The correlation of long non-coding RNA NEAT1 and its targets microRNA (miR)-21, miR-124, and miR-125a with disease risk, severity, and inflammation of allergic rhinitis

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Abstract
The present study aimed to investigate the correlation of long non-coding RNA nuclear-enriched abundant transcript 1 (lncRNA NEAT1) with microRNA (miR)-21, miR-124, and miR-125a, and their associations with disease risk, severity, and inflammatory cytokines of allergic rhinitis (AR).

Totally 70 AR patients and 70 non-atopic obstructive snoring patients (as controls) were recruited. Inferior turbinate mucosa samples were collected from all participants for lncRNA NEAT1, its targets (miR-21, miR-124, and miR-125a), interleukin (IL)-4, IL-6, IL-10, and IL-17 detection via reverse transcription quantitative polymerase chain reaction. Disease severity of AR patients was assessed using individual nasal symptom score (INSS) and total nasal symptom score (TNSS).

LncRNA NEAT1 was upregulated, while miR-21, miR-124, and miR-125a were downregulated in AR patients compared with controls. Additionally, IncRNA NEAT1, miR-21, and miR-125a displayed good values in differentiating AR patients from controls, while miR-124 could only slightly differentiate AR patients from controls. In AR patients, IncRNA NEAT1 was negatively associated with miR-21 and miR-125a, but not miR-124. However, in controls, no correlation of IncRNA NEAT1 with miR-21, miR-124, or miR-125a was observed. Furthermore, in AR patients, IncRNA NEAT1 was positively, while miR-21 and miR-125a was negatively associated with INSS (rhinorrhea, itching, congestion scores), TNSS and inflammatory cytokines; however, correlation of miR-124 with INSS, TNSS, and inflammatory cytokines was slight.

LncRNA NEAT1 and its targets (miR-21 and miR-125a) present close correlations with disease risk, severity, and inflammation of AR, suggesting their potential as biomarkers for AR assessment.

Abbreviations: AR = Allergic rhinitis, AUC = area under the ROC curve, ceRNA = competing endogenous RNA, IgE = immunoglobulin E, IL-4 = interleukin 4, INSS = individual nasal symptom score, IQR = interquartile range, IncRNA NEAT1 = LncRNA nuclear-enriched abundant transcript 1, LncRNAs = Long non-coding RNAs, LPS = lipopolysaccharide, miR-124 = microRNA-124, ROC = Receiver-operating characteristic, SD = standard deviation, TLR4 = Toll-like receptor, TNSS = Total nasal symptom score.

Keywords: allergic rhinitis, disease severity, inflammation, long non-coding RNA NEAT1, microRNA-124, microRNA-125a, microRNA-21

1. Introduction
Allergic rhinitis (AR) is an allergic disease of the nasal mucosa characterized by paroxysmal repetitive sneezing, watery rhinorrhea, and nasal congestion. According to recent epidemiologic studies, the prevalence of AR presents a rising trend over the past few decades, affecting 10% to 40% of the population globally and causing major health-care burden worldwide.[2,3] Existing evidence reveals that the cause of AR is specific immunoglobulin E (IgE)-mediated inflammatory reactions against inhaled allergens, hence, AR management mainly includes allergen avoidance,
targeted pharmacotherapy, and allergen immunotherapy.\textsuperscript{[14,15]} However, AR symptom remission is unsatisfactory under current AR treatment and the disease reoccurrence of AR is still frequent, therefore, it is essential to conduct research to allow the understanding of AR pathology and discover novel biomarker for disease assessment and treatment guidance.

Long non-coding RNAs (lncRNAs) have been recognized to be involved in the transcription of inflammatory gene expressions, and emerge as critical regulators on the inflammatory and immune responses.\textsuperscript{[6,7]} LncRNA nuclear-enriched abundant transcript 1 (lncRNA NEAT1), as one of commonly investigated lncRNAs, is implicated in the activation of inflammasome activity, and promotes the production of chemokines in response of inflammatory-related stimuli, involving in diverse inflammatory-related diseases, such as sepsis, lupus, asthma.\textsuperscript{[8–10]} One clinical report exhibits that lncRNA NEAT1 expression is positively correlated with exacerbation risk, systematic inflammation level, and poor lung function via interaction with AR.\textsuperscript{[11–13]} There was no study related to the involvement of lncRNA NEAT1 and its potential targets (miR-21, miR-124, and miR-125a) in the pathology of AR.\textsuperscript{[11–13]} However, there was no study related to the involvement of lncRNA NEAT1 and its potential targets (miR-21, miR-124, and miR-125a) in the pathology of AR.

Therefore, we conducted the present study to investigate the correlation of lncRNA NEAT1 with miR-21, miR-124, and miR-125a, and their association with disease risk, severity and inflammatory of AR.

2. Methods

2.1. Patients and controls

Seventy AR patients who were treated in our hospital between January 2019 and November 2019 were consecutively enrolled in this study. All patients were required to meet the following inclusion criteria:

1. diagnosed as AR based on symptoms, duration of symptoms onset, skin prick test, serum IgE antibody test and aeroallergen nasal provocation test in accordance with Chinese Society of Allergy Guidelines for Diagnosis and Treatment of AR\textsuperscript{[15];}
2. age ≥ 18 years;
3. voluntary to participate in the present study and receive the collection of nasal mucosa tissue.

Patients were excluded from the study if they had bronchial asthma, chronic rhinosinusitis, nasal polyposis, nasal abnormalities or chronic obstructive pulmonary disease (COPD), nasal infection or other active infections, or solid tumor. Meanwhile, pregnant woman were also excluded. Besides, 70 non-atopic obstructive snoring patients were recruited as controls. All controls were required to have no history of AR, asthma, COPD, inflammatory or autoimmune disease and not concomitant with infections or solid tumors. The Institutional Review Board of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology approved the present study, and written informed consents were collected from all participants.

2.2. Data collection and AR severity assessment

Demographics of AR patients and controls were recorded after enrollment. Serum IgE antibody level of AR patients was also documented after diagnostic test via enzyme linked immunosorbent assay (ELISA), which was described in the following section. Disease severity of AR patients was assessed using individual nasal symptom score (INSS), which consisted of rhinorrhea score, sneezing score, itching score, and congestion score. Each symptom was scored according to severity, as follows: 0 = no symptom, 1 = mild symptom, 2 = moderate symptom, and 3 = severe symptom. Total nasal symptom score (TNSS) was the sum of rhinorrhea score, sneezing score, itching score, and congestion score, ranging from 0 to 12.

2.3. ELISA

The serum IgE antibody level was determined by ELISA with human Immunoglobulin E ELISA kit (IgE) (Abcam, ab83707, USA), which was ready-to-use, according to the instructions of manufacturer. In brief, firstly, samples or standards were added to the 96-well plate, followed by the antibody mix. After incubation, the wells were washed to remove unbound material. Tetramethylbenzidine (TMB) substrate was added, generating blue coloration. This reaction was then stopped by addition of Stop Solution completing any color change from blue to yellow. Signal was generated proportionally to the amount of bound analyte (Biotek, Winooski, VT) and the intensity was measured at 450 nm.

2.4. Sample collection and determination

Inferior turbinate mucosa of AR patients and controls were sampled under local anesthesia, then were washed using normal saline and cut into pieces. After that, the samples were immediately treated with RNAlater (Sigma–Aldrich, Burlington, MA) to stabilize and protect RNA with immediate RNase inactivation, then stored at −70°C for subsequent detection. The expressions of lncRNA NEAT1 and its target miRNAs including miR-21, miR-124, and miR-125a in samples were detected by reverse transcription quantitative polymerase chain reaction (RT-qPCR). In addition, the mRNA expressions of inflammatory cytokines including interleukin 4 (IL)-4, IL-6, IL-10, and IL-17 in turbinate mucosa were also determined by RT-qPCR as describe followed.

2.5. RT-qPCR assay

Total RNA was extracted from the sample with the use of TRIzol Reagent (Thermo Fisher Scientific, Waltham, MA). Then, cDNAs from each sample were synthesized with iScript cDNA Synthesis Kit (Bio-Rad, Hercules, CA) and were subjected to qPCR with THUNDERBIRD SYBR qPCR Mix (Toyobo, Osaka, Kansai, Japan). The instrument used for real-time quantitative Polymerase Chain Reaction (RT-qPCR) assay was the CFX-96 real-time PCR system (Bio-Rad, Hercules, CA). The detailed thermocycling conditions were as follows: initial denaturation at 95°C for 1 min,
followed by denaturation at 95°C for 15 s and 40 cycles of 30 s at 61°C. After that, the expressions of IncRNA NEAT1, miR-21, miR-124, miR-125a, IL-4, IL-6, IL-10, and IL-17 were calculated using the 2−ΔΔCt methods. GAPDH was used as internal reference for IncRNA and mRNA, and U6 for miRNA. The primers used in RT-qPCR were listed in Table 1. The specificity of each primer was confirmed by melting curve analysis, which revealed single peak melting curve, implying uncompromised specificity.

### 2.6. Statistical analysis

Quantitative data were described as mean with standard deviation (SD), or median with interquartile range (IQR). Qualitative data were described as count (percentage). Comparison of quantitative data between AR patients and controls was determined by Student’s t test or Wilcoxon rank-sum test, and correlation of qualitative data between AR patients and controls was determined by Chi-Square test. Receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to assess the ability of variables in discriminating AR patients from controls. All statistical analyses were performed with the use of SPSS 24.0 software (IBM, Chicago, IL), and figures were plotted using GraphPad Prism 8.01 software (GraphPad Software, La Jolla, CA). A two-side P value < .05 was considered as statistically significant.

### 3. Results

#### 3.1. Comparison of clinical characteristics between AR patients and controls

The mean age of AR patients and controls were 26.9±5.3 years and 28.0±6.9 years, respectively (Table 2). Furthermore, there were 31 (44.3%) males and 39 (55.7%) females in AR patients, and there were 32 (45.7%) males and 38 (54.3%) females in controls. No difference of age (P=.318) or gender (P=.865) was observed between AR patients and controls. In addition, the level of serum IgE (P<.001), mucosa IL-4 (P<.001), mucosa IL-6 (P<.001), and mucosa IL-17 (P<.001) were higher, but the level of mucosa IL-10 (P<.001) was lower in AR patients compared with controls (Supplementary Figure 1, http://links.lww.com/MD/F434). Additionally, in AR patients, as for INSS, the rhinorrhea, itching, sneezing and congestion scores were 1.9±0.7, 1.8±0.5, 2.2±0.7, and 2.0±0.7, respectively; meanwhile, the TNSS was 7.9±1.6. The detailed information of clinical characteristics between AR patients and controls was displayed in Table 2.

#### 3.2. Correlation of IncRNA NEAT1 and its target miRNA expressions with AR risk

IncRNA NEAT1 relative expression was increased in AR patients (2.595 [1.839–3.038]) compared with controls (1.018 [0.657–1.337]) (P<.001) (Fig. 1A), while miR-21 (0.306 [0.192–0.530] vs. 1.019 [0.705–1.440]) (P<.001) (Fig. 1B), miR-124 (0.714 [0.486–1.074] vs. 0.992 [0.566–1.510]) (P=.016) (Fig. 1C), and miR-125a (0.361 [0.187–0.565] vs. 0.998 [0.634–1.213]) (P<.001) (Fig. 1D) relative expressions were decreased in AR patients compared with controls. Further ROC curves indicated that IncRNA NEAT1 (AUC: 0.907, 95%CI: 0.857–0.956) and miR-21 (AUC: 0.903, 95%CI: 0.854–0.953) were of remarkably good values in differentiating AR patients from controls, and miR-125a (AUC: 0.863, 95%CI: 0.803–0.923) presented a good value in distinguishing AR patients from controls, while miR-124 could only slightly differentiate AR patients from controls (AUC: 0.618, 95%CI: 0.525–0.711) (Fig. 1E). These implied that IncRNA NEAT1, miR-21, and miR-125a expressions were closely associated with AR risk.

### Table 1

| Gene Forward (5′→3′) | Reverse (5′→3′) |
|---------------------|----------------|
| LncRNA NEAT1        | AGAGGAGACAGTTCTCGAG |
| miR-21-5p           | TGGCTGAGTGGGCAATTC |
| miR-124-5p          | TGTTGGATGTCCCTTGTTG |
| miR-125a-5p         | CCGCATCTGAGCAGTTCTG |
| IL-4                | CTCAGGACGCTTCGGCAG |
| IL-6                | GCCTGCTTCACCACCTTCTTGA |
| IL-10               | TGTGACCCAGTCCATGCCATC |
| IL-17               | TCACGGACACCAGTATCTTCTC |
| GAPDH               | TCGCTGTCGTCCTGTCG |
| U6                  | TGTCGTGGAGTCGGCAATTC |

### Table 2

| Characteristics of AR patients and controls. | Controls (N = 70) | AR patients (N = 70) | P |
|---------------------------------------------|------------------|---------------------|---|
| Age (years), mean±SD                        | 28.0±6.9         | 26.9±5.3            | .318 |
| Gender, No. (%)                             |                   |                     | .865 |
| Male                                        | 32 (45.7)        | 31 (44.3)           | .618 |
| Female                                      | 38 (54.3)        | 39 (55.7)           | .318 |
| Serum IgE (IU/mL), median (IQR)             | 22.0 (15.2–33.4) | 290.3 (169.5–496.8) | .001 |
| IL-4 mRNA, median (IQR)                     | 0.997 (0.592–1.571) | 3.394 (2.005–4.368) | .001 |
| IL-6 mRNA, median (IQR)                     | 0.987 (0.572–1.226) | 2.506 (1.392–3.351) | .001 |
| IL-10 mRNA, median (IQR)                    | 0.935 (0.496–1.408) | 0.420 (0.255–0.659) | .001 |
| IL-17 mRNA, median (IQR)                    | 0.960 (0.518–1.337) | 3.621 (2.253–4.931) | .001 |
| INSS, mean±SD                               |                   |                     | .001 |
| Rhinorrhea score                            | –                 | 1.9±0.7             | –   |
| Itching score                               | –                 | 1.8±0.5             | –   |
| Sneezing score                              | –                 | 2.2±0.7             | –   |
| Congestion score                            | –                 | 2.0±0.7             | –   |
| TNSS, mean±SD                               | 7.9±1.6           |                     | .001 |

AR = allergic rhinitis, IgE = immunoglobulin E, L = interleukin, INSS = individual nasal symptom score, IQR = interquartile range, SD = standard deviation, TNSS = total nasal symptom score.
3.3. Correlation of IncRNA NEAT1 with its target miRNA expressions in AR patients and controls

In AR patients, IncRNA NEAT1 relative expression was negatively associated with miR-21 ($r = -0.468$, $P < .001$) (Fig. 2A) and miR-125a ($r = -0.517$, $P < .001$) relative expressions (Fig. 2C), while was not correlated with miR-124 relative expression ($r = -0.172$, $P = .155$) (Fig. 2B). In controls, no association of IncRNA NEAT1 relative expression with miR-21 ($P = .711$) (Fig. 2D), miR-124 ($P = .263$) (Fig. 2E) or miR-125a ($P = .512$) (Fig. 2F) relative expression was observed.

Figure 1. IncRNA NEAT1, miR-21, miR-124, and miR-125a were dysregulated in AR patients compared with controls. Comparison of IncRNA NEAT1 (A), miR-21 (B), miR-124 (C), miR-125a (D) relative expressions between AR patients and controls. The performance of IncRNA NEAT1, miR-21, miR-124, and miR-125a in differentiating AR patients from controls (E). AR = allergic rhinitis, AUC = area under curve, CI = confidence interval, IncRNA NEAT1 = long non-coding RNA nuclear-enriched abundant transcript 1, miR = microRNA.

Figure 2. IncRNA NEAT1 was negatively correlated with miR-21 and miR-125a but not miR-124 in AR patients. Correlation of IncRNA NEAT1 with miR-21 (A), miR-124 (B), miR-125a (C) in AR patients. Correlation of IncRNA NEAT1 with miR-21 (D), miR-124 (E), miR-125a (F) in controls. AR = allergic rhinitis, IncRNA NEAT1 = long non-coding RNA nuclear-enriched abundant transcript 1, miR = microRNA.
3.4. Correlation of lncRNA NEAT1 with disease severity in AR patients

In AR patients, lncRNA NEAT1 relative expression was positively correlated with rhinorrhea score ($r = 0.297$, $P = .013$) (Fig. 3A), itching score ($r = 0.313$, $P = .008$) (Fig. 3B), congestion score ($r = 0.267$, $P = .025$) (Fig. 3D) and TNSS ($r = 0.458$, $P < .001$) (Fig. 3E), but was not correlated with sneezing score ($r = 0.223$, $P = .063$) (Fig. 3C). These results revealed that lncRNA NEAT1 was positively correlated with disease severity.

3.5. Correlation of miR-21, miR-124, and miR-125a with disease severity in AR patients

In AR patients, miR-21 relative expression was negatively correlated with rhinorrhea score ($r = -0.341$, $P = .004$), sneezing score ($r = -0.259$, $P = .031$), congestion score ($r = -0.315$, $P = .008$), TNSS ($r = -0.457$, $P < .001$) (Table 3). Furthermore, miR-124 relative expression was negatively correlated with rhinorrhea score ($r = -0.250$, $P = .037$) and TNSS ($r = -0.285$, $P = .017$). In addition, miR-125a relative expression was...
negatively correlated with rhinorrhea score \( (r = -0.252, P = 0.035) \), itching score \( (r = -0.235, P = 0.050) \), sneezing score \( (r = -0.236, P = 0.049) \), congestion score \( (r = -0.385, P = 0.001) \), and TNSS \( (r = -0.469, P < 0.001) \). The detailed information was disclosed in Table 3. These suggested that miR-21 and miR-125a expressions were closely associated with disease severity, while the association of miR-124 with disease severity was slight with low correlation coefficient.

3.6. Correlation of lncRNA NEAT1 and its target miRNAs with inflammation in AR patients

In AR patients, lncRNA NEAT1 was positively correlated with mucosa IL-4 \( (r = 0.412, P < 0.001) \), IL-17 \( (r = 0.382, P = 0.001) \), but negatively correlated with mucosa IL-10 \( (r = -0.268, P = 0.025) \) (Table 4). Furthermore, miR-21 was negatively associated with mucosa IL-4 \( (r = -0.382, P = 0.001) \), IL-6 \( (r = -0.304, P = 0.011) \), IL-17 \( (r = -0.344, P = 0.004) \), while positively correlated with mucosa IL-10 \( (r = 0.310, P = 0.009) \). Meanwhile, miR-124 was only negatively correlated with mucosa IL-4 \( (r = -0.249, P = 0.038) \). Moreover, miR-125a was negatively correlated with mucosa IL-4 \( (r = -0.304, P = 0.010) \), mucosa IL-6 \( (r = -0.257, P = 0.032) \), but was positively associated with mucosa IL-10 \( (r = 0.276, P = 0.021) \). These results implied that lncRNA NEAT1, miR-21, and miR-125a expressions were closely correlated with inflammation, while correlation of miR-124 with inflammation was slight with low correlation coefficient.

4. Discussion

In our present study, we found that

1. lncRNA NEAT1 might promote the production and activation of several inflammasomes (such as NLRP3) in macrophages, which promoted excessive caspase-1-mediated secretion of proinflammatory cytokines and pyroptosis, contributing to allergic inflammatory processes for the initiation of AR.\([16,24]\)

2. Additionally, lncRNA NEAT1 might serve as a ceRNA by targeting miR-21 in upregulating TGFBR2 expression, further enhancing IgE production and thus promoting onset as well as development of AR.\([16,24]\)

3. Furthermore, according to the previous study, miR-125a overexpression diminishes M1 pro-inflammatory phenotype expressions but promotes M2 anti-inflammatory marker expressions, inactivating allergic inflammatory responses.\([25]\)

   Given the existing evidence, we speculated that lncRNA NEAT1 might contribute to activation of inflammatory responses, thereby enhanced the disease risk of AR via interaction with miR-125a.

4. Meanwhile, the unobvious effect of miR-124 in differentiating AR patients from controls was consistent with the prior founding in our study that the difference of miR-124 between AR and controls was not as significant as miR-21 and miR125a. This might be explained by the bidirectional regulation effects of miR-124 in inflammatory response.\([26]\)

Subsequently, we further validated that lncRNA NEAT1 expression was negatively correlated with miR-21 and miR-125a but not miR-124 in AR patients. The possible reasons might be:

1. Due to the existence of allergic inflammation response in AR patients, the level of lncRNA NEAT1 was increased and the levels of miR-21 and miR-125a were decreased, therefore, the correlation of lncRNA NEAT1 with its targets was enhanced in AR patients.

2. Meanwhile, the bidirectional regulation effects of miR-124 in inflammatory response could explain the lack of correlation with lncRNA NEAT1 in AR patients.\([26]\)
In addition, results displayed that high lncRNA NEAT1 but low miR-21 and miR-125a expressions were correlated with increased disease severity and inflammation in AR patients. This might be attributable to the following reasons:

1. LncRNA NEAT1 might aggravate the IgE allergic inflammatory response by increasing the pro-inflammatory cytokine level via inhibiting anti-inflammatory effect of miR-21 and miR-125a in the upper respiratory tract, leading to advanced disease severity in AR patients.

2. Furthermore, the cascade of lncRNA NEAT1-induced NF-κB pathway was set to be motion, leading to release of preformed bioactive mediators (such as histamine), and newly formed lipid mediators (such as leukotrienes) and further causing smooth muscle contraction, enhanced vascular permeability and mucus secretion, which contributed the higher inflammation and severity of AR.

Some limitations exist in the present study.

1. First, this study was a single-center study with a relatively small sample size, which might lead to insufficient statistical power and selection bias.

2. Secondly, lncRNA NEAT1 was speculated to be involved in the allergic inflammation response of AR via targeting miR-21 and miR-125a, whereas the detailed molecular mechanisms needed further exploration.

3. Thirdly, the study did not evaluate the correlation of lncRNA NEAT1 and its targets (miR-21, miR-124, miR-125a) with AR reoccurrence, therefore, further study with long-term observation was needed.

4. Inferior turbinate mucosa samples were collected for mRNA detection of inflammatory cytokines via RT-qPCR, and except for RT-qPCR, immunohistochemistry assay and western blot assay were needed for further protein detection of these inflammatory cytokines in the future.

5. Conclusion

In conclusion, lncRNA NEAT1 correlates with increased disease risk, severity, and inflammation of AR, and its targets miR-21 and miR-125a exhibit opposite trends, suggesting their potential as biomarkers for AR assessment.

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