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RESEARCH ARTICLE

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Cell division cycle 42 reflects disease risk, symptoms, Th1/Th2 disproportion, and its short-term variation indicates symptom amelioration after treatment in allergic rhinitis patients

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Abstract

Background: Cell division cycle 42 (CDC42) modulates the pathogenesis of allergic rhinitis (AR) through regulating immunity, allergic response, and T-helper (Th)1/Th2 imbalance. This study aimed to evaluate the potential of CDC42 to reflect disease risk, symptom scores, and Th1/Th2 axis of AR and the correlation of its vertical change with symptom amelioration after treatment.

Methods: CDC42, Th1 cells, and Th2 cells in the peripheral blood mononuclear cells (PBMCs) and interferon-γ and interleukin-4 in the serum were determined in 200 AR patients. Simultaneously, PBMC CDC42 was detected in 50 non-atopic obstructive snoring patients [as disease controls (DCs)] and 50 healthy controls (HCs).

Results: CDC42 was increased in AR patients compared with DCs and HCs (both $p < 0.001$) but showed no difference between DCs and HCs ($p = 0.054$). In AR patients, CDC42 was positively linked to rhinorrhea, itching, sneezing, and total nasal symptom scores (TNSS) (all $p < 0.05$), but not congestion score ($p = 0.052$). Meanwhile, CDC42 showed positive correlations with Th2 cells ($p < 0.001$) and interleukin-4 ($p = 0.005$), a negative correlation with Th1/Th2 axis ($p = 0.001$), but no correlation with Th1 cells ($p = 0.095$) or interferon-γ ($p = 0.174$). Notably, CDC42 at week 4 after treatment (W4) was reduced compared with that at enrollment (W0) ($p < 0.001$) and positively correlated with TNSS at W4 ($p < 0.001$); from W0 to W4, CDC42 change also positively correlated with TNSS change ($p = 0.004$).

Conclusion: CDC42 is elevated and positively correlates with symptom scores and Th2 cells, whose short-term reduction reflects symptom alleviation in AR patients.

KEYWORDS
allergic rhinitis, cell division cycle 42, disease risk, symptom scores, T-helper 1/T-helper 2 axes

1 | INTRODUCTION

Allergic rhinitis (AR) is an allergic reaction in the nasal mucosa to inhaled allergens, which is associated with several physiological procedures such as the production of allergen-specific immunoglobulin E (IgE), activation of T-helper (Th) cells, and chronic inflammation.[1,2] Globally, AR is a prevalent disease with steadily increasing incidence in low- and middle-income countries, partly

due to the increasing level of pollutants such as traffic waste and particulate matter 2.5 (PM2.5).[3–5] The current medical management for AR mainly includes antihistamines, intranasal corticosteroids, and allergen-specific immunotherapy; however, these treatments merely relieve the symptoms of AR.[6–8] Considering that AR not only severely affects patients' quality of life but also heavily affects the public health system, it is crucial to explore novel biomarkers to reflect AR risk and characteristics, thus improving the personalized management of AR.[9–11]

Cell division cycle 42 (CDC42) participates in various biological processes, such as inflammation and immune response.[12–14] Recent studies have implied the potential involvement of CDC42 in AR. For instance, it is reported that CDC42 deletion suppresses Th2 cell differentiation, thus decreasing the progression of allergic airway inflammation.[15,16] Another study suggests that CDC42 activation facilitates Ca^{2+} mobilization in mutant RBL mast cells, thus modulating allergic response.[17] More importantly, an interesting study uses bioinformatics analysis to investigate the potential molecular mechanisms of AR, which reveals that CDC42 is listed in the differential co-expression network in seasonal AR samples compared with non-allergic normal samples, suggesting that CDC42 may directly participate in the pathogenesis of AR.[18] However, the clinical implication of CDC42 in AR remains to be clarified.

Considering the scenario mentioned above, the current study aimed to evaluate the correlation of CDC42 with disease risk, severity, and the Th1/Th2 axis of AR, as well as the relation of CDC42 vertical change with symptom amelioration after treatment.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was conducted between June 2021 and March 2022 at Ningbo Yinzhou No.2 Hospital. The ethics were approved by the Institutional Review Board of Ningbo Yinzhou No.2 Hospital. Each participant signed the written informed consent.

Two hundred AR patients meeting the following inclusion criteria were recruited: (1) diagnosed as AR according to the clinical practice guideline of AR[19]; (2) older than 18 years. Their exclusion criteria were (1) had systemic inflammatory diseases; (2) had immune deficiency or underwent immunotherapy treatment; (3) had malignant diseases.

During the same period, fifty age- and sex-matched non-atopic obstructive snoring patients (aged 18–45, male: female ratio equaled 1:1) were recruited as disease controls (DCs). The DCs were required to have no allergic, systemic inflammatory, or tumor diseases and no cardiovascular, hepatic, renal, or hematopoietic systems diseases. Besides, fifty age- and sex-matched health controls (aged 18–45, male: female ratio 1:1) were also included as HCs. The HCs were excluded if they had a history of respiratory, allergic, systemic inflammatory, immune, or malignant disease.

2.2 | Clinical data and sample collection

All participants' age, gender, and serum IgE were recorded by case report form. AR patients' individual nasal symptom score (INSS) was assessed at enrollment (W0). AR patients' total nasal symptom score (TNSS) was calculated at W0 and 4 weeks after enrollment (W4). Blood samples of 200 AR patients, 50 DCs, and 50 HCs were collected at enrollment, and 160AR patients were collected at W4. Within 24 h after blood collection, peripheral blood mononuclear cells (PBMCs) and serum were isolated by density gradient centrifugation and centrifugation, respectively.

2.3 | Sample determination

The Th1 cells (%) and Th2 cells (%) in PBMCs were detected using flow cytometry with the employment of the Human Th1/Th2 Phenotyping Kit (BD Biosciences, United States). The Th1/Th2 axis was calculated as Th1 cells (%) divided by Th2 cells (%). The levels of serum interferon (IFN)-γ and interleukin (IL)-4 were determined by commercial enzyme-linked immunosorbent assay (ELISA) kits (Invitrogen™).

2.4 | Reverse transcriptional-quantitative polymerase chain reaction (RT-qPCR) assay

Total RNA of the PMBCs was isolated with TRIzol™ Reagent (Invitrogen™), followed by reverse transcription using QuantiNova Reverse Transcription Kit (Qiagenis). Next, KOD SYBR® qPCR Mix (Toyobo) was used to perform qPCR. The relative mRNA expression of CDC42 was calculated by the $2^{-\Delta\Delta Ct}$ method with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) used as the internal reference.[20] The primers were designed according to a previous study.[21]

2.5 | Statistical analysis

The statistical analyses were calculated by SPSS V 26.1 (IBM Corp.). The figures were drawn by GraphPad Prism V 8.00 (GraphPad Software Inc.). The normality test was conducted by Shapiro–Wilk test. Difference analyses between AR patients, DCs, and HCs were performed by the Kruskal–Wallis test. The post hoc test was detected by Dunn Kruskal–Wallis multiple comparisons, and the *p* value was adjusted with the Bonferroni method. The receiver operating characteristic (ROC) curve evaluated the diagnostic

performance of CDC42. The correlation between the two variables was calculated by Spearman's rank correlation test. Differences in CDC42 expression and TNSS at W0 and W4 were analyzed via Wilcoxon signed-rank test. A p value <0.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Characteristics of AR patients, DCs and HCs

The median [interquartile range (IQR)] ages of AR patients, DCs, and HCs were 27.0 (23.0–34.0), 29.5 (23.0–39.3), and 30.5 (22.0–38.0) years, respectively. There were 92 (46.0%) females and 108 (54.0%) males in AR patients, 25 (50.0%) females and 25 (50.0%) males in DCs, and 25 (50.0%) females and 25 (50.0%) males in HCs. The comparison analysis revealed no difference in age or gender among AR patients, DCs, and HCs (both $p > 0.05$). Whereas serum IgE level was highest in AR patients [356.0 (267.3–508.3) IU/ml], followed by DCs [39.0 (30.0–49.0) IU/ml], and lowest in HCs [31.5 (25.8–37.3) IU/ml] ($p < 0.001$). In AR patients, the mean levels of rhinorrhea, itching, sneezing, and congestion scores were 1.7±0.8, 1.9±0.7, 1.7±0.8, and 1.7±0.8, respectively; meanwhile, the median (IQR) level of TNSS was 7.0 (6.0–8.0) (Table 1).

3.2 | CDC42 expression in AR patients, DCs, and HCs

CDC42 was differentially expressed among AR patients, DCs, and HCs [median (IQR): 2.815 (1.933–3.928) vs. 1.440 (1.198–2.040) vs. 0.990 (0.700–1.570)] ($p < 0.001$). Meanwhile, multiple comparisons illustrated that CDC42 was higher in AR patients than in DCs and HCs (both $p < 0.001$). However, it was similar between DCs and HCs ($p = 0.054$) (Figure 1). Simultaneously, CDC42 well-discriminated AR patients from DCs (Figure 2A) and HCs (Figure 2B) with area under the curve (AUC) of 0.786 [95% confidence interval (CI): 0.719–0.852] and 0.890 (95% CI: 0.845–0.935), separately. However, CDC42 showed a low value in discriminating DCs from HCs with an AUC of 0.702 (95% CI: 0.598–0.805) (Figure 2C).

3.3 | Correlation of CDC42 expression with symptom scores in AR patients

Regarding INSS score, CDC42 presented a positive correlation with rhinorrhea score ($r_s = 0.202$, $p = 0.004$) (Figure 3A), itching score ($r_s = 0.231$, $p = 0.001$) (Figure 3B), and sneezing score ($r_s = 0.177$, $p = 0.012$) (Figure 3C); CDC42 also showed a trend to be positively correlated with congestion score but did not reach statistical significance ($r_s = 0.137$, $p = 0.052$) (Figure 3D). In terms of TNSS, a positive correlation was found between CDC42 and TNSS ($r_s = 0.336$, $p < 0.001$) (Figure 3E).

3.4 | Correlation of CDC42 expression with Th1 and Th2 cells in AR patients

CDC42 was not correlated with Th1 cells ($r_s = -0.118$, $p = 0.095$) (Figure 4A); it showed a positive correlation with Th2 cells ($r_s = 0.297$, $p < 0.001$) (Figure 4B) while a negative correlation with Th1/Th2 axis ($r_s = -0.227$, $p = 0.001$) (Figure 4C). Concurrently, serum levels of IFN-γ and IL-4, the cytokines mainly secreted by Th1 and Th2 cells, were also detected to verify the above findings. The data presented that no correlation was found between CDC42 and IFN-γ ($r_s = -0.096$, $p = 0.174$) (Figure 4D), while a positive linkage

TABLE 1 Clinical characteristics

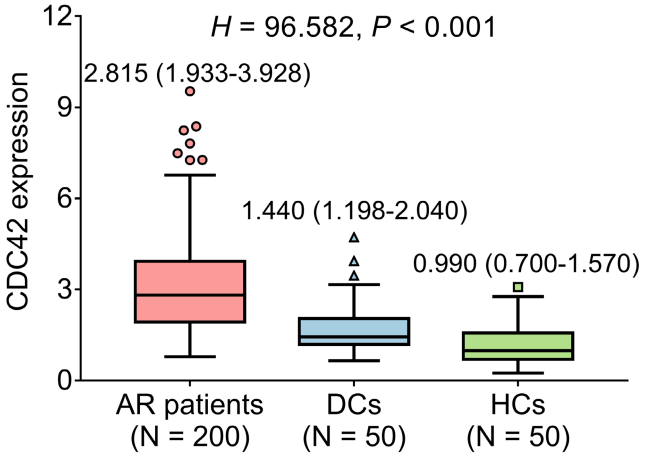
Items	AR patients (N = 200)	DCs (N = 50)	HCs (N = 50)	Statistics (Z, χ^2)	p Value
Age (years), median (IQR)	27.0 (23.0–34.0)	29.5 (23.0–39.3)	30.5 (22.0–38.0)	4.000	0.135
Gender, n (%)				0.428	0.807
Female	92 (46.0)	25 (50.0)	25 (50.0)		
Male	108 (54.0)	25 (50.0)	25 (50.0)		
Serum IgE (IU/ml), median (IQR)	356.0 (267.3–508.3)	39.0 (30.0–49.0)	31.5 (25.8–37.3)	200.178	<0.001
INSS, mean±SD				-	-
Rhinorrhea score	1.7±0.8	-	-		
Itching score	1.9±0.7	-	-		
Sneezing score	1.7±0.8	-	-		
Congestion score	1.7±0.8	-	-		
TNSS, median (IQR)	7.0 (6.0–8.0)	-	-	-	-

Abbreviations: AR, allergic rhinitis; DCs, disease controls; HCs, health controls; IgE, immunoglobulin E; INSS, individual nasal symptom score; IQR, interquartile range; TNSS, total nasal symptom score.

was observed between CDC42 and IL-4 (r_s = 0.198, p = 0.005) (Figure 4E).

3.5 | Role of CDC42 variation in monitoring AR severity

At W4, 40 patients lost to follow-up and CDC42 was detected in 160 patients at W4. CDC42 was reduced at W4 compared with that at W0 [median (IQR): 1.685 (1.160–2.150) vs. 2.815 (1.933–3.928)] (p <0.001) (Figure 5). In addition, the TNSS was decreased at W4 compared with that at W0 [median (IQR): 7.0 (6.0–8.0) vs. 4.0 (3.0–5.0)] (p <0.001) (Figure 6A). Moreover, CDC42 at W4 illustrated a positive correlation with TNSS at W4 (r_s = 0.314, p <0.001) (Figure 6B); CDC42 change from W0 to W4 was also positively associated with TNSS change from W0 to W4 (r_s = 0.225, p = 0.004) (Figure 6C).



Dunn Kruskal-Wallis multiple comparison

	Statistics (Z)	Adjusted P value
AR patients vs. DCs	5.893	<0.001
AR patients vs. HCs	8.885	<0.001
DCs vs. HCs	2.366	0.054

FIGURE 1 Comparison of CDC42 among AR patients, DCs and HCs

4 | DISCUSSION

Previous studies have shown that CDC42 is involved in the pathogenesis and progression of allergic diseases.[16–18] However, the clinical implication of CDC42 in allergic diseases remains unclear, not to mention its clinical role in AR. Only one previous study using bioinformatic analysis revealed that CDC42 is involved in the differential co-expression network in nasal epithelial cells from AR patients compared with those from normal subjects[18]; however, this study only uses seven AR samples and five normal samples, and this finding should be verified in a larger sample size. In the current study, we found that CDC42 was elevated in AR patients compared with DCs and HCs, while it remained similar between DCs and HCs. The possible explanation might be that: (1) CDC42 might exaggerate allergic response in several ways including Th2 cell differentiation and mast cell activation,[16,17] thus leading to AR; therefore, CDC42 was elevated in AR patients. (2) The allergic reaction was low and similar between DCs and HCs. Thus, CDC42 remained similar between these two kinds of subjects. At present, the diagnosis of AR is a complex procedure, which is based on clinical history, nasal examinations, skin tests, serum-specific IgE examination, etc.[22] Meanwhile, clinicians should discriminate AR from other diseases such as non-allergic rhinitis, infectious rhinitis, and hormonal rhinitis.[23] Therefore, it is critical to establish an accurate and convenient method to help the diagnosis of AR. In the current study, CDC42 showed a good value to discriminate AR patients from DCs and HCs, which implied it might be used to help diagnose AR. However, this finding should be further verified. Previous studies have also shown novel biomarkers for predicting the risk of AR. For instance, Song et al. reveal that long noncoding RNA growth arrest-specific 5 and its targets microRNA-21 and microRNA-140 are correlated with AR

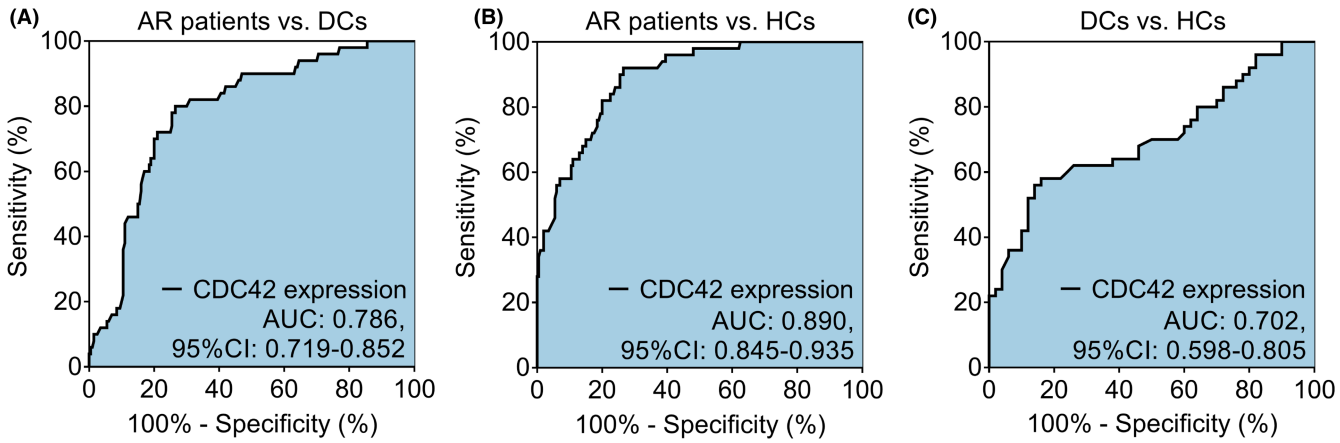


FIGURE 2 Ability of CDC42 to discriminate AR patients from DCs and HCs. The value of CDC42 to differentiate AR patients from DCs (A) and HCs (B). The value of CDC42 to differentiate DCs from HCs (C)

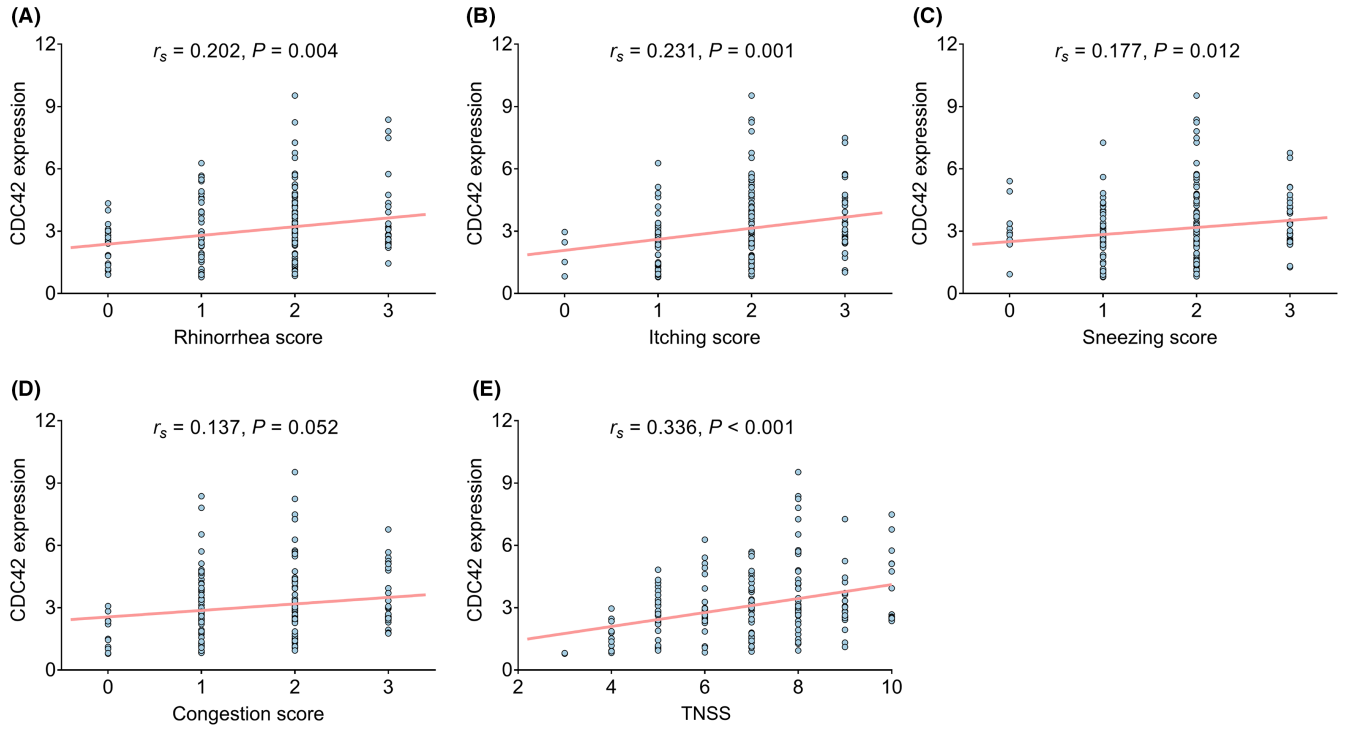


FIGURE 3 Linkage of CDC42 with symptom scores in AR patients. Correlation of CDC42 with rhinorrhea score (A), itching score (B), sneezing score (C), congestion score (D), and TNSS (E)

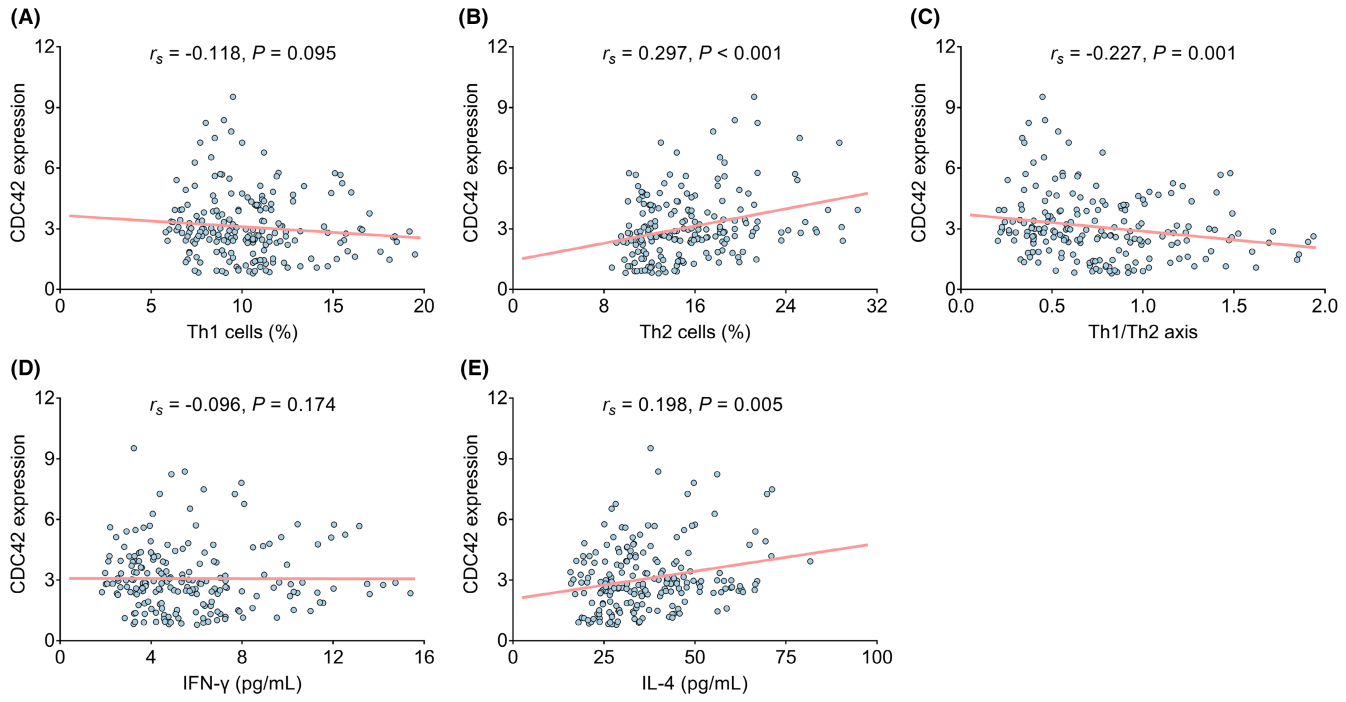


FIGURE 4 Linkage of CDC42 with Th1/Th2 axis in AR patients. Correlation of CDC42 with Th1 cells (A), Th2 cells (B), Th1/Th2 axis (C), IFN-γ (D), and IL-4 (E)

risk.[24] Meanwhile, Li et al. uncover a low level of nasal exhaled hydrogen sulfide in seasonal AR patients, which may serve as a potential indicator of AR risk.[25] Our study also suggested that CDC42 in PBMCs could help predict AR risk.

The treatment of AR is generally based on the symptoms of AR patients.[6,7] However, most symptom scoring system is based on patients' self-evaluation of the symptoms, which could lead to self-evaluation bias and sometimes inappropriate treatment based on

the symptom scores. In the current study, we also explored the correlation of CDC42 with INSS and TNSS, which revealed that CDC42 was positively correlated with rhinorrhea, itching, sneezing scores, and TNSS. These data suggested that CDC42 was related to more severe symptoms in AR patients. A possible explanation was that CDC42 could amplify the allergic reaction and inflammatory procedure, leading to more severe symptoms in AR patients.[16,26] These findings suggest that CDC42 might serve as an objective biomarker to reflect the symptoms of AR, thus improving the management of AR patients. In addition, our study also discovered that CDC42 was positively correlated with Th2 cells. Previous studies also report that CDC42 shows a positive linkage with Th2 cells,[21,27] which may be explained by the that CDC42 could positively regulate Th2 cell differentiation.[16]

Moreover, the current study also found that CDC42 was reduced at W4, and its expression at W4 displayed a positive linkage with the TNSS at W4. Meanwhile, the change of CDC42 from W0 to W4 exhibited a positive relation to the TNSS change from W0 to W4. A possible explanation might be that the allergic reaction and symptoms in AR patients were relieved after treatment.[28] Meanwhile, since CDC42 regulates allergic reactions[16,17] and reflects symptoms of AR (mentioned above), it was also reduced at W4. Thus, CDC42 change was also positively linked to TNSS change from W0 to W4.

There were some limitations in this study. Firstly, CDC42 was detected in the PBMCs of AR patients, while whether other sources of CDC42 could serve as a potential biomarker in AR should be further investigated. Secondly, the long-term variation of CDC42 in AR patients was not evaluated, which could be explored in the future. Thirdly, the clinical role of CDC42 in pediatric AR should be inquired about in the future. Fourthly, this was a single-center study, which could lead to regional bias; thus, our findings should be verified in other centers.

Collectively, CDC42 is elevated and positively correlates with symptom scores and Th2 cells, whose short-term reduction reflects symptom alleviation in AR patients.

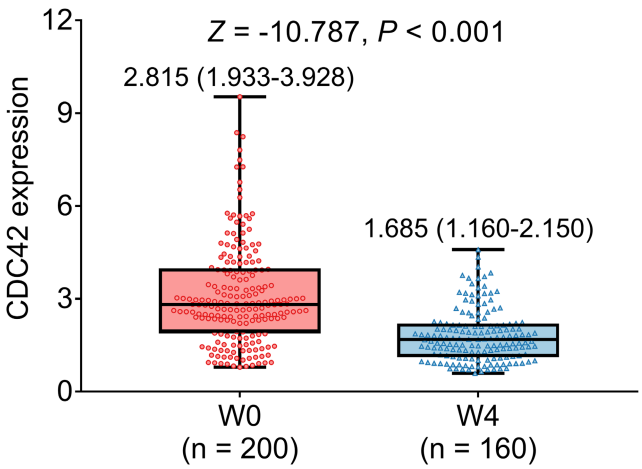


FIGURE 5 Comparison between CDC42 at W4 and at W0 in AR patients

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None.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

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

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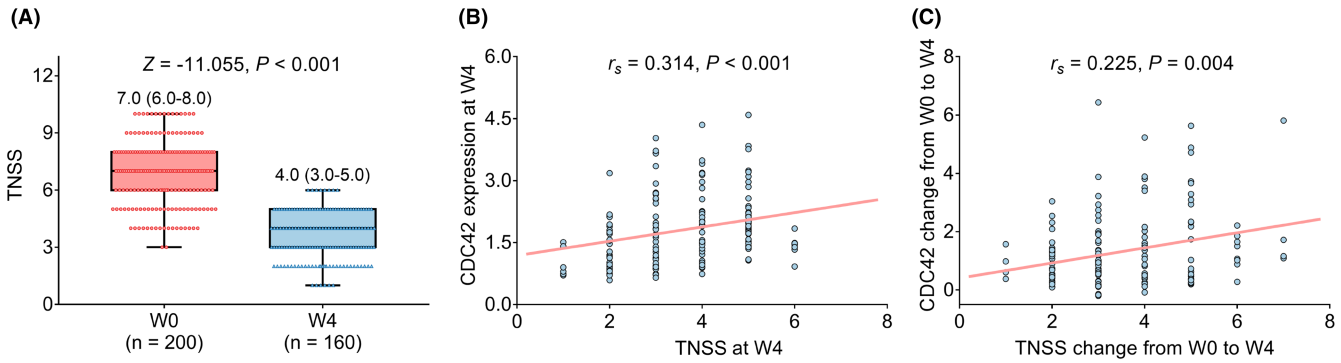

FIGURE 6 Linkage of CDC42 change with TNSS changes from W0 to W4 in AR patients. Comparison between TNSS at W4 and at W0 (A). Correlation of CDC42 at W4 with TNSS at W4 (B). Correlation of CDC42 change from W0 to W4 with TNSS change from W0 to W4 (C)

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