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Long non-coding RNA antisense non-coding RNA in the INK4 locus expression correlates with increased disease risk, severity, and inflammation of allergic rhinitis

Xiaoqiong Qian, MD, Song Shi, MD, Guijuan Zhang, MD*

Abstract

The aim of the current study was to investigate the expression of long non-coding RNA (lncRNA) antisense non-coding RNA in the INK4 locus (ANRIL) in allergic rhinitis (AR) patients, and to further explore the association of lncRNA ANRIL expression with AR risk, severity, and inflammation.

In this case-control study, 96 AR patients and 96 non-atopic obstructive snoring patients who underwent adenoid surgery were consecutively recruited. Disease severity of AR patients was assessed via individual nasal symptom score (INSS) and total nasal symptom score (TNSS). Nasal mucosa samples were collected from AR patients and controls, then lncRNA ANRIL and inflammatory cytokine levels were assessed via quantitative polymerase chain reaction.

LncRNA ANRIL expression was increased in AR patients (3.605 [1.763–4.981]) compared with controls (1.183 [0.438–2.985]), and it well distinguished AR patients from controls with an area under curve of 0.746 (95% CI: 0.679–0.814). Correlation analyses revealed that lncRNA ANRIL expression was positively associated with itching score and congestion score, while it was not associated with nasal rhinorrhea score or sneezing score. Besides, lncRNA ANRIL was also positively correlated with TNSS, tumor necrosis factor α, interleukin (IL)-4, IL-6, IL-13, and IL-17, while negatively associated with IL-10 and interferon-γ. And no association of lncRNA ANRIL expression with IL-1β, IL-5, or IL-8 expression was discovered.

LncRNA ANRIL expression correlates with increased AR risk, severity, and inflammation, implying that lncRNA ANRIL might be involved in the pathogenesis of AR.

Abbreviations: ANRIL = antisense non-coding RNA in the INK4 locus, AR = allergic rhinitis, ARIA = allergic rhinitis and its impact on asthma, AUC = area under curve, CAD = cardiovascular diseases, COPD = chronic obstructive pulmonary disease, COX-2 = cyclooxygenase-2, ECs = endothelial cells, GAPDH = phosphoglyceraldehyde dehydrogenase, HCAECs = human coronary artery endothelial cells, HUVECs = human umbilical vein endothelial cells, ICAM-1 = intercellular adhesion molecule 1, IFN = interferon, IgE = immunoglobulin E, IL = interleukin, iNOS = inducible nitric oxide synthases, INSS = individual nasal symptom score, lncRNA = long non-coding RNA, NCs = normal controls, NF-κB = NF-kappa B, ROC = receiver-operating characteristic, SLE = systemic lupus erythematosus, SLEDAI = systemic lupus erythematosus disease activity index, SLICC = systemic lupus international collaborating clinics, TNF = tumor necrosis factor, VCAM-1 = vascular cell adhesion molecule 1, YY1 = Yin Yang 1.

Keywords: allergic rhinitis, disease severity, inflammation, long non-coding RNA antisense non-coding RNA in the INK4 locus, nasal mucosa

1. Introduction

Allergic rhinitis (AR), characterized by nasal rhinorrhea, itching, sneezing, and congestion, is a common disorder of nose that affects approximately 8% of the American population and 17.6% of Chinese adult population.[1,2] AR is induced by inflammatory responses of immune system to allergens, during which several inflammatory cells (such as mast cells, basophils, T cells, and eosinophils) are activated and various inflammatory mediators (including interleukin [IL]-3, IL-4, IL-5, IL-1β, and tumor necrosis factor [TNF]-α) are released, contributing to the increased inflammation of AR.[1–3]

Long non-coding RNA (lncRNA) refers to a class of RNAs with >200 nucleotides while without open reading frame.[4,5] Accumulating studies reveal that lncRNA is implicated in pathological processes of various diseases, including AR.[6,7] In a recent study, 150 dysregulated lncRNAs are identified in mice model of AR compared with normal controls (NCs), and further analysis reveals that FR022494, FR255904, and FR169472 are significantly upregulated while FR288904, FR285768, and

Editor: Abdelouahab Bellou.

XQ and SS have contributed equally to this work.

This study was supported by a scientific research fund at Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine, the ID of the fund was TRYJ201602.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Department of ENT, Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine, China.

* Correspondence: Guijuan Zhang, Department of ENT, Tongren Hospital, Shanghai JiaoTong University School of Medicine, No. 1111, Xianxia Road, Shanghai 200336, China (e-mail: zgj_zhanguijuan@163.com).

Medicine (2019) 98:20(e15247)

Received: 24 October 2018 / Received in final form: 1 March 2019 / Accepted: 19 March 2019

http://dx.doi.org/10.1097/MD.0000000000015247

FR301516 are significantly downregulated in mice model of AR.[7] Another study discovered 1033 upregulated lncRNAs and 1226 downregulated lncRNAs in AR patients compared with NCs by microarray, and these dysregulated lncRNAs are mostly enriched in positive regulation of interleukin-13 secretion, Fc epsilon RI signaling pathway, and NF-kappa B (NF-κB) signaling pathway.[6] Despite these findings, no specific lncRNA is reported to be associated with AR inflammatory responses until now.

Antisense non-coding RNA in the INK4 locus (ANRIL), also known as lncRNA ANRIL, is one of the earliest discovered lncRNAs.[8] It is observed to be involved in inflammatory activities of several diseases, such as atherosclerotic systemic lupus erythematosus (SLE), cardiovascular diseases (CAD), and so on.[9–12] For example, lncRNA ANRIL expression is increased in atherosclerotic SLE patients compared with controls and positively correlates with disease activity and inflammation of atherosclerotic SLE patients.[12] More interestingly, lncRNA ANRIL is observed to promote inflammatory cytokine release in human coronary artery endothelial cells (HCAECs) through mediating NF-κB signaling pathway, and its expression is negatively correlated with cumulative survival of CAD patients.[13] Since AR was also an inflammation-mediated disease, we hypothesized that lncRNA ANRIL was engaged in inflammatory activities of AR as well. Therefore, we conducted the current study to investigate the expression of lncRNA ANRIL in AR patients, and more importantly, to explore the association of lncRNA ANRIL expression with AR risk, severity, and inflammation.

2. Materials and methods

2.1. Participants

From July 2016 to June 2017, 96 AR patients treated at Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine were consecutively recruited in this case-control study. The inclusion criteria were as follows: diagnosed as AR by medical history, symptoms, and skin prick test according to the criteria of the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline (version 2010)[14]; agreed to collect nasal mucosa tissue for study. Following patients were excluded: patients with bronchial asthma, chronic rhinosinusitis, nasal polyposis, excessive septal deviation, nasal abnormalities, or chronic obstructive pulmonary disease (COPD); patients with concurrent purulent nasal infection or other active infections; current smokers; patients who received anti-histamines within 10 days before enrollment; patients who were treated with systemic or topical corticosteroids within 4 weeks before enrollment; patients with history of autoimmune disease, hematological malignancies, or solid tumor; pregnant woman. In addition, a total of 96 non-atopic obstructive snoring patients who underwent adenoid surgery at Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine were recruited as controls, and the exclusion criteria were: a history of asthma, COPD, inflammatory or autoimmune disease, concurrent severe infections or malignancies.

2.2. Ethics statement

This study was approved by the Institutional Review Board of Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine, and written informed consents were obtained from all participants before enrollment.

2.3. Evaluation of AR severity

Disease severity of AR patients was assessed by individual nasal symptom score (INSS), which included rhinorrhea, sneezing, nasal itching and congestion, and each item was scored as 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. Subsequently total nasal symptom score (TNSS) was calculated by summing the scores of rhinorrhea, sneezing, nasal itching, and congestion.

2.4. Determination of lncRNA ANRIL and mRNAs of inflammatory cytokines

Nasal mucosa samples were collected from AR patients and controls after enrollment, and then total RNA was extracted from the sample with the use of Trizol Reagent (Invitrogen, USA) according to the manufacturer's instructions. NanoDrop 2000 (Thermo Fisher Scientific, USA) was utilized to exam the concentration, purity, and integrity of RNA. Then cDNAs from each sample were synthesized with iScript cDNA Synthesis Kit (Bio-Rad, USA) and were subjected to qPCR with DyNAmo Flash SYBR Green qPCR Kit (Thermo Fisher Scientific, USA). The PCR amplification procedures were as follows: 94 °C for 4 minutes, followed by 40 cycles of 94 °C for 10 seconds then 60 °C for 30 seconds. After that, the expressions of lncRNA ANRIL and mRNAs of inflammatory cytokines were calculated using the $2^{-\Delta\Delta Ct}$ methods with phosphoglyceraldehyde dehydrogenase (GAPDH) as internal reference. The primers used in the study were shown in Table 1.

Table 1

Primers used in the study.

Gene	Species	Forward (5′–>3′)	Reverse (5′–>3′)
LncRNA ANRIL	Human	TGCTCTATCCGCCAATCAGG	GGGCCTCAGTGGCACATACC
TNF-α	Human	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
IL-1β	Human	ATCTGTACCTGTCCTGCGTGTTG	TTCTGCTTGAGAGGTGCTGATGT
IL-4	Human	AGCAGTTCCACAGGCACAAG	CTCTGGTTGGCTTCCTTCACA
IL-5	Human	GATAGCCAATGAGACTCTGAGGATT	TTGACTCTCCAGTGTGCCTATTC
IL-6	Human	GGTACATCCTCGACGGCATCTC	GCTCTGGCTTGTTCCTCACTACT
IL-8	Human	CTCTTGGCAGCCTTCCTGATTTCT	CGCAGTGTGGTCCACTCTCAAT
IL-10	Human	CTCTGTTGCCTGGTCCTCCT	CGCCTTGATGTCTGGGTCTTG
IL-13	Human	CCACGGTCATTGCTCTCACTT	GCTGTCAGGTTGATGCTCCATA
IL-17	Human	TTACTACAACCGATCCACCTCAC	CCACGGACACCAGTATCTTCTC
IFN-γ	Human	TGGAGACCATCAAGGAAGACAT	GCGACAGTTCAGCCATCAC
GAPDH	Human	GGAGCGAGATCCCTCCAAAAT	GGCTGTTGTCATACTTCTCATGG

ANRIL = antisense non-coding RNA in the INK4 locus, GAPDH = phosphoglyceraldehyde dehydrogenase, IFN = interferon, IL = interleukin, lncRNA = long non-coding RNA, TNF = tumor necrosis factor.

Table 2

Characteristics of AR patients.

Characteristics	AR patients (N = 96)
Age, y	23.7 ± 7.4
Gender (n/%)	
Male	48 (50.0)
Female	48 (50.0)
INSS	
Nasal rhinorrhea	1.9 ± 0.7
Itching	1.9 ± 0.6
Sneezing	2.3 ± 0.7
Congestion	2.0 ± 0.7
TNSS	8.0 ± 1.6
TNF-α mRNA	2.237 (1.364–3.086)
IL-1β mRNA	2.769 (1.504–4.227)
IL-4 mRNA	1.737 (0.807–3.047)
IL-5 mRNA	1.309 (0.690–2.453)
IL-6 mRNA	1.745 (0.965–2.506)
IL-8 mRNA	2.237 (1.359–3.540)
IL-10 mRNA	1.985 (1.208–3.878)
IL-13 mRNA	1.319 (0.707–2.468)
IL-17 mRNA	2.417 (1.557–3.443)
IFN-γ mRNA	1.870 (0.991–3.618)

Data were presented as mean value ± standard deviation, count (percentage) or median (25th–75th quantiles).

AR = allergic rhinitis, IL = interleukin, INSS = individual nasal symptom score, TNF = tumor necrosis factor, TNSS = total nasal symptom score.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (SPSS, Chicago, IL) and GraphPad Prism 7.00 (GraphPad Software, La Jolla, CA). Data were depicted as mean ± standard deviation, median (25th–75th quantiles), or count (percentage). Comparison of the lncRNA ANRIL relative expression between AR patients and controls was determined by Wilcoxon rank-sum test, and correlation analyses were performed with the use of Kruskal-Wallis H rank sum test or Spearman test. Receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to assess the ability of lncRNA ANRIL relative expression to discriminate between AR patients and controls. P value $<.05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

Among the 96 AR patients, 48 (50.0%) were men while 48 (50.0%) were women, and mean age was 23.7 ± 7.4 years. Nasal rhinorrhea score, itching score, sneezing score, congestion score, and TNSS were 1.9 ± 0.7, 1.9 ± 0.6, 2.3 ± 0.7, 2.0 ± 0.7, and 8.0 ± 1.6, respectively. Besides, mRNA expressions of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17, and IFN-γ were 2.237 (1.364–3.086), 2.769 (1.504–4.227), 1.737 (0.807–3.047), 1.309 (0.690–2.453), 1.745 (0.965–2.506), 2.237 (1.359–3.540), 1.985 (1.208–3.878), 1.319 (0.707–2.468), 2.417 (1.557–3.443), and 1.870 (0.991–3.618), respectively (Table 2). As to controls, there were 42 (43.8%) men and 54 (56.2%) women, and mean age was 24.8 ± 7.9 years. No difference in sex ($P = .386$) or age ($P = .321$) was observed between AR patients and controls.

3.2. Comparison of lncRNA ANRIL expression between AR patients and controls

Wilcoxon rank-sum test was used to compare the lncRNA ANRIL expressions between AR patients and controls, which showed that lncRNA ANRIL expression was increased in AR patients (3.605 [1.763–4.981]) compared with controls (1.183 [0.438–2.985], $P < 0.001$, Fig. 1A). Subsequently, ROC curve revealed that lncRNA ANRIL well discriminated AR patients from controls with an AUC of 0.746 (95% CI: 0.679–0.814), and the sensitivity and specificity were 81.3% and 56.3% at best cut-off point (expression of lncRNA ANRIL was 1.459), where the value of sensitivity plus specificity was the largest (Fig. 1B). These data revealed that lncRNA ANRIL might be involved in the development of AR.

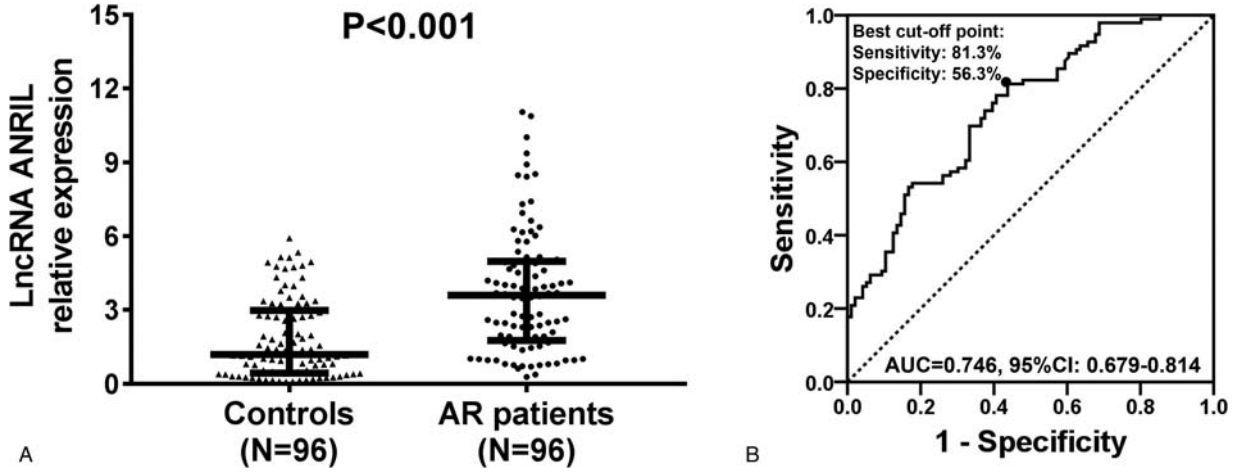

Figure 1. LncRNA ANRIL expressions between AR patients and controls. LncRNA ANRIL expression in AR patients was elevated compared with controls (A) and it discriminated AR patients from controls with an AUC of 0.746 (95% CI: 0.679–0.814) (B). Comparison between 2 groups was determined by Wilcoxon rank sum test, ROC curve was used to assess the ability of lncRNA ANRIL expression to discriminate between AR patients and controls. $P < .05$ was considered significant. ANRIL = antisense non-coding RNA in the INK4 locus, AR = allergic rhinitis, AUC = area under curve, lncRNA = long non-coding RNA, ROC = receiver-operating characteristic.

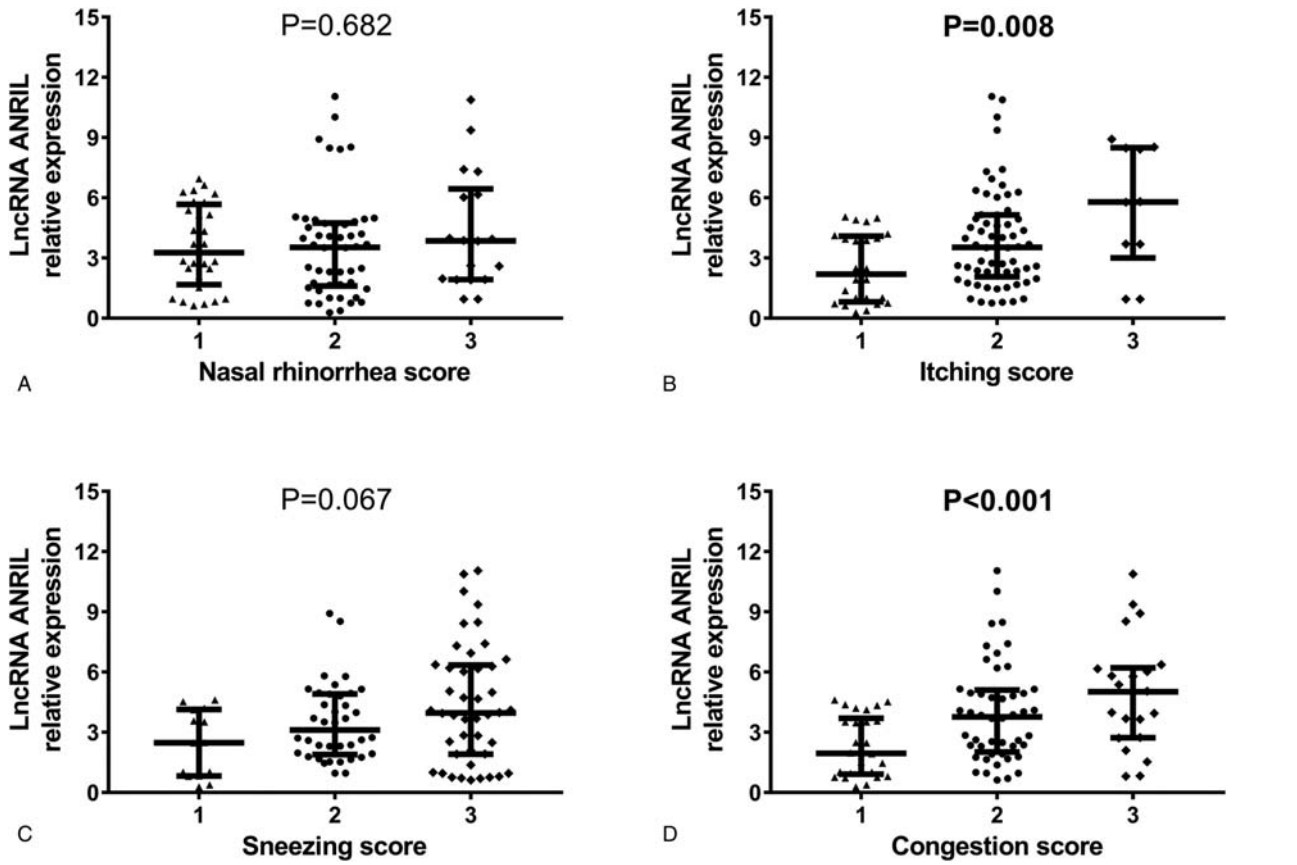

Figure 2. Association of lncRNA ANRIL expression with INSS scores. No correlation of lncRNA ANRIL expression with nasal rhinorrhea score (A) or sneezing score (C) was observed, whereas lncRNA ANRIL expression was positively correlated with itching score (B) and congestion score (D). Correlation analysis of lncRNA ANRIL with INSS was performed with the use of Kruskal-Wallis H rank sum test, $P < .05$ was considered significant. ANRIL = antisense non-coding RNA in the INK4 locus, INSS = individual nasal symptom score, lncRNA = long non-coding RNA.

3.3. Correlation of lncRNA ANRIL expression with INSS and TNSS scores

In order to assess the correlation of lncRNA ANRIL expression with disease severity of AR, Kruskal-Wallis H rank sum test was utilized (Fig. 2A–D). The data revealed that lncRNA ANRIL expression was positively associated with itching score ($P = .008$, Fig. 2B) and congestion score ($P < .001$, Fig. 2D), while not correlated with nasal rhinorrhea score ($P = .682$, Fig. 2A) or sneezing score ($P = .067$, Fig. 2C). As for association of lncRNA ANRIL with TNSS score, Spearman test disclosed that lncRNA ANRIL was positively correlated with TNSS score ($P < .001$, Fig. 3). These analyses indicated that lncRNA ANRIL might be implicated in the progression of AR, http://links.lww.com/MD/C962.

3.4. Association of lncRNA ANRIL expression with mRNA expressions of inflammatory cytokines

lncRNA ANRIL expression was positively correlated with TNF-α ($P = .004$, Fig. 4A), IL-4 ($P = .026$, Fig. 4C), IL-6 ($P = .016$, Fig. 4E), IL-13 ($P = .039$, Fig. 4H), and IL-17 ($P = .003$, Fig. 4I), while negatively associated with IL-10 ($P = .012$, Fig. 4G) and IFN-γ ($P = .012$, Fig. 4J). Besides, no association of lncRNA ANRIL expression with mRNA expressions of IL-1β ($P = .193$, Fig. 4B), IL-5 ($P = .133$, Fig. 4D), or IL-8 ($P = .257$, Fig. 4F) was discovered. Therefore, lncRNA ANRIL might be engaged in inflammation regulation of AR.

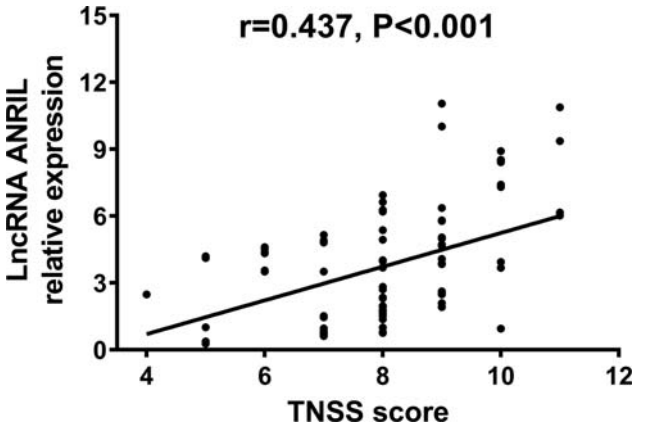

Figure 3. Correlation of lncRNA ANRIL expression with TNSS score. LncRNA ANRIL was positively associated with TNSS score. Correlation analysis of lncRNA ANRIL with TNSS score was performed by Spearman test, $P < .05$ was considered significant. ANRIL = antisense non-coding RNA in the INK4 locus, lncRNA = long non-coding RNA, TNSS = total nasal symptom score.

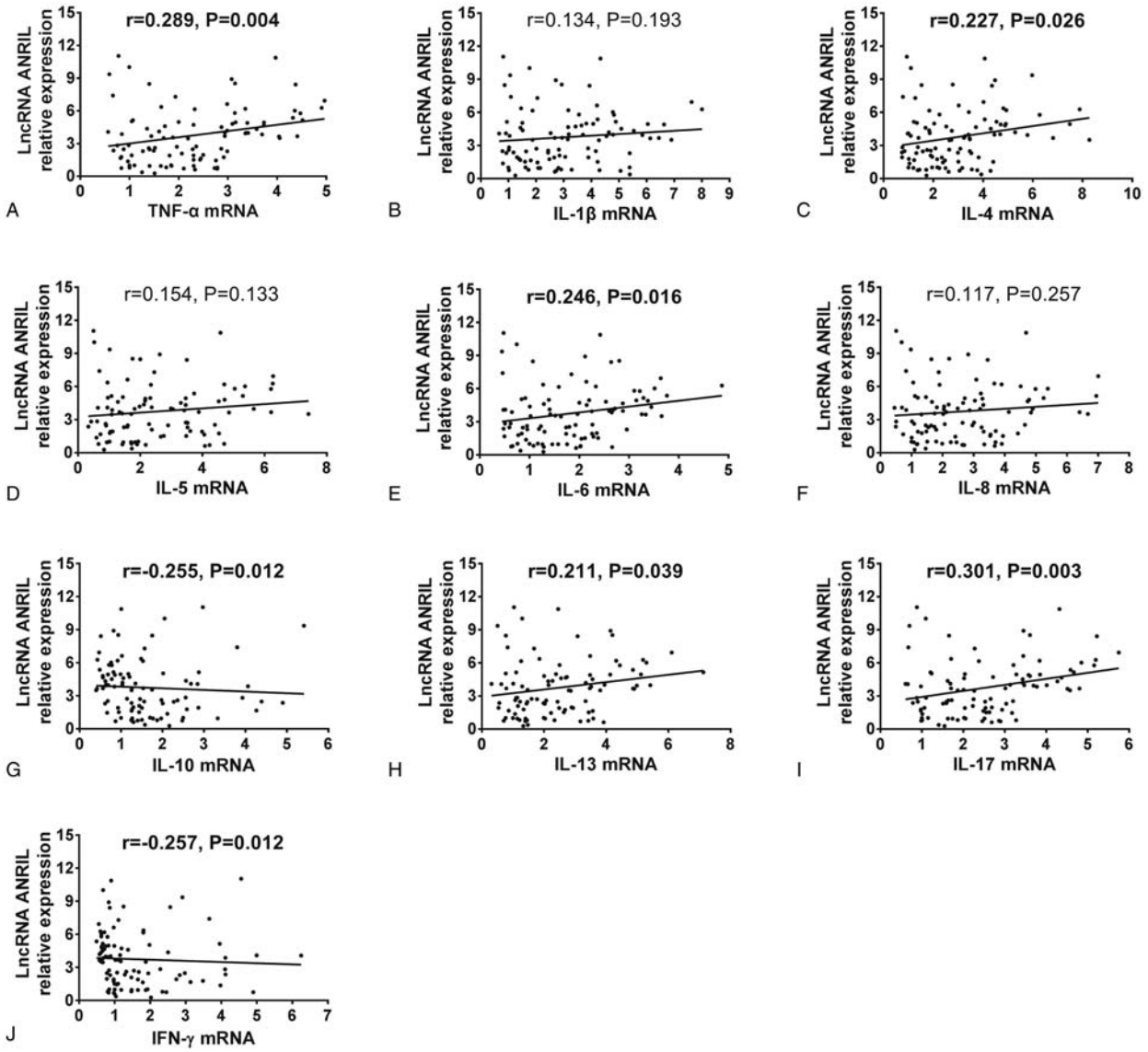

Figure 4. Association of lncRNA ANRIL expression with inflammatory cytokine expressions. lncRNA ANRIL expression was positively associated with TNF-α (A), IL-4 (C), IL-6 (E), IL-13 (H), and IL-17 (I) expressions, but negatively associated with IL-10 (G) and IFN-γ (J) expressions. No correlation of lncRNA ANRIL expression with IL-1β (B), IL-5 (D), or IL-8 (F) expression was found. Correlation analysis of lncRNA ANRIL with inflammatory cytokine expressions was performed by Spearman test, $P < .05$ was considered significant. ANRIL = antisense non-coding RNA in the INK4 locus, IFN = interferon, IL = interleukin, lncRNA = long non-coding RNA, TNF = tumor necrosis factor.

4. Discussion

In the current study, we found that lncRNA ANRIL was upregulated in AR patients compared with controls, and it was positively associated with itching, congestion, and TNSS scores, implying its positive correlation with AR risk and severity; lncRNA ANRIL expression was also correlated with increased TNF-α, IL-4, IL-6, IL-13, and IL-17, while decreased IL-10 and IFN-γ mRNA expressions, suggesting that it was associated with elevated inflammation.

AR patients often complicate with a couple of diseases such as bronchial asthma, allergic conjunctivitis and upper airway cough syndrome, which not only decrease patients' working performance and social functioning, but also induce psychology disorders such as anxiety and depression.[15,16] The high prevalence of AR and its negative impacts on patients' quality of life cause great economic burdens worldwide, which are reported to bring in a medical cost of 2 billion dollars each year.[17] It is widely known that AR belongs to type I hypersensitivity that is mainly mediated by allergen immunoglobulin E (IgE) antibodies.[1,2] In the initial sensitization phase, the allergen is presented to $CD4^+$ T cells, which then activate B cells and subsequently synthesize IgE antibodies that bind to FcεRI receptors on the surface of mast cells as well as basophils. Once immune system is sensitized to allergen, re-exposure to the same allergen triggers a cascade of events which finally induce the symptoms of AR. In brief, both inflammatory cells and inflammatory mediators play important roles in pathology of AR.[1,2,17]

lncRNA ANRIL, a 3.8k nt non-coding RNA encoded in chromosome 9p21 region, is discovered to be implicated in

several inflammation-mediated diseases, including CAD, atherosclerotic SLE, and so on.[12,13,18,19] According to a recent study, lncRNA ANRIL expression is increased in HCAECs compared with human umbilical vein endothelial cells (HUVECs), and it is also upregulated in peripheral blood of CAD patients compared with healthy controls.[13] Besides, lncRNA ANRIL expression is discovered to be positively correlated with hypertension, hyperlipidemia, cholesterol, triacylglycerol, and homocysteine, whereas it is negatively associated with cumulative survival rate, indicating that lncRNA ANRIL is correlated with increased disease risk and severity of CAD.[13] In atherosclerotic SLE patients, lncRNA expression is higher than that in non-atherosclerotic SLE patients, and it is found to be positively associated with SLE duration, systemic lupus erythematosus disease activity index (SLEDAI), and systemic lupus international collaborating clinics (SLICC), suggesting that lncRNA is also correlated with elevated disease risk and severity of atherosclerotic SLE.[12] These studies indicate that lncRNA ANRIL is involved in development and progression of inflammation-related diseases. In order to illuminate the underlying association of lncRNA ANRIL with AR, we conducted the current study, which showed that lncRNA ANRIL expression in nasal mucosa of AR patients was upregulated compared with controls, and it was positively correlated with AR severity. The possible explanation might be that: lncRNA ANRIL was capable of promoting the synthesis and release of pro-inflammatory cytokines such as IL-6 and IL-17 (as described in next paragraph), then activated B cells immune response and upregulated IgE expression through multiple signaling pathways, thereby contributing to AR development and progression.[1,20]

LncRNA ANRIL is also observed to be associated with increased inflammation of CAD and atherosclerotic SLE.[12,13] In a recent study, transfection of HCAECs with pcDNA-ANRIL results in the release of various inflammatory mediators including IL-6, IL-8, inducible nitric oxide synthases (iNOS), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and cyclooxygenase-2 (COX-2), suggesting that lncRNA ANRIL is able to aggravate inflammatory activities in HCAECs.[13] Another interesting study discovers that lncRNA ANRIL upregulates IL-6 and IL-8 expression in human endothelial cells (ECs) through binding to an ANRIL binding transcriptional factor (Yin Yang 1 [YY1]). In addition, comparison of gene expression profiles between ANRIL knockdown HUVECs and normal HUVECs reveals that 473 genes were upregulated and 553 genes were down-regulated (fold change >2, $P<.001$) in ANRIL knockdown HUVECs compared with normal HUVECs, and these dysregulated genes are mostly enriched in inflammation-related pathways including cytokine–cytokine receptor signaling, Toll-like receptor pathway, cell adhesion molecules, and extracellular matrix–receptor interaction.[11] These indicate that lncRNA ANRIL is widely implicated in inflammation activities via multiple signaling pathways. Partly in consistent with these 2 reported studies, our studies found that lncRNA expression was positively associated with TNF-α, IL-4, IL-6, IL-13, and IL-17, while negatively associated with IL-10 and IFN-γ expressions in nasal mucosa of AR patients. The possible reasons might be: lncRNA ANRIL might be engaged in inflammatory responses of AR through regulating some anti-inflammation miRNAs, such as miR-181b and miR-let-7e.[13,17,21–24] Take miR-181b as an example: miR-181b is reported to downregulate IL-6, IL-8, and TNF-α expressions in HCAECs through NF-κB signaling pathways, while lncRNA ANRIL is able to sponge miR-181b, thus lncRNA ANRIL might upregulate pro-inflammatory cytokine expressions of AR patients via sponging miR-181b.[13,21,22] As previously described, lncRNA ANRIL might also be implicated in inflammatory responses of AR through binding to YY1, thereby upregulating IL-6 and IL-8 expressions.[11] Our study suggested that lncRNA ANRIL might be implicated in the inflammation mediation of AR thereby contributed to its pathogenesis, whereas the detailed molecular mechanisms need further investigation.

There were some limitations in this study. Firstly, this study was a small sample study, which might decrease statistical power. Secondly, the detailed mechanisms of lncRNA ANRIL being positively correlated with AR risk, severity and inflammation were still unclear, which needs to be further investigated. Lastly, the study did not evaluate the treatment efficacy and recurrence of AR. Therefore, the association of lncRNA ANRIL with prognosis in AR patients was not assessed.

In conclusion, lncRNA ANRIL expression correlates with increased AR risk, severity and inflammation, implying that lncRNA ANRIL might be involved in the pathogenesis of AR.

Author contributions

Conceptualization: Guijuan Zhang.
Writing – original draft: Xiaoqiong Qian, Song Shi.
Writing – review & editing: Guijuan Zhang.
Guijuan Zhang orcid: 0000-0001-6091-2456.

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