides, the mean TNSS of AR children was 7.7 ± 1.9. The detailed clinical characteristics were shown in Table 1.

3.2 | Lnc-PVT1 expression

Lnc-PVT1 expression was differed among AR children, DCs, and HCs ($p < 0.001$); in detail, it was upregulated in AR children compared with DCs and HCs (both adjusted $p < 0.001$) (Figure 1A). Moreover, lnc-PVT1 could differentiate AR children from DCs (area under the curve (AUC): 0.835, 95% confidence interval (CI): 0.751–0.919; Figure 1B) and AR children from HCs (AUC: 0.892, 95% CI: 0.828–0.956; Figure 1C).

3.3 | Correlation of lnc-PVT1 with clinical characteristics of AR

Lnc-PVT1 was positively related to nasal rhinorrhea score ($r_s = 0.302$, $p = 0.019$), itching score ($r_s = 0.302$, $p = 0.019$), congestion score ($r_s = 0.283$, $p = 0.029$), and TNSS ($r_s = 0.441$, $p < 0.001$)

TABLE 1 Clinical characteristics

Items	AR children (*N* = 60)	Disease controls (*N* = 30)	Health controls (*N* = 30)	*p*-value
Age (years), mean ± SD	6.4 ± 2.7	7.3 ± 1.8	7.4 ± 2.1	0.074
Gender, *n* (%)				
Male	31 (51.7)	12 (40.0)	13 (43.3)	0.529
Female	29 (48.3)	18 (60.0)	17 (56.7)	
Height (cm), mean ± SD	118.1 ± 17.6	123.2 ± 14.3	123.1 ± 12.0	0.209
Weight (kg), mean ± SD	23.7 ± 9.3	24.9 ± 6.9	25.6 ± 6.0	0.537
Serum IgE (IU/ml), median (IQR)	255.2 (133.8–391.8)	28.5 (18.5–46.7)	19.9 (15.9–27.1)	<0.001
INSS, mean ± SD				
Nasal rhinorrhea score	2.0 ± 0.8	–	–	–
Itching score	1.9 ± 0.7	–	–	–
Sneezing score	2.0 ± 0.9	–	–	–
Congestion score	1.9 ± 0.9	–	–	–
TNSS, mean ± SD	7.7 ± 1.9	–	–	–

Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E; INSS, individual nasal symptom score; IQR, interquartile range; SD, standard deviation; TNSS, total nasal symptom score.

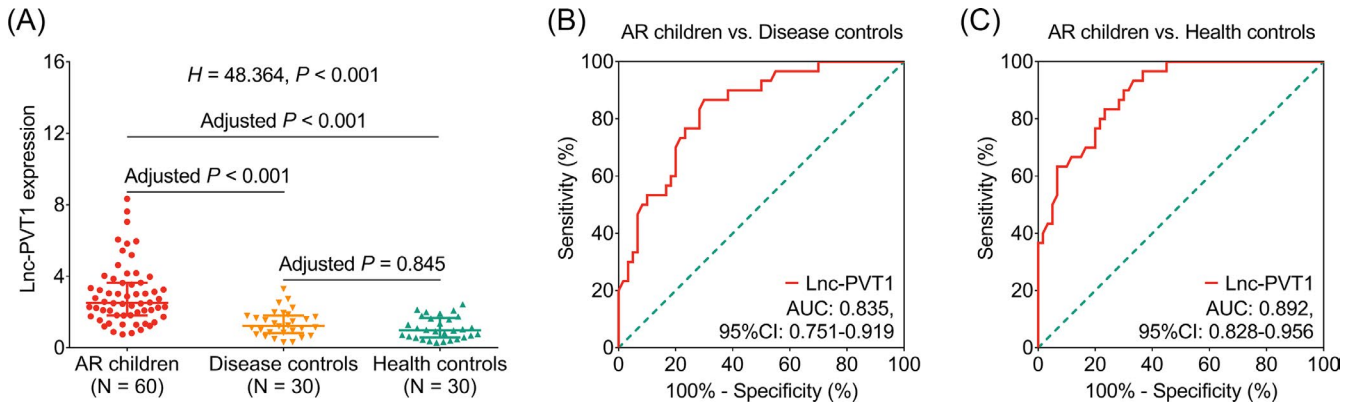


FIGURE 1 Lnc-PVT1 was overexpressed in AR children compared with DCs and HCs. The expression of lnc-PVT1 in AR children, DCs, and HCs (A). The value of lnc-PVT1 in differentiating AR children from DCs (B) and AR children from HCs (C)

in AR children, but did not link with sneezing score (r_s = 0.205, p = 0.115) (Figure 2A-E). In addition, Lnc-PVT1 was not correlated with age or gender in AR children, DCs, and HCs (all p>0.050, table S1). Besides, lnc-PVT1 was not correlated with disease types of AR children (p = 0.755). Furthermore, lnc-PVT1 was varied in AR children who received different treatments (p = 0.001).

3.4 | Correlation of lnc-PVT1 with Th1, Th2 cells, and their secreted cytokines in AR children

Lnc-PVT1 was negatively associated with Th1 cells in AR children (r_s = −0.285, p = 0.028) and also exhibited a negative correlation trend with IFN-γ (but without statistical significance) (r_s = −0.240, p = 0.065) (Figure 3A-B). Differently, lnc-PVT1 was positively related to Th2 cells (r_s = 0.321, p = 0.012) and IL-10 (r_s = 0.297, p = 0.021) in AR children (Figure 3C-D). Additionally, lnc-PVT1 was negatively correlated with Th1 cells/Th2 cells ratio (r_s = −0.429, p = 0.002) in AR children (figure S1).

3.5 | Changes in lnc-PVT1 and TNSS after treatment and their intercorrelation

Lnc-PVT1 was reduced at W4 after treatment in AR children (1.770 (interquartile range (IQR): 1.375–2.675) vs. 2.515 (IQR: 1.813–3.638), p < 0.001; Figure 4A). In terms of TNSS, it was also declined at W4 after treatment in AR children (4.5 ± 1.9 vs. 7.7 ± 1.9, p < 0.001;

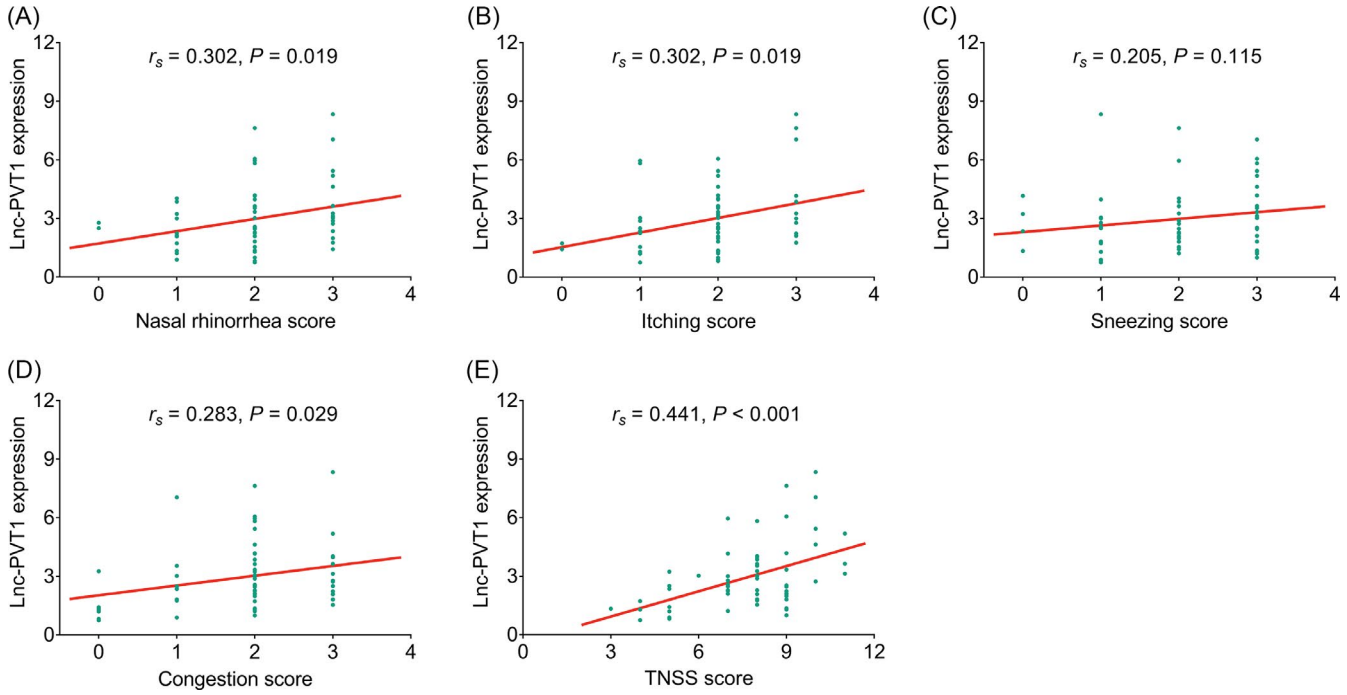
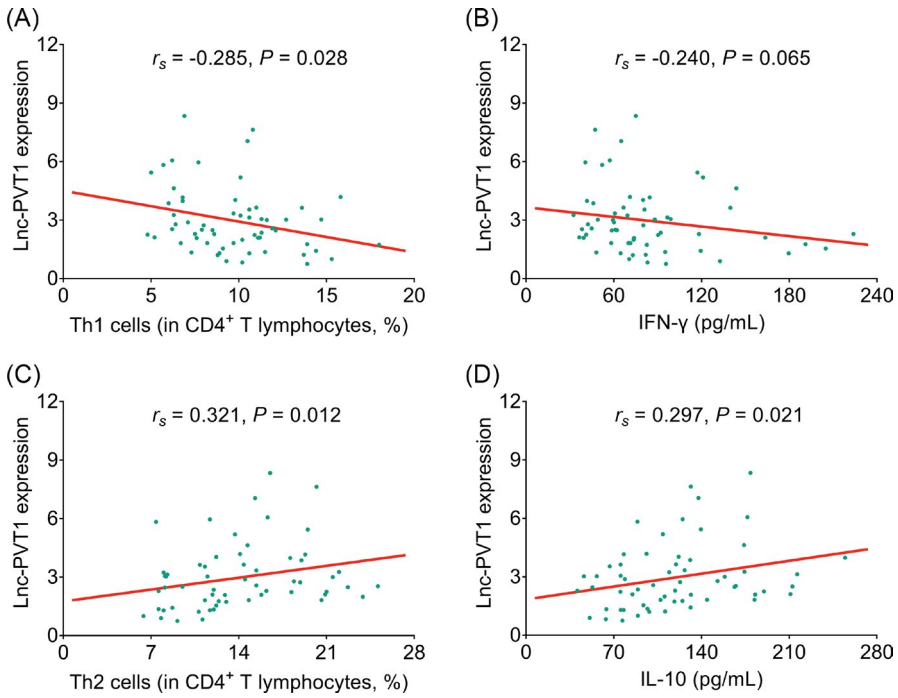


FIGURE 2 Lnc-PVT1 linked with severe clinical symptoms in AR children. The association of lnc-PVT1 with nasal rhinorrhea score (A), itching score (B), sneezing score (C), congestion score (D), and TNSS (E) in AR children



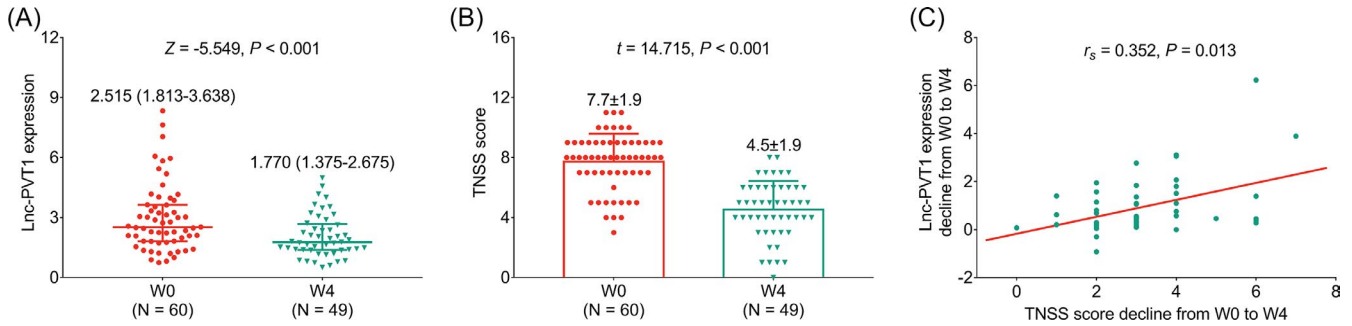


FIGURE 3 Lnc-PVT1 correlated with Th1 and Th2 cells in AR children. The relationship of lnc-PVT1 with Th1 cells (A), IFN-γ (B), Th2 cells (C), and IL-10 (D) in AR children

FIGURE 4 Decrements of lnc-PVT1 and TNSS were intercorrelated in AR children. Comparison of lnc-PVT1 before and after treatment in AR children (A). Comparison of TNSS before and after treatment in AR children (B). Correlation of lnc-PVT1 expression decline with TNSS decline in AR children (C)

Figure 4B). Besides, lnc-PVT1 expression decline from W0 to W4 was positively correlated with TNSS decline from W0 to W4 in AR children ($r_s = 0.352$, $p = 0.013$; Figure 4C).

4 | DISCUSSION

AR is a common pediatric allergic disease, whose occurrence is due to the non-infectious inflammation in nasal mucosa after exposure to allergens (including dust mite and pollens).[3,27,28] Remarkably, TH1/TH2 imbalance is closely related to the onset of AR.[29] Besides, one previous study highlights that lnc-PVT1 facilitates Th1/Th2 imbalance in asthma via activating phosphatidylinositol 3 kinase (PI3K)-protein kinase B (AKT) signaling pathway.[22] Hence, we hypothesized that lnc-PVT1 might closely correlate with inflammation level and involve in the pathological process of AR. Therefore, we performed this study and discovered that lnc-PVT1 was upregulated in AR children compared with DCs and HCs; besides, its overexpression correlated with Th1/Th2 imbalance and elevated disease severity in AR children. Possible explanations might follow: (1) Lnc-PVT1 was positively linked with Th2 cells, which was excessively secreted in AR children.[30] Hence, lnc-PVT1 was upregulated in AR children compared with DCs and HCs. (2) Lnc-PVT1 induced the differentiation of T cells into Th2 cells, which indirectly declined the proportion of Th1 cells in AR children.[22] Thus, lnc-PVT1 was negatively associated with Th1 cells in AR children and exhibited a negative correlation trend with IFN-γ, while it was positively related to Th2 cells and IL-10. (3) As mentioned above, lnc-PVT1 promoted Th1/Th2 imbalance, which would aggravate disease severity in AR children.[31] Therefore, lnc-PVT1 was positively related to nasal rhinorrhea score, itching score, congestion score, and TNSS in AR children.

Apart from the correlation of lnc-PVT1 with Th1/Th2 imbalance and disease severity, this study also disclosed that lnc-PVT1 and TNSS were reduced after treatment in AR children; moreover, the decrement of lnc-PVT1 from W0 to W4 was positively correlated with the decline of TNSS from W0 to W4 in AR children. The possible reasons to explain these results were as follows: (1) After receiving treatment, the symptoms (including nasal

rhinorrhea, itching, sneezing, and congestion) of AR children were alleviated.[12,13] Thus, TNSS in AR children was decreased after treatment. Moreover, as what we had disclosed, lnc-PVT1 was positively related to TNSS in AR children. Therefore, lnc-PVT1 was also declined after treatment in AR children. (2) Lnc-PVT1 positively associated with Th2 cells, whose reduction after treatment enhanced epithelial cell barrier and helped AR children defense against invasion of allergens; then, disease severity of AR children was attenuated.[32] Hence, the decrement of lnc-PVT1 from W0 to W4 was positively correlated with the decline of TNSS from W0 to W4 in AR children.

Some limitations existed in this study. Firstly, the sample size of the current study was relatively small, which might cause a weak statistical power. Secondly, it was a single-center study, which would lead to selection bias. Hence, a multi-center research in diverse regions was necessary to further verify our findings. Thirdly, lnc-PVT1 in AR children was only detected at W0 and W4, which might be insufficient to reflect its long-term clinical value; thus, a study with longer follow-up duration was needed. Fourthly, the detailed mechanism needed further investigation in both *in vivo* and *in vitro* studies.

In conclusion, lnc-PVT1 works as a biomarker, whose aberrant expression is related to disease severity, Th1/Th2 imbalance, and its decrement can reflect treatment outcome in AR children.

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None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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