Glucocorticoid-Induced Transcription Factor 1 (GLCCI1) Variant Impacts the Short-Term Response to Intranasal Corticosteroids in Chinese Han Patients with Seasonal Allergic Rhinitis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Genetic correlations with the response to intranasal corticosteroids (INCS) in seasonal allergic rhinitis (SAR) treatment are unknown. This study aimed to evaluate the role of gene polymorphisms in the response to INCS in Chinese Han patients with moderate to severe SAR.

Material/Methods: In this study, 286 Chinese Han patients with SAR were genotyped for 4 candidate genes: the glucocorticosteroid receptor (NR3C1) gene, glucocorticoid-induced transcription factor 1 (GLCCI1) gene, T-box 21 gene (TBX21), and ATP binding cassette subfamily B member 1 (ABCB1) gene. Patients were treated with INCS for 4 weeks. The total nasal symptom score (TNSS), total ocular symptom score (TOSS), and visual analogue scale (VAS) score were assessed at baseline and on week 4. The primary endpoint was the effective rate after 4 weeks of INCS therapy.

Results: In addition to the known contributing factors, one genotype of GLCCI1, namely, rs37973, was significantly associated with the INCS response (OR=0.598, 95% confidence interval: 0.41 to 0.87, P=0.007). The effective rate of the GG group was lower than those of the AA and AG groups (AA vs. GG: 73.7% vs. 51.6%, P=0.007; AG vs. GG: 78.8% vs. 51.6%, P=0.000). In addition, the TNSS, TOSS, and VAS were higher for the patients in the GG group than for those in the AA and AG groups on week 4.

Conclusions: The GLCCI1 rs37973 variant is a risk factor for glucocorticoid resistance in Chinese patients with SAR who receive short-term INCS treatment.

MeSH Keywords: **Glucocorticoids • Pharmacogenetics • Polymorphism, Single Nucleotide • Rhinitis, Allergic, Seasonal**

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Background

Seasonal allergic rhinitis (SAR) is an IgE-mediated inflammatory disease characterized by obstruction, rhinorrhea, sneezing, and itching and is often accompanied by ocular symptoms [1]. The incidence rate of SAR shows an increasing tendency, and SAR severely affects the quality of life and medical expenditures of patients [2,3]. Intranasal corticosteroids (INCS) are the primary medications in the control and management of SAR because INCS can reduce the production of inflammatory cytokines and induce the apoptosis of inflammatory cells, especially eosinophils [4]. Although INCS appears to provide effective treatment, the response to corticosteroids is characterized by high individual variance in the clinic [5]. Following INCS therapy, some patients show no significant improvements in their symptoms, an outcome known as steroid insensitivity. Steroid resistance occurs in asthma, nephrotic syndrome, and other diseases, thereby making clinical treatment challenging. Early diagnosis can prevent the use of unnecessary hormones and enable the use of other alternative and effective treatments in a timely manner. The factors that affect hormone response are varied, and several mechanisms, including allergen exposure, neutrocytosis, and drug gene polymorphisms, have been extensively studied [6].

Several single nucleotide polymorphisms (SNPs) in candidate genes are reportedly relevant to the glucocorticoid response. The T-box 21 (*TBX21*) gene, glucocorticosteroid receptor (*NR3C1*) gene, and ATP binding cassette subfamily B member 1 (*ABCB1*) gene may be associated with improvements in pulmonary function after treatment with inhaled corticosteroids (ICS) [7–9]. The glucocorticoid-induced transcription factor 1 (*GLCCI1*) gene, which maps to 7p21.3, is expressed in both lung and immune cells and may be an early marker of hormone-induced apoptosis. rs37973 has been identified as a functional SNP and is reported to be associated with the response of white patients with asthma to ICS [10]. The effects of genetic factors on the treatment of asthma with ICS has been extensively studied, but the effects of genetic factors on the INCS treatment of SAR remain unknown. Both asthma and SAR are type I allergic reactions, and they are very similar in terms of etiology, immunology, pathogenesis, and other aspects [11]. Based on the concept of combined allergic rhinitis and asthma syndrome (CARAS), researchers have assumed that genes affecting ICS therapy might also affect the efficacy of INCS.

In the present study, 4 genes, namely, *GLCCI1* (rs37973), *TBX21* (rs9910408), *ABCB1* (rs1045642), and *NR3C1* (rs41423247), were assessed in Chinese Han patients with moderate to severe SAR for correlations between gene polymorphisms and the response to INCS.

Material and Methods

Patients and study design

Patients aged 10 to 60 years with a history of moderate to severe SAR for at least 1 year from the Nasal Department of Tongren Hospital (Beijing, China) were enrolled for this non-interventional, prospective cohort study. The patients were of Han ethnicity and planned to be treated with INCS monotherapy. In addition, the patients had no significant medical conditions or nasal abnormalities that were known to interfere with the study (e.g., severe asthma, nasal septal deviation, nasal polyps, or nasosinusitis). The diagnosis was established according to the Clinical Practice Guideline: Allergic Rhinitis recommendations [3], based on clinical symptoms, nasal endoscopy examination, and serum IgE allergen detection. This study was conducted from April to September during the weed, grass, and tree pollen seasons in northern China.

Approximately 2 mL of residual peripheral blood that had been used for serum IgE allergen detection was collected for genotyping. Eligible patients received an INCS treatment for 4 weeks before evaluation. Medications known to affect allergy symptoms, to be associated with poor compliance, or to be associated with adverse reactions during the observation period were excluded. This study was in compliance with the Helsinki declaration and was approved by the Ethics Committee of Beijing Tongren Hospital (TREC2015-KY03). The informed consent process was performed, and an informed consent form was signed by each patient.

Data collection

At the baseline visit, a well-designed self-administered questionnaire was used to collect the following information: demographic information, medical history, allergy history, smoking history, and family history of SAR. Before and after treatment, the total nasal symptom score (TNSS), total ocular symptom score (TOSS), and visual analogue scale (VAS) score were assessed to reflect the real symptom load. The TNSS was the sum of the scores for obstruction, sneezing, rhinorrhea, and nasal itching; the TOSS was the sum of scores for itchy eyes, tearing, and eye redness on a 4-point rating scale (0=none, 1=mild, 2=moderate, and 3=severe) [12]. The VAS score has been employed in multiple kinds of diseases and is sufficiently sensitive for the detection of changes in severity [13]. Briefly, to assess the severity from no symptoms (0 cm) to intolerable symptoms (10 cm), a 10-cm line was utilized. Patients graded their symptoms for the previous 24 hours by making marks on the line. Children were helped by their parents.

Taking "change of TNSS=0.55" as the boundary, the patients were divided into 2 categories: good response and poor
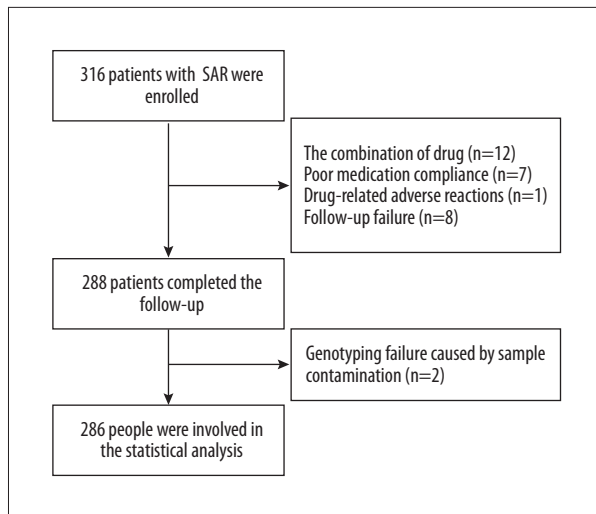
Figure 1. Inclusion-exclusion flow chart.

response [14]. The primary endpoint was the response rate after one 4-week INCS therapy course, and the secondary endpoints included changes in the TNSS, TOSS, and VAS and the nasal symptoms from before and after treatment.

Genotyping

Genomic DNA was extracted from peripheral blood. *GLCCI1* (rs37973), *TBX21* (rs9910408), *ABCB1* (rs1045642), and *NR3C1* (rs41423247) polymorphisms were genotyped with the improved Multiple Ligase Detection Reaction (iMLDR), with technical support from the Center for Human Genetics Research, Shanghai Genesky Biotechnology Company [15]. In addition, 15% of the DNA samples were genotyped again with different methods for quality control purposes.

Statistical analysis

The Hardy-Weinberg equilibrium of the allele and the genotype frequencies were analyzed. The Kruskal-Wallis or chi-Square tests were used to assess the differences in age, gender, body mass index, and disease characteristics at baseline between different genotype groups. One-way ANOVA was adopted to assess whether the changes in the TNSS, TOSS, and VAS score and the nasal symptom scores from before and after treatment differed according to genotype. Univariate and multivariate logistic regression models were performed to explore the association between SNPs and treatment outcomes. The odds ratio (OR), 95% confidence interval (CI), and P value for each analysis were calculated. Statistical analysis was carried out using SPSS 23.0 for Windows (SPSS, Inc., IBM). In all tests, $P \leq 0.05$ was considered statistically significant.

Results

Patient profiles and *GLCCI1* rs37973 frequency

From July 2015 to June 2017, 316 patients with SAR were enrolled, and 286 people were included in the statistical analysis (Figure 1). Among the studied SNPs, only rs37973 of *GLCCI1* was associated with the INCS treatment response. No statistically significant differences in terms of demographic and disease characteristics (TNSS, TOSS, VAS and nasal symptom scores before and after treatment) were evident among the rs37973 groups at baseline (Table 1). The rs37973 frequency in the Han Chinese population was as follows: AA (n=76, 26.6%), AG (n=146, 51.0%), and GG (n=64, 22.4%). The distributions of all SNPs were in the Hardy-Weinberg equilibrium.

Changes in the TNSS, TOSS and VAS before and after treatment according to rs37973

The mean values for the TNSS, TOSS, and VAS assessed by the clinician at baseline and week 4 for the rs37973 groups are shown in Figure 2. The nasal and ocular symptoms of the SAR patients improved significantly after INCS treatment. The AA and AG groups had significantly greater decreases in their scores than the GG group as assessed with the TNSS (AA *vs.* GG: −68.4% *vs.* −58.1%, P=0.004; AG *vs.* GG: −69.5% *vs.* −58.1%, P=0.001), but the decrease between the AA and AG groups was not significant. By comparison, the TOSS was significantly reduced in the AA group compared with the AG and GG groups (AA *vs.* AG: −93.8% *vs.* −84.6%, P=0.043; AA *vs.* GG: −93.8% *vs.* −81.3%, P=0.002). The VAS showed improvements that were similar to those of the TNSS in the AG and GG groups (−67.1% *vs.* −57.8%, P=0.008). Briefly, the GG group had higher scores than the AA or AG groups on week 4 in terms of the TNSS, TOSS, and VAS. The actual scores, improvement percentages, and P values are shown in Table 2.

Changes in the nasal symptoms before and after treatment in terms of rs37973

The clinician-based assessments of the mean scores for the individual nasal symptoms, namely, obstruction, rhinorrhea, itching, and sneezing at baseline and on week 4, are presented in Figure 3. A decrease in mean scores was evident from baseline to week 4. Although no statistically significant difference between groups was observed for nasal itch (P=0.811), significant differences were demonstrated for obstruction (AA *vs.* GG: −66.2% *vs.* −55.1%, P=0.021; AG *vs.* GG: −67.9% *vs.* −55.1%, P=0.004), rhinorrhea (AA *vs.* GG: −71.4% *vs.* −61.8%, P=0.031; AG *vs.* GG: −72.7% *vs.* −61.8%, P=0.006), and sneezing (AA *vs.* GG: −68.9% *vs.* −52.8%, P=0.001; AG *vs.* GG: −72.4% *vs.* −52.8%, P=0.000). The improvements in the nasal symptoms (obstruction, rhinorrhea, and sneezing) were significantly fewer for

Table 1. Patient characteristics according to *GLCCI1* rs37973 genotype.

	rs37973		
	AA (n=76)	**AG (n=146)**	**GG (n=64)**
Gender (male/female), n	42/34	74/72	29/35
Age, years	34.6 (10.5)	35.2 (10.3)	34.7 (10.4)
BMI, kg/m^2	21.1 (2.1)	21.9 (2.0)	21.6 (2.1)
Smoking history (never), %	75.0	74.7	78.1
Family history of SAR (none), %	75.0	73.3	65.6
TNSS at baseline, scores	7.38 (1.52)	7.38 (1.36)	7.81 (1.71)
Obstruction, scores	1.95 (0.69)	1.96 (0.63)	2.05 (0.58)
Rhinorrhea, scores	2.59 (0.66)	2.56 (0.73)	2.67 (0.62)
Itching, scores	1.53 (0.81)	1.40 (0.67)	1.50 (0.71)
Sneezing, scores	1.32 (0.80)	1.54 (0.79)	1.59 (0.96)
TOSS at baseline, scores	2.25 (1.95)	2.14 (1.99)	2.56 (2.06)
VAS at baseline, scores	7.71 (0.99)	7.5 (0.97)	7.66 (1.17)

Results were presented as mean (SD). *P*>0.05 for all characteristics according to the Kruskal-Wallis or Chi-Square test. BMI – body mass index; TNSS – total nasal symptoms score; TOSS – total ocular symptoms score; VAS – visual analogue scale.
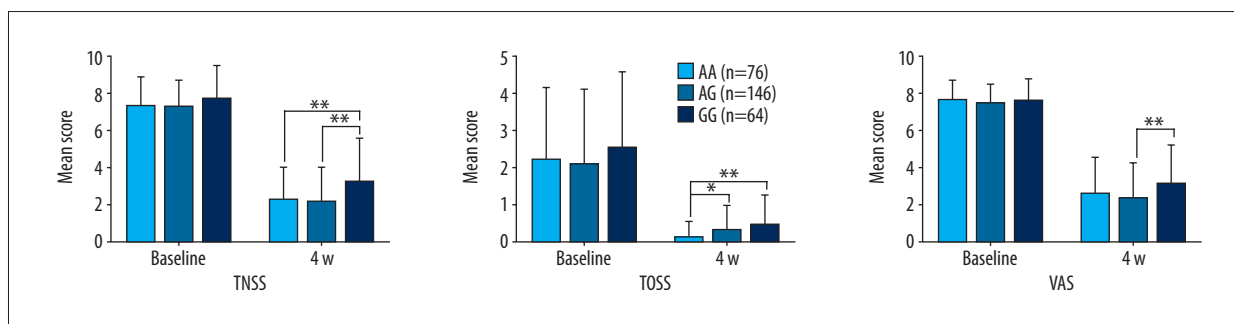

Figure 2. Changes in the TNSS, TOSS, and VAS before and after treatment. The TNSS, TOSS, and VAS decreased significantly after INCS treatment. The GG genotype was associated with poor improvements in the TNSS, TOSS, and VAS, relative to the AA or AG genotype. Data are presented as the mean ±SD. * *P*<0.05; ** *P*<0.01.

the GG group than for the AA and AG groups after INCS treatment for 4 weeks.

Correlation between *GLCCI1* rs37973 and the INCS treatment response

The distribution frequency of treatment response was as follows: AA (good response/poor response=56/20), AG (115/31), and GG (33/31). The percentage of patients with good responses on week 4 is presented in Figure 4. The effective rate of the GG group was significantly lower than those of the AA and AG groups (AA *vs.* GG: 73.7% *vs.* 51.6%, *P*=0.007; AG *vs.* GG: 78.8% *vs.* 51.6%, *P*=0.000) and was not affected by smoking history or family history of SAR.

Meanwhile, the rs37973 genotype showed a correlation with the INCS treatment response by univariate analysis (OR=0.598, 95% CI: 0.41 to 0.87, *P*=0.007). The multivariate analysis is presented in Table 3, after adjustments for demographic characteristics and the TNSS at baseline. The results indicate that the therapeutic effect of INCS might decrease gradually along with the increase in the G allele frequency. In addition, age may be a factor that affects efficacy according to the logistic regression analysis (OR=0.97, 95% CI: 0.95 to 1.00, *P*=0.033), and older patients may have poor treatment outcomes.

Table 2. Assessment of AR severity before and after treatment according to rs37973.

Assessment	Rs37973								
	AA (n=76)			AG (n=146)			GG (n=64)		
	Mean	SD	Change	Mean	SD	Change	Mean	SD	Change
TNSS									
Baseline	7.38	1.52	−5.05 (−68.4%)	7.38	1.36	−5.13 (−69.5%)	7.81	1.71	−4.54 (−58.1%)
4w	2.33	1.72		2.25	1.81		3.27	2.37	
P value*	AA vs. AG: p=0.782			AA vs. GG: p=0.004			AG vs. GG: p=0.001		
TOSS									
Baseline	2.25	1.95	−2.11 (−93.8%)	2.14	1.99	−1.81 (−84.6%)	2.56	2.06	−2.08 (−81.3%)
4w	0.14	0.42		0.33	0.67		0.48	0.78	
P value*	AA vs. AG: p=0.043			AA vs. GG: p=0.002			AG vs. GG: p=0.105		
VAS									
Baseline	7.71	0.99	−5.00 (−64.9%)	7.50	0.97	−5.03 (−67.1%)	7.66	1.17	−4.43 (−57.8%)
4w	2.71	1.90		2.47	1.87		3.23	2.02	
P value*	AA vs. AG: p=0.379			AA vs. GG: p=0.107			AG vs. GG: p=0.008		

* One-Way ANOVA test comparing treatment means of rs37973 groups.
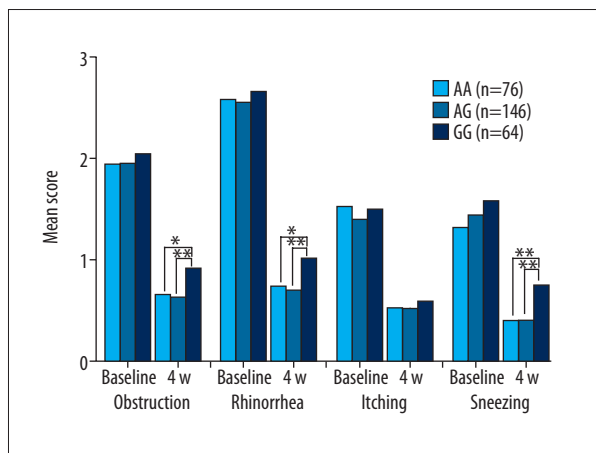

Figure 3. Changes in the nasal symptoms before and after treatment. After INCS treatment, all nasal symptoms were significantly improved. The GG genotype was associated with poor improvements in obstruction, rhinorrhea and sneezing, relative to the AA or AG genotype. No significant differences between genotypes were observed for itching. Data are presented as the mean. * P<0.05; ** P<0.01.
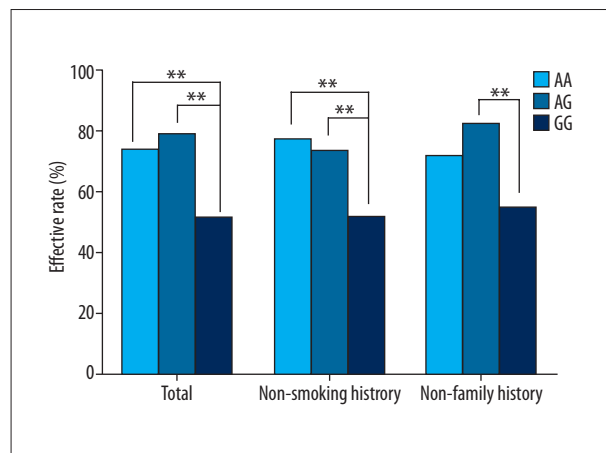

Figure 4. Assessment of treatment response according to rs37973. The effective rate of the GG genotype was significantly lower than those of the AA and AG genotypes and was not affected by the smoking history or family history of the SAR patients. * P<0.05; ** P<0.01.

Associations between other SNPs and the INCS treatment response

The assessments of the other SNPs, namely, the SNPs of *TBX21* (rs9910408), *ABCB1* (rs1045642), and *NR3C1* (rs41423247), showed no connections with the INCS response (Table 4).

Discussion

Glucocorticoid resistance is an important issue in the management of allergic diseases (e.g., allergic dermatitis, asthma, and allergic rhinitis) and may lead to treatment failure. Several pharmacogenetic studies have been performed to investigate genetic effects on glucocorticoid resistance, and several candidate genes have been identified (e.g., *CRHR1, FCER2, TBX21,* and *NR3C1*) [6,16–21]. However, correlation studies have not

Table 3. Effects of clinical indices and *GLCCI1* rs37973 on the treatment response.

	Multivariate analysis		
	OR	95% C.I.	P' value
rs37973 genotype	0.58	0.40 to 0.86	0.007**
Gender	0.95	0.52 to 1.75	0.87
Age	0.97	0.95 to 1.00	0.033*
BMI	1.04	0.91 to 1.19	0.58
Smoking history	1.56	0.75 to 3.22	0.23
Family history of SAR	0.76	0.43 to 1.35	0.35
TNSS at baseline	1.09	0.91 to 1.31	0.33

* $p<0.05$; ** $p<0.01$. C.I. – confidence interval; BMI – body mass index; TNSS – total nasal symptoms score.

Table 4. Effects of other SNPs on INCS treatment response.

SNP	OR	95% C.I.	P value	P' value*
rs9910408	1.335	0.88 to 2.02	0.172	0.199
rs1045642	0.918	0.63 to 1.33	0.653	0.455
rs41423247	0.901	0.57 to 1.42	0.653	0.700

* Effects were adjusted for gender, age, BMI, smoking history, family history of SAR, and TNSS at enrollment. C.I. – confidence interval.

precisely approximated clinical relevance. The expression product of *GLCCI1* was presumed to reduce the apoptosis of inflammatory cells [22]. Related SNP mutations may decrease *GLCCI1* expression, which may inhibit inflammatory cell apoptosis and lead to glucocorticoid resistance. More recently, a genome-wide association study (GWAS) by Tantisira et al. revealed that *GLCCI1* acts as a candidate gene in the response to ICS therapy in asthmatic patients. The G allele of rs37973 might down-regulate *GLCCI1* expression and decrease patient corticoid sensitivity [10]. Since this report, further studies have confirmed the association between *GLCCI1* gene polymorphisms and the glucocorticoid response [23–25], though the findings of other relevant studies were not consistent with those of the original findings [26,27]. In 2016, Hu C et al. successfully repeated the finding in a Chinese adult population [25]. However, these studies were mostly limited to a disease model of asthma, and the conclusion needs to be extended to other allergic diseases.

Our study showed that SAR patients with the GG genotype at the rs37973 locus of the *GLCCI1* gene might have poor responses to INCS short-term treatment as measured by changes in the TNSS, TOSS, and VAS score. In this study, all assessments of nasal and ocular symptoms showed less improvement in the GG group than in the AA or AG groups. For example, the mean TNSS of the GG patients decreased by approximate 58% from baseline to week 4 compared with a decrease of 68% for the same period for the AA patients. However, no significant difference regarding the improvement in nasal itching

was evident in the rs37973 group. Our study suggested that the therapeutic effect of INCS might decrease gradually along with the increase in the G allele frequency (OR=0.598, 95% CI: 0.41 to 0.87, P=0.007). This result was similar to that the study by Tantisira et al., which suggested that patients with GG were approximately two and a half times more likely to have poor responses to ICS than those with AA in a non-Hispanic white asthmatic population [10]. Hence, we can reasonably conceive that *GLCCI1* variations may affect the INCS responses of SAR patients.

Some studies have concluded that smoking may affect the therapeutic effect of ICS on asthma [24], but our findings suggested that the smoking and family histories of SAR patients did not affect the therapeutic effect of INCS. In addition, according to our research, older patients may have poor treatment outcomes. This association with age may be because the anatomical structure of the nasal cavity changes as age increases, resulting in changes to nasal airflow and a reduction in the nasal mucosa cilia beat frequency, leading to a decreased ability to eliminate allergens. Based on the hypothesis that the *GLCCI1* variant influences the effects of endogenous hormones, the GG genotype of rs37973 is expected to be associated with worse symptoms at baseline. Hu C et al. found that the rs37973 variant was associated with a higher baseline forced expiratory volume in 1 second (FEV1) in a Chinese population [25]. However, our study did not find any association between the rs37973 polymorphism and baseline clinical

severity. The baseline TNSS, TOSS, and VAS score showed no statistical significance among the groups.

Anton Lopert et al. showed that the *TBX21* gene might be associated with improvements in pulmonary function after ICS treatment for at least 3 years in asthmatic patients [7]. The rs41423247 polymorphism of the *NR3C1* gene was reported to be associated with improvements in FEV1 at 4 h in children with moderate to severe asthma who were treated with high-dose ICS [8]. In addition, the *ABCB1* gene polymorphism may influence the efficacy of the salmeterol/fluticasone combination therapy in stable chronic obstructive pulmonary patients [9]. However, those SNPs did not show any association with INCS effect in our study.

There were several limitations in our study design. First, no healthy control group was set up to explore the association between rs37973 and SAR susceptibility. Second, the correction for confounding factors was not as strict as that of clinical trials because of non-intervention. Third, the study lacked objective indicators for the evaluation of clinical symptoms.

Despite these limitations, this gene correlation study will be meaningful toward shedding light on further research.

Conclusions

In conclusion, the *GLCCI1* rs37973 polymorphism may be a pharmacogenetic factor in the response to INCS treatment in Chinese SAR patients.

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Conflicts of interest

None.

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