CELL CYCLE
2023, VOL. 22, NO. 20, 2280–2287
https://doi.org/10.1080/15384101.2023.2286802

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RESEARCH PAPER



# Association of LOX gene G473A polymorphism with the occurrence of allergic rhinitis and efficacy of montelukast sodium in children

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**ABSTRACT**

Allergic rhinitis (AR) is very common in adolescents, and current treatment options are complex and unsatisfactory. The objective of this study was to analyze the association of lysyl oxidase (LOX) gene G473A polymorphism with susceptibility to AR in children. In addition, we analyzed the therapeutic effect of montelukast sodium on AR. Forty-five children with AR (research group, 8.16 ±2.88 years old) and 51 healthy children (control group, 8.22±3.87 years old) during the same period were selected. The LOX gene G473A polymorphism was detected with polymerase chain reaction (PCR)-restriction fragment length polymorphism method. The effect of G473A polymorphism in the occurrence of AR was assessed by logistic regression analysis. In addition, the levels of C-reactive protein (CRP), Interleukin (IL-6), and IL-8 were measured to observe the relationship between G473A polymorphism and inflammatory factors. Finally, montelukast sodium was given to children with AR to investigate the effect of G473A polymorphism on clinical outcomes. The number of G473A polymorphisms in the research group was not significantly different from the control group for GA-type ($P$ = 0.521). However, the number of GG-type polymorphisms was less while the number of type AA was more than the control group ($P$ = 0.044 and 0.046). Children carrying the AA gene had an approximately 4-fold increased risk of AR, while those carrying the GG gene had a decreased risk ($P$ < 0.001). Moreover, children carrying the GG gene had lower levels of CRP, IL-6, and IL-8 and better clinical outcomes, while those carrying the AA gene had higher levels of inflammatory factors and worse outcomes (P<0.05). LOX gene G473A polymorphism is closely associated with AR pathogenesis and may have an important research value in antagonizing the therapeutic effect of montelukast sodium.

**ARTICLE HISTORY**
Received 17 July 2023
Revised 24 October 2023
Accepted 26 October 2023

**KEYWORDS**
Allergic rhinitis; lysyl oxidase; G473A polymorphism; inflammation; montelukast sodium

## Introduction

Allergic rhinitis (AR) refers to a noninfectious inflammatory disease of the nasal mucosa in which exposure to allergens in atopic individuals is followed by the release of mediators (mainly histamine) mediated primarily by IgE and the involvement of a variety of immunoreactive cells and cytokines [1]. As a common chronic inflammatory disease of the upper respiratory tract, AR is found in children and young adults, and has a high prevalence worldwide, with more than 500 million cases, and a prevalence of 12–30% in developed countries such as Western Europe and North America [2]. The main symptoms of most AR patients are nasal itching, paroxysmal sneezing, nasal discharge, and nasal congestion which affect the normal life of patients [3]. Also, a small number of acute AR or severe AR may also induce bronchial asthma and serious problems such as anaphylaxis, which could endanger the life safety of patients [4]. In clinical practice, it is believed that the most prominent cause of AR development is still related to inhaled allergens or food allergens, such as dust mites, pollen, animal dander secretions, fungi, and various types of food, so its treatment modality is mainly focused on controlling AR development and to avoid allergens to prevent reoccurrence [5]. However, screening for allergens is not only extremely complex and lengthy, but the accuracy of the final screening results is not high. Even if allergens are identified, patients may still not be able to completely avoid

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them in their normal social life, resulting in reoccurrence [6]. Therefore, there is an urgent clinical need to find a new tool that is more suitable for AR diagnosis and treatment.

As research progressed, multiple manifestations of AR were found to be under strong genetic control with a polygenic genetic predisposition [7]. Recently, more and more studies have focused on molecular investigations to find new diagnostic and treatment modalities for AR [8,9]. Lysyl oxidase (LOX) is an enzyme that catalyzes the cross-linking of elastin and collagen polymerization in the extracellular matrix (ECM) and has a role in enhancing the stability of the ECM [10]. Studies have pointed out that LOX has a significant role in allergic inflammatory diseases such as bronchial asthma, allergic conjunctivitis, and atopic dermatitis [11], and has been hailed as a new direction for the future treatment of allergic diseases [12]. Studies on the relationship between LOX and AR are still relatively rare, and there is a lack of reliable clinical references and theoretical guidance. LOX is localized on human chromosome 5 and is a copper-dependent enzyme secreted by fibroblasts that triggers the cross-linking of collagen and elastin and stabilizes the ECM [13]. When LOX was first identified, researchers believed that LOX activity was associated with fibrotic diseases such as pulmonary and hepatic fibrosis and atherosclerosis, while reduced LOX activity was associated with sulfate-induced emphysema and impaired copper metabolism (e.g. Menkes syndrome) in animal models [14]. Thus, LOX plays an important role in organ morphogenesis and tissue repair. Among them, the molecular principle of the G473A locus of the LOX gene is the mutation of G to A at locus 473, resulting in the mutation of arginine 158 of the peptide to glutamine [15]. It is well known that glutamine, as a precursor for the synthesis of mucins, is greatly increased by the demand for glutamine by intestinal mucosal cells and rapidly proliferating cells during systemic inflammation syndrome, leading to an imbalance of glutamine in the body, as well as a strong sensitizing effect [16]. Polymorphism of G473A is considered to be most closely related to inflammation and several other diseases [15,17]. However, the role of G473A polymorphism in AR is not known. Therefore, the present study focused on the relationship between G473A polymorphism and AR.

In addition, montelukast sodium is one of the commonly used drugs for AR treatment today, and its effectiveness has been proven many times over [18]. Pharmacological studies on montelukast have shown that its mechanism is related to the inhibition of leukotriene receptors [19]. The leukotriene receptor is also a receptor protein in the ECM, so there may be a potential link between the therapeutic effect of montelukast sodium on AR and LOX as well, but there are no studies to confirm this idea.

Building on this, our study aims to further explore the correlation between LOX and AR by exploring the relationship between LOX gene polymorphisms and AR and the therapeutic effect of montelukast sodium in AR children.

## Patients and methods

### Patients and controls

Forty-five children with AR (8.16 ± 2.88 years old) admitted to our hospital from June 2021 to August 2022 and 51 healthy children (8.22 ± 3.87 years old) during the same period were selected for the prospective analysis. Children with AR were the research group and healthy children were the control group. The study was conducted in strict compliance with the Declaration of Helsinki, and an informed consent form was signed by the guardians of the study subjects. This study was approved by the Ethics Committee of the Sunshine Union Hospital.

### Inclusion and exclusion criteria

The inclusion criteria for the research group subjects was: significant AR symptoms, consistent with AR diagnostic guidelines [20], confirmed AR diagnosis after examination, absence of other chronic diseases and stable AR progression; complete clinical data. The inclusion criteria for the control group subjects was: children were routinely examined in our hospital, and all had normal physical examination results; no significant previous medical history; complete clinical data. The exclusion criteria were the same for both group

subjects except children with severe allergies (such as anaphylaxis and generalized urticaria) in the research group were also excluded. Other exclusion criteria were: children with congenital heart disease, abnormal or impaired liver and kidney function; children who have taken glucocorticoids or receptor antagonists within 3 months before admission.

### Treatment methods

Children with AR were treated with montelukast sodium (Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd., J20130047), 5 mg/d, 1 time/d, for 2 months.

### Genotyping analysis

Genomic DNA was extracted from 5 ml of frozen whole blood using a DNA extraction kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The LOX G473A polymorphism (SNP number: rs1800449; G473A; c.473 G>A; Arg158Gln; R158Q) was discovered using a polymerase chain reaction (PCR)-restriction fragment length polymorphism method. Using Primer Premier software, version 5.0 (Premier Biosoft International, Palo Alto, CA, USA), the two PCR primers were designed based on the GenBank® reference sequence for LOX. The PCRs were run in a 35 uL reaction mixture that contained 100 ng of genomic DNA, 12.5 pmol of each primer, 0.1 mM of each dNTP, 1×PCR buffer, 1.0 mM of MgCl2, and 1.5 U of Taq DNA polymerase (Fermentas). A thermal cycler (Biometra) was used to carry out the reactions following the manufacturer's instructions. The primers for LOX G473A polymorphism detection were designed and constructed by Suzhou Genewiz Biotechnology, upstream: 5'-TTCCAAGGTGGGTACTCGAC-3', downstream: 5'-CAGGTCTGGGGCTT-TCATAA-3'.
Amplification was completed according to the amplification kit (GenScript Biotechnology, E00007–1000) and PCR reactions were performed. Reaction conditions: 94°C for 5 min, 94°C for 30s, 57°C for 40s, 72°C for 30s, total 35 cycles. The PCR results were verified by 1.5% agarose gel electrophoresis to ensure accuracy. Following DNA amplification, the PCR products were digested with 10 U of the specialized restriction endonuclease PstI (Fermentas International), which cleaves the A allele, for an overnight period of time at 37°C. After being separated on a 2% agarose gel and stained with ethidium bromide, the digestion products were then visualized under an ultraviolet light source. Following electrophoresis, homozygous G alleles which contain the CG site were recognized by DNA bands at 142 bp in length. An uncut fragment of 228 bp indicated the homozygous A alleles free of the CG site, and the heterozygous GA genotype was displayed as a 114 bp band (Figure 1). To verify the genotyping results, 20% of the PCR-amplified DNA samples

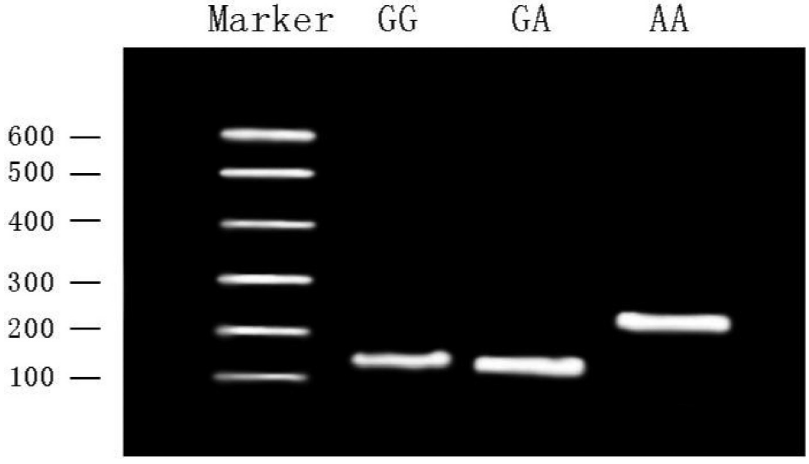


**Figure 1.** PCR- restriction fragment length polymorphism (PCR-RFLP) analysis for LOX G473A. After electrophoresis, homozygous G alleles which contain the CG site were recognized by DNA bands at 142 bp in length. An uncut fragment of 228 bp indicated the homozygous a alleles free of the CG site, and the heterozygous GA genotype was displayed as a 114 bp band.

were chosen at random by a computer and sent to the Qingdao Zhongding Company (Qingdao, China) for DNA sequencing. Results from PCR and DNA sequencing analysis agreed exactly. The results of the DNA sequencing analysis and PCR were completely consistent.

### Determination of inflammatory mediators

Blood samples were collected in EDTA tubes and were assayed for IL-6 and IL-8 using the ELISA kits (R&D Systems). Samples were also assayed for high-sensitivity- C-reactive protein (CRP) on a BN II analyzer (Dade Behring).

### Efficacy determination of AR

The clinical outcome of children treated with montelukast sodium was assessed with reference to AR treatment guidelines, as described previously [21]. *Markedly effective*: After treatment, the clinical symptoms of sneezing, runny nose and nasal congestion disappeared completely, and the edema of the nasal mucosa disappeared completely on rhinoscopy, and there was no recurrence for more than 3 months. *Effective*: After treatment, children's clinical symptoms disappeared or improved significantly, the edema of the nasal mucosa disappeared or was relieved by rhinoscopy, and the number of episodes decreased. *Ineffective*: There was no improvement or worsening of clinical symptoms and rhinoscopy after treatment.

### Statistical analysis

SPSS 21.0 software was used for statistical analysis, and genotype frequencies were compared using the Hardy-Weinberg Equilibrium (HWE). $P = 0.05$ indicated that the gene frequencies of the selected sample population were representative in accordance with the law of heritage balance. The counting data [n (%)] was compared using chi-square test, while the measurement data ($\overline{x}\pm s$) was compared using independent samples t-test. The correlation factors were analyzed using logistic regression, and differences were considered statistically significant at $P < 0.05$.

## Results

### Comparison of clinical characteristics between the two groups

Table 1 displays the clinical characteristics of all subjects. There were no statistically significant differences in age, gender, and only child between the two groups ($P > 0.05$), but more children in the research group had a family history of AR than the control group ($P < 0.05$) (Table 1).

### Comparison of LOX gene G473A polymorphism

The results of the LOX gene G473A polymorphism detection revealed that the G473A polymorphism in both groups was predominantly GG type, followed by GA type, and AA type was the least. Comparison between the two groups manifested that there was no significant difference between the number of G473A polymorphisms in the research group and the control group as GA type ($P > 0.05$). However, the number of GG type was significantly less than the control group and the number of AA type was significantly more than the control group ($P < 0.05$) (Table 2).

### Effect of LOX gene G473A polymorphism on the development of AR

Two groups of study subjects were grouped according to the genotype of the G473A polymorphism, with a total of 51 cases of the GG gene, 31 cases of the GA gene, and 14 cases of

**Table 1.** Comparison of clinical characteristics between the two groups.

| Group | n | Male/Female | Age | Only child Yes/No | Family history of disease Yes/No |
|---|---|---|---|---|---|
| Control group | 51 | 29 (56.86%)/22 (43.14%) | 8.22 ± 3.87 | 36 (70.59%)/15 (29.41%) | 10 (19.60%)/41 (80.39%) |
| Research group | 45 | 23 (51.11%)/22 (48.89%) | 8.16 ± 2.88 | 34 (75.56%)/11 (24.44%) | 15 (33.33%)/30 (66.67%) |
| $x^2$ | | 0.319 | 0.085 | 0.299 | 0.840 |
| P-value | | 0.573 | 0.932 | 0.585 | 0.041 |

**Table 2.** Comparison of differences of G473A polymorphism of LOX gene between both groups.

| Group | n | GG | GA | AA |
|---|---|---|---|---|
| Control group | 51 | 32 (62.75%) | 15 (29.41%) | 4 (7.84%) |
| Research group | 45 | 19 (42.22%) | 16 (35.56%) | 10 (22.22%) |
| $x^2$ | | 4.043 | 0.413 | 3.968 |
| P-value | | 0.044 | 0.521 | 0.046 |

**Table 3.** Effect of LOX gene G473A polymorphism on the development of RA.

| Polymorphism | β | S.E. | Wald $x^2$ | P | OR | 95% CI |
|---|---|---|---|---|---|---|
| GG | 2.623 | 1.642 | 10.842 | 0.000 | 0.742 | 0.261–1.489 |
| GA | 0.292 | 1.142 | 0.728 | 0.162 | 1.162 | 0.426–2.842 |
| AA | 1.843 | 0.773 | 13.842 | 0.000 | 4.362 | 2.942–10.142 |

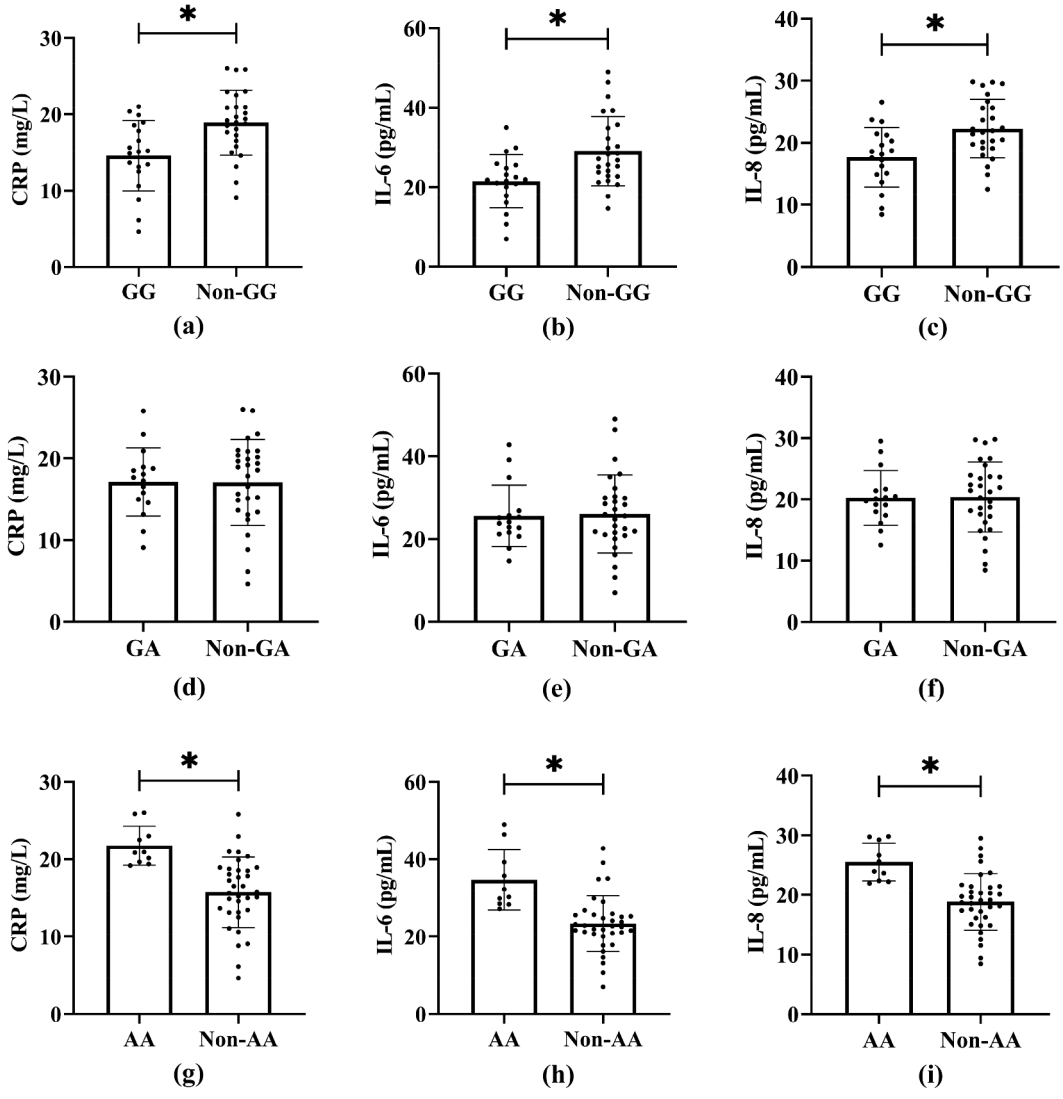


**Figure 2.** Association of LOX gene G473A polymorphism with the degree of inflammation in RA. (a-c) Comparison of inflammatory factors in children with type GG and non-GG. (d-f) Comparison of inflammatory factors in children with type GA and non-GA. (g-i) Comparison of inflammatory factors in children with type AA and non-AA. * indicates that the difference between the two groups was statistically significant ($P < 0.05$).

the AA gene. Subsequently, Logistic regression analysis was performed with genotype as a covariate and whether AR occurred in the study subjects as the dependent variable. The output manifested that the GA gene was not significantly associated with the development of AR ($P > 0.05$), while children carrying the AA gene had an approximately 4-fold increased risk of AR ($P < 0.05$). Similarly, it was also noticed that children carrying the GG gene had significantly higher risk of developing AR ($P < 0.05$) (Table 3).

### Association of LOX gene G473A polymorphism with the degree of inflammation in AR

The children in the research group were grouped according to the results of the LOX gene G473A polymorphism, namely, GG type ($n = 19$); non-GG type ($n = 26$); GA type ($n = 16$); non-GA type ($n = 29$); AA type ($n = 10$); and non-AA type ($n = 35$), respectively. It was noticed that there was no marked difference in the levels of inflammatory factors between the children with type GA and non-GA ($P > 0.05$). Notably, the CRP, IL-6 and IL-8 levels were lower in children with type GG than in those with non-GG ($P < 0.05$), while the CRP, IL-6 and IL-8 levels were higher in children with type AA than in those with non-AA ($P < 0.05$) (Figure 2).

### Association of LOX gene G473A polymorphism with clinical efficacy of AR

After treatment with montelukast sodium, the children were divided into effective group [clinical efficacy was markedly effective ($n = 11$) and effective ($n = 17$), in total, $n = 28$)] and ineffective group (clinical efficacy was ineffective, $n = 17$) according to their clinical efficacy. Results demonstrated that there was no statistically significant difference between the effective and ineffective groups in the number of children carrying the GA type gene ($P > 0.05$), however, the effective group had more children carrying the GG type gene and fewer children carrying the AA type gene. This difference was statistically significant ($P < 0.05$) (Table 4).

## Discussion

As molecular science is gaining importance in the field of medicine, it is believed that targeted therapy from a genetic perspective may be the key to overcoming AR in the future [22]. The present study, by analyzing the relationship between LOX gene polymorphisms and AR, has important reference significance for the subsequent research on the diagnosis and treatment of AR.

The results of our study demonstrated that the gene frequency of the G473A polymorphism was predominantly GG type and least AA type in both children with AR and healthy controls. However, the number of children with AR carrying the GG gene was significantly less than that of normal children. Similarly, children carrying the AA gene was significantly more in AR than the control group, suggesting that the G473A polymorphism in LOX gene may have a close relationship with the occurrence and development of AR. In a previous study, the G473A polymorphism was also considered to be an important player in bronchial asthma and atopic dermatitis [23], which is consistent with the results of the current study. In line with this, when G473A polymorphism was analyzed in relation to breast cancer, colorectal cancer, and other tumor diseases, it was found that the majority of patients with severe disease carried the AA type gene [24,25], suggesting that the alteration of G473A polymorphism may have an important pathological role.

We also found that fewer children in the research group carried the GG-type gene and more carried the AA-type gene than the control group, suggesting that the G mutation to A in

**Table 4.** Association of LOX gene G473A polymorphism with clinical efficacy.

| Groups | n | GG | GA | AA |
|---|---|---|---|---|
| Effective group | 28 | 16 (57.14%) | 9 (32.14%) | 3 (10.71%) |
| Invalid group | 17 | 3 (17.65%) | 7 (41.18%) | 7 (41.18%) |
| $x^2$ | | 6.764 | 0.377 | 5.679 |
| P-value | | 0.009 | 0.539 | 0.017 |

G473A may be critical in affecting AR, and the mechanism may be related to that of glutamine as described above. This data is consistent with the result of a previous study in which Ren et al. [26] demonstrated that G mutation to A in G473A can increase breast cancer susceptibility. Through logistic regression analysis, we observed that carrying the AA type gene and not carrying the GG type gene may lead to an increased risk of AR development, which also suggests that our future targeted regulatory drugs regarding the G473A polymorphism of LOX gene may be a new research direction for the treatment of AR. Moreover, in the investigation of the relationship between the G473A polymorphism of the LOX gene and the inflammation, children carrying the AA-type gene generally had higher levels of inflammation, while those carrying the GG-type gene had lower levels, which tentatively supports our view that the GG-type gene contributes more to the regulation of the degree of inflammation in children with AR. These results are in agreement with the findings of a previous study regarding the G473A polymorphism of the LOX gene [27].

Montelukast sodium is one of the important drugs for the treatment of allergic rhinitis, with a strong action on the main target receptors of pathogenesis, stimulating airway mucus production, reducing nasal mucus secretion, and effectively improving clinical symptoms in children [28]. In our study, we found that the efficacy of treatment was generally worse in children carrying the AA gene and better in those carrying the GG gene, which also suggests that the G473A polymorphism has a moderate effect on montelukast sodium antagonism. From this data, we can speculate that the current recurrence of AR may also be due to the fact that the affected children carry the type of AA gene in G473A.

There are several limitations in our study that needs to be addressed. Firstly, due to limited experimental conditions, we did not analyze LOX family members LOX1-LOX5 in detail. Secondly, it is not clear whether other loci polymorphisms of LOX are also associated with AR. Thirdly, we need to carry out more in-depth experimental analysis on the relationship between LOX gene G473A polymorphism and AR, so as to provide a more comprehensive clinical reference.

## Conclusion

The result of our study suggests that G mutation to A in the G473A polymorphism of the LOX gene is associated with an increased risk of AR in children. Additionally, children carrying the AA-type gene but not carrying the GG-type gene have increased susceptibility to AR. Furthermore, these polymorphisms have an antagonistic effect on the therapeutic effect of montelukast sodium. Thus, future research on the G473A polymorphism of LOX gene may become a new direction in the diagnosis and treatment of AR.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

The author(s) reported there is no funding associated with the work featured in this article.

## Availability of data and material

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

## Authors contributions

MC conceived and designed the experiments. XY, YL, and HJ contributed significantly to the experiments, and arranging data. WM performed data analyses. XY and YL wrote the draft manuscript. MC revised the manuscript. All authors read and approved the final manuscript.

## Ethics statement

All patients provided their written, voluntarily informed consent. All procedures were carried out in accordance with the guidelines outlined in the Helsinki Declaration and this study was approved by the Ethics Committee of the Sunshine Union Hospital.

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